When the brain is split, is space still unified?

by

Rebecca Ann Berman

BA, Vassar College, 1994

MA, University of Pittsburgh, 1999

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FACULTY OF ARTS AND SCIENCES

This dissertation was presented

by

Rebecca Ann Berman

It was defended on

April 23, 2004

and approved by

Marlene Behrmann, Ph.D.

Julie Fiez, Ph.D.

Tai Sing Lee, Ph.D.

Douglas P. Munoz, Ph.D.

Carl R. Olson, Ph.D.
Committee Chairperson

Carol L. Colby, Ph.D.
Dissertation Director

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Rebecca Ann Berman, PhD

University of Pittsburgh, 2004

How does the brain keep track of relevant spatial locations when the eyes move? In extrastriate, parietal and frontal cortex, and in the superior colliculus, neurons update stimulus representations in conjunction with eye movements. This updating reflects a transfer of visual information, from neurons that encode a salient location before the saccade, to neurons that encode the location after the saccade. Copies of the oculomotor command – corollary discharge signals – likely initiate this transfer. Spatial updating, or remapping, is thought to contribute to the maintenance of stable spatial representations as the eyes move.

We investigated the circuitry that supports spatial updating in the primate brain. Our central hypothesis was that the forebrain commissures provide the primary route for remapping spatial locations across visual hemifields, which entails the interhemispheric transfer of visual information. Further, we hypothesized that these commissures provide the primary route for corollary discharge signals, generated in one hemisphere, to initiate spatial updating in the opposite hemisphere. We tested these hypotheses by measuring spatial behavior and neural activity in two split-brain macaques. In behavioral experiments, we observed striking initial impairments in the monkeys' ability to update stimuli across visual hemifields. Surprisingly, however, we found that both animals were ultimately capable of performing these across-hemifield sequences. Both monkeys readily performed the same spatial task when updating required an interhemispheric transfer of corollary discharge signals, suggesting that these signals are transferred via subcortical pathways in the normal monkey. In physiological experiments, we found that neurons in lateral intraparietal cortex of the split-brain monkey can remap stimuli

across visual hemifields, albeit with a reduction in the strength of remapping activity. These neurons were robustly active when within-hemifield updating was initiated by a saccade into the opposite hemifield. Our findings suggest that both visual and corollary discharge signals from opposite hemispheres can converge to update spatial representations in the absence of the forebrain commissures. These investigations provide new evidence that a unified and stable representation of visual space is supported by a redundant circuit, comprised of cortical as well as subcortical pathways, with a remarkable capacity for reorganization.

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Chapter 1: General Introduction

WHY DOES THE WORLD STAY STILL WHEN OUR EYES MOVE?

Our interactions with the visual world are deceptively simple. We perceive a visual world that is richly detailed, stable, and continuous. This perception affords a range of spatial behaviors, from reaching for a cup of coffee, to navigating through a busy street. The ease of our spatial perception gives the impression that our sensory experience is a direct – and passive – reflection of the world around us. Our perception, however, is by no means a transparent read-out of sensory inputs. The active nature of perception is readily appreciated when we consider the mechanisms of vision. We explore and analyze the visual world using the high-acuity center of the retina, the fovea. In order to direct the fovea toward objects of interest we make rapid eye movements, called saccades, about three times each second. Nearly every 300 milliseconds, then, the brain receives a new image from the retina. As a result, a given location in the world corresponds to a new retinal location each time the eyes move. For example, each time our eyes fixate a new point in this paragraph, the number at the bottom of the page occupies a new place on the retinotopic map. We are oblivious to these nearly continuous displacements of the retinal image. Our visual perception, then, must be far more than a simple read-out of inputs to the retina. What we perceive is an internal representation of the visual world, which seamlessly compensates for the movement of our eyes.

How does the mind achieve stable visual perception from such constantly changing input? Psychologists have considered this puzzle for more than a hundred years. In 1866, Helmholtz observed that when he passively displaced his eye by gently pressing it, the image of the world was also displaced (Helmholtz, 1866). In contrast, when he displaced his eye by

generating a voluntary eye movement, the image of the world remained still. Helmholtz proposed that our perception of the visual world is kept stable by the "effort of will" associated with making an eye movement. This "effort of will," placed in the context of contemporary physiological studies, is a copy of the motor command that generates the saccadic eye movement. This copy of the motor command can support the computations needed to anticipate what the visual world will look like once the eyes reach their new location. By using this information, the brain can update the internal representation of space, keeping it in register with the incoming retinal signals. In this manner, the brain compensates for the retinal displacements caused by eye movements, providing a stable perception of objects in the visual world. This dynamic process, called spatial updating, is the focus of the present experiments.

The ultimate aim of this research is to understand the neural mechanisms that support spatial updating in the primate brain. One of the first steps toward achieving this aim is to characterize the relevant circuitry. In the present experiments, we sought to identify critical pathways for the transfer of the visual and oculomotor signals thought to be integral to spatial updating. Our experiments build on existing knowledge of the neural circuitry of spatial updating. The goal of this chapter is to review this existing knowledge. We first describe a compelling neurophysiological phenomenon, called remapping, and its relation to spatial constancy. We then review the current understanding of brain mechanisms that support the updating or "remapping" of spatial locations. Finally, we set forth the two experimental aims of the present study.

PART I: REMAPPING ACTIVITY: THE PHENOMENON AND ITS FUNCTIONAL SIGNIFICANCE

Neurons remap stimulus representations

In the past two decades, neurophysiological studies have provided considerable insight into neural mechanisms that likely contribute to the phenomenon of spatial constancy. Single-unit recording studies in awake, behaving monkeys indicate that several brain areas participate in updating spatial representations when the eyes move. In parietal, frontal, and extrastriate cortex, and in the superior colliculus, neurons respond to a memory trace of a stimulus location, which has been updated in conjunction with an eye movement. Visual neuroscientists have developed a paradigm, known as the single-step task, which reveals this updating activity (Duhamel et al., 1992a). An example is shown in Figure 1. The activity of a neuron in lateral intraparietal cortex (LIP) was monitored during the single-step task (Duhamel et al., 1992a). In this task (panel A), the monkey simply looked from an initial fixation point (FP1) to a new fixation point (FP2). At the same moment that the new fixation point appeared, a stimulus was flashed briefly, outside the neuron's receptive field. The stimulus was positioned so that, once the eyes reached FP2, its location would fall within the neuron's receptive field. The task timing (panel B) illustrates a critical feature of the task: the stimulus was extinguished before the eyes began to move. If the neuron operated as a simple photoreceptor, it would not respond in this task, because no physical stimulus was ever present in its receptive field. Yet the neuron exhibited a burst of activity at the time of the eye movement. This reflects the neuron’s response to an updated memory trace of the previous stimulus. Duhamel and colleagues chose the term remapping to describe this phenomenon. The term emphasizes the idea that the brain has mapped the original stimulus location onto an internal representation; this representation is then updated or re-mapped when the eyes move, to be in register with the new retinotopic coordinates.

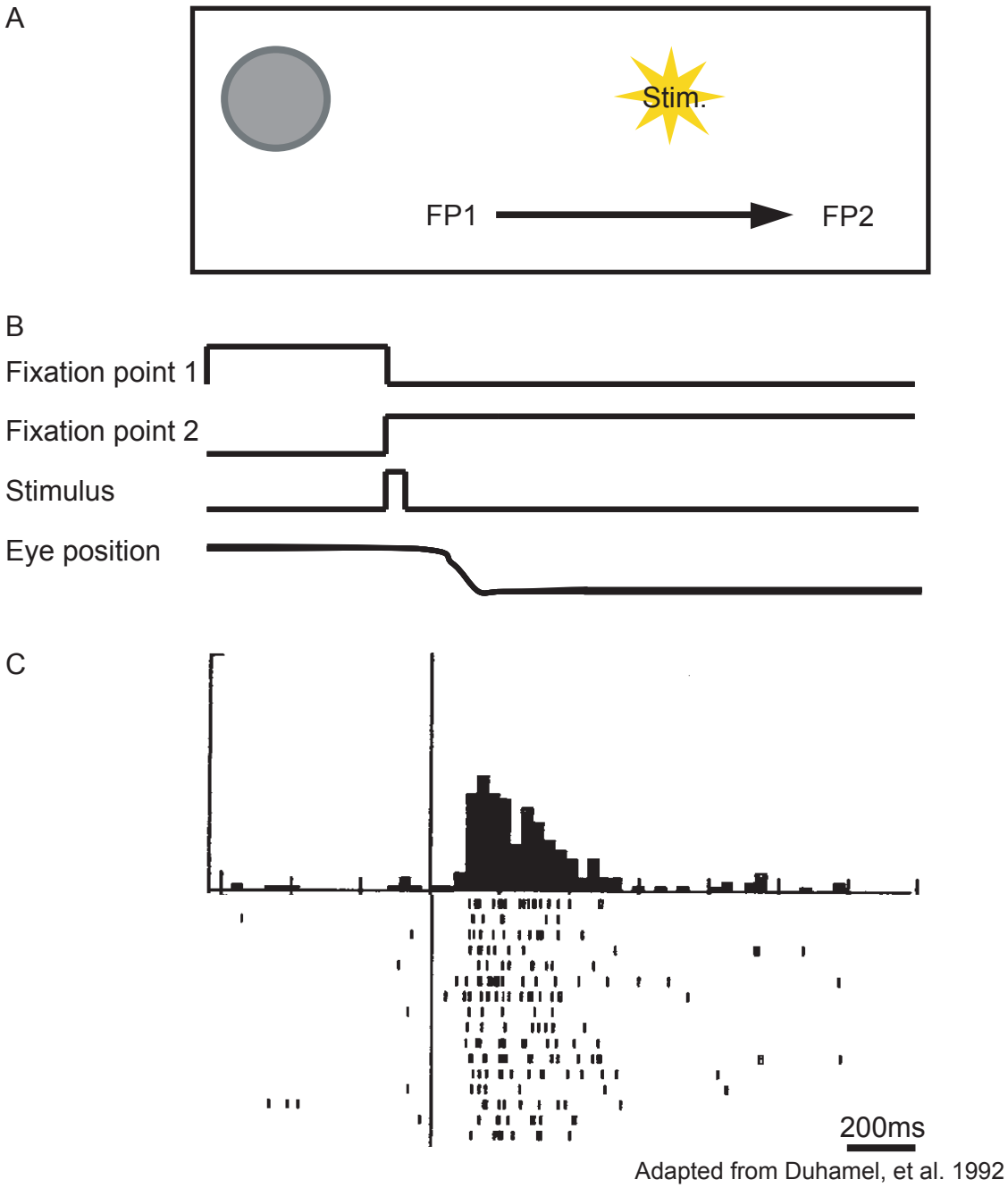


Figure 1. Remapping activity observed in a single LIP neuron during the single-step task. The spatial configuration of the task is shown in panel A. The neuron's receptive field is indicated by the grey circle. The monkey makes a single rightward saccade from FP1 to FP2, bringing the neuron's receptive field onto the location where the stimulus had previously appeared. The timing of events is indicated in the middle panel. The new fixation point (FP2) and the stimulus appear simultaneously when the initial fixation point (FP1) disappears. Critically, the stimulus has been extinguished by the time the monkey initiates the saccade to FP2. This means that there is no physical stimulus in the receptive field either before or after the saccade. The neuron nevertheless responds with a strong burst of activity after the eye movement. This is shown in panel C. The histogram is aligned on saccade onset, and represents the summed activity across all trials. The rasters below show activity on individual trials, where each tic mark represents a single action potential. Vertical scale bar indicates a firing rate of 100 spikes/sec.

Remapping is thought to contribute to a dynamic, eye-centered representation of spatial locations, which is impervious to displacements of the retinal image (Goldberg and Colby, 1990; Duhamel et al., 1992a; Colby et al., 1995). This contribution is understood most readily by considering the events and signals involved in the single-step task (Figure 2). In this example, the neuron under study is located in the right parietal cortex, and consequently has a receptive field in the left visual field. The eyes begin at the first fixation point, FP1 (panel A). When the stimulus is flashed (panel B), the neuron being monitored cannot "see" the stimulus; the stimulus location is outside its receptive field. A different set of neurons (orange asterisk), with receptive fields located up and to the right, encode the retinal location of the stimulus. Some of these neurons will continue to fire even after the stimulus has disappeared, maintaining a memory trace of its location (panel C). Once the eyes move to FP2, however, this mnemonic representation will be out of register with the incoming retinal image. For this memory trace to be useful for stimulus localization, it must be transferred to those cells that will encode this location after the eye movement to FP2 (panel D). The neuron under study is part of this population of cells, with receptive fields encompassing the new retinal location of the flashed stimulus. The neuron's firing reflects a continued retinotopic representation of the location where the stimulus had appeared. In this way, remapping is a mechanism for keeping track of locations as the eyes move and retinal images shift.

We now turn to the functional significance of remapping. We highlight two aspects of spatial updating that indicate its utility for guiding efficient, accurate spatial behavior.

A

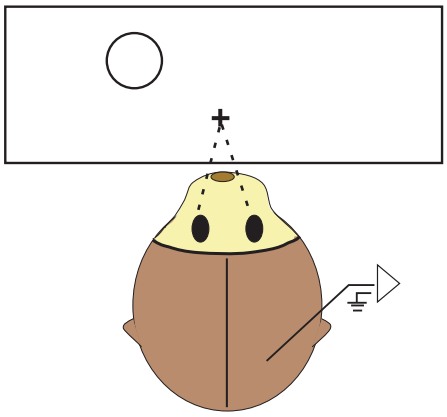
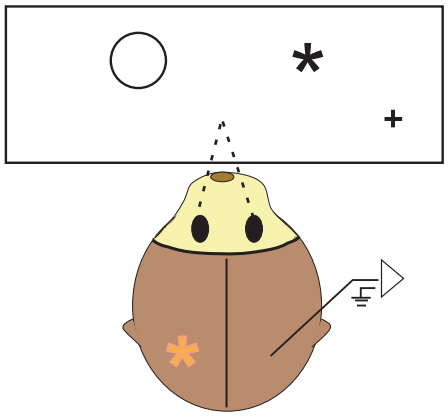


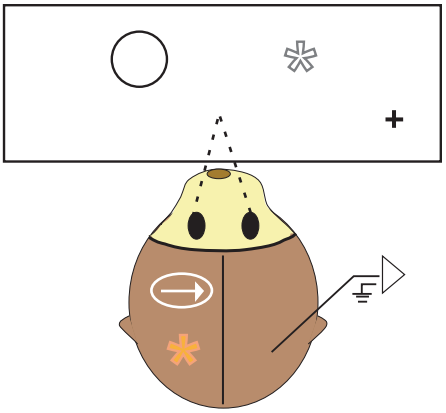
Figure 2. Updating of a stimulus trace in the single-step task. Panel A shows the beginning of the trial. The monkey's gaze is directed toward an initial fixation point (FP1, central crosshair). The neuron under study, located in the right hemisphere, has a receptive field in the upper left visual field (open circle). Electrode indicates the recording site.

B



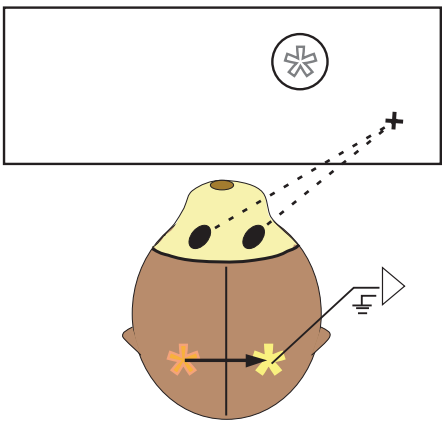
Panel B illustrates the initial representation of the stimulus. Three sensory events take place simultaneously. FP1 disappears, a new fixation point appears (FP2, peripheral crosshair), and a stimulus is flashed briefly in the upper right visual field (asterisk). The eyes have not yet left FP1. As a result, the stimulus is outside the current receptive field of the neuron. The stimulus is encoded by neurons in the left hemisphere. This visual representation is indicated by the orange asterisk in the left hemisphere.

C



Panel C illustrates the memory trace of the stimulus location, and the corollary discharge signal. The stimulus disappears before the monkey initiates a saccade to FP2. The open asterisk on the screen indicates the location where the stimulus appeared. This location is still encoded by visual neurons with memory-related activity. The memory trace is indicated by the orange asterisk in the left hemisphere. The arrow in the left hemisphere represents a copy of the motor command to move the eyes to the right. This corollary discharge signal is used to update the visual representation of the stimulus location.

D



Panel D illustrates the transfer of memory trace activity in conjunction with the saccade. The monkey makes a saccade to FP2, bringing the neuron's receptive field onto the previously stimulated location. Activity is transferred from the neurons that encoded the initial retinal location of the stimulus (orange asterisk in the left hemisphere) to the neurons that encode the retinal location from the new eye position at FP2 (yellow asterisk in right hemisphere). As a result, the neuron under study fires in response to the updated memory trace of the stimulus. This remapping providing a continued, retinotopic representation of the salient location where the stimulus appeared.

Updating is a selective process

One of the essential features of spatial updating is that the brain employs it selectively, remapping only locations that are behaviorally significant. This was demonstrated in an elegant experiment by Gottlieb, Kusunoki and Goldberg (1998). In this experiment, they monitored the activity of neurons in parietal cortex while varying the behavioral significance of the to-be-updated stimulus. In the single-step task, as described above, neurons fire when a receptive field is brought onto a location where a flash had just appeared. Gottlieb and colleagues demonstrated that neurons do not respond when the receptive fields are brought onto a stable, continuously visible stimulus that is embedded in a stable, continuously visible array. In other words, non-relevant stimuli are not remapped. They further demonstrated that remapping of an embedded stimulus *is* observed when the stimulus is behaviorally significant. This behavioral significance can be achieved either by virtue of exogenous factors (e.g., the stimulus is flashed) or by virtue of endogenous factors (e.g., the stimulus is the target for an eye movement). From these findings, we can infer that spatial updating is an efficient process, and one that is closely affiliated with selective spatial attention. The selectivity of spatial updating supports adaptive behavior, allowing us to keep track of salient sensory events and goals for action. In the next section, we describe evidence that spatial updating contributes to the ability to localize stimuli of interest.

Updating supports accurate spatial behavior

Is updating useful for accurate spatial behavior? This question has been addressed using a classic visuospatial paradigm, the double-step saccade task (Hallett and Lightstone, 1976; Mays and Sparks, 1980; Goldberg and Bruce, 1990). This task provides direct insight into the ability to keep track of a spatial location when the eyes move. In the double-step task, the subject must

make eye movements to two successively flashed targets, T1 and T2 (Figure 3, panel A). The critical feature of this task is that the second target (T2) disappears before the eyes leave the fixation point (FP). If the subject generates the sequence based only on the retinal location of the second target, the second saccade will be incorrect (panel B). For accurate performance of the sequence, the location of T2 must be updated in conjunction with the first saccade (panel C).

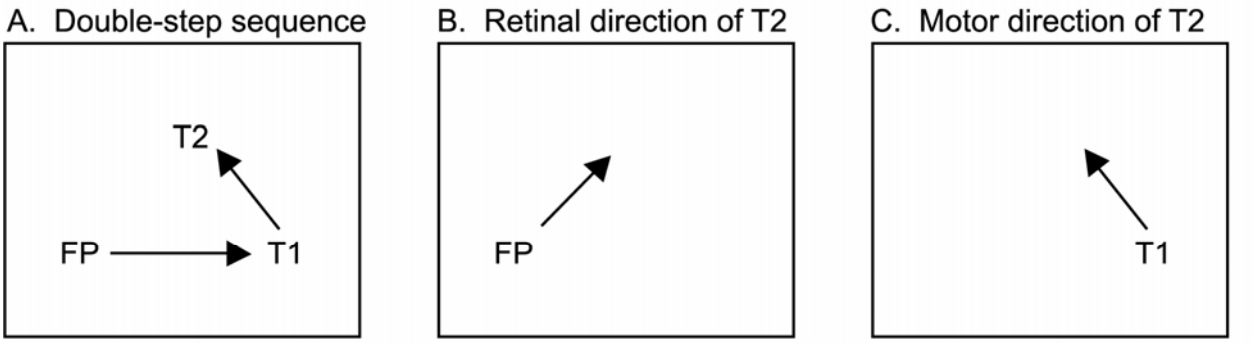


Figure 3. Performance of the double-step saccade task requires spatial updating. Panel A shows the double-step sequence. Subjects make two consecutive saccades, to the first target (T1) and then to the second target (T2). The second target appears very briefly, and so is visible only when the eyes are at initial fixation (FP). This introduces a mismatch between the retinal direction of the saccade (panel B) and the motor direction of the saccade required to attain the T2 location from the eyes' position at T1 (panel C). When the eyes are at fixation, the retinal location of T2 is up and to the right (panel B). If the subject generates this retinal saccade from T1, however, it will be inaccurate. For accurate completion of the sequence, the location of T2 must be updated to take the saccade to T1 into account. Updating allows the T2 location to be encoded in the new retinotopic coordinates, centered at T1, which dictates the saccade trajectory needed to acquire the target (panel C).

In parietal and frontal cortex, and in the superior colliculus, neurons are active in the double-step task (Mays and Sparks, 1980; Goldberg et al., 1990; Goldberg and Bruce 1990; Walker et al., 1995). This activity has been interpreted as reflecting a response to the updated memory trace of the T2 stimulus (Goldberg et al., 1990; Goldberg and Bruce 1990). In this context, remapping activity provides an updated representation of the second target, in retinal coordinates – the very coordinates needed to generate the second saccade. Neuropsychological studies have demonstrated that performance of the double-step task is impaired in patients with

damage to parietal cortex (Duhamel et al., 1992b; Heide et al., 1995). This observation implies that the remapping activity observed in parietal cortex is critical for spatial localization across eye movements. Taken together, these neurophysiological and neuropsychological findings suggest that remapping activity contributes to the ability to keep track of salient locations when the eyes move.

PART II: WHAT IS THE NEURAL CIRCUITRY OF SPATIAL UPDATING?

Our current experiments are founded on a working model of spatial updating that emerges from existing neurophysiological knowledge. In the next two sections, we briefly describe the working model and review the relevant brain areas that participate in spatial updating.

Signals of spatial updating

What neural signals are required for spatial updating? A simple model of updating postulates the combination of two primary signals (Quaia et al., 1998; Figure 2). One of these signals is visual in nature: when the eyes move, there is a transfer of activity associated with the representation of the visual stimulus. As described above in Figure 2, the stimulus is represented by one set of neurons *before* the eye movement (the "pre" neurons). These neurons transfer their memory trace activity to the neurons that will encode the stimulus location *after* the eye movement (the "post" neurons). The other signal is motoric in nature: a copy of the motor command, known as the corollary discharge signal, is thought to initiate the transfer of visual information. In the example in Figure 2, updating occurs in conjunction with a rightward eye movement. A copy of this eye movement command, generated by the left hemisphere, is sent to the areas responsible for updating the visual representation. For example, if the eyes are going to move ten degrees to the right, news of the impending saccade is sent to visual areas, initiating a transient ten degree

shift in receptive field locations (Quaia et al., 1998). The current experiments investigate the pathways supporting the convergence of these visual and oculomotor signals.

Brain areas that participate in spatial updating

Neurophysiological studies have identified several cortical and subcortical areas where neurons exhibit remapping (Figure 4). Remapping was observed first in regions closely allied with the oculomotor system: the lateral intraparietal cortex (LIP), the frontal eye field (FEF), and the intermediate layers of the superior colliculus (SC; Mays and Sparks, 1980; Bruce and Goldberg, 1990; Duhamel et al., 1992a; Walker et al, 1995; Umeno and Goldberg, 1997, 2001). Recent research has shown that remapping is not limited to areas allied with the oculomotor system; neurons in extrastriate visual cortex also exhibit updating activity (Nakamura et al., 2002). The existence of remapping in early visual areas indicates that it is more widespread than previously believed. Moreover, this finding suggests that eye movements are taken into account at remarkably early stages of visual processing.

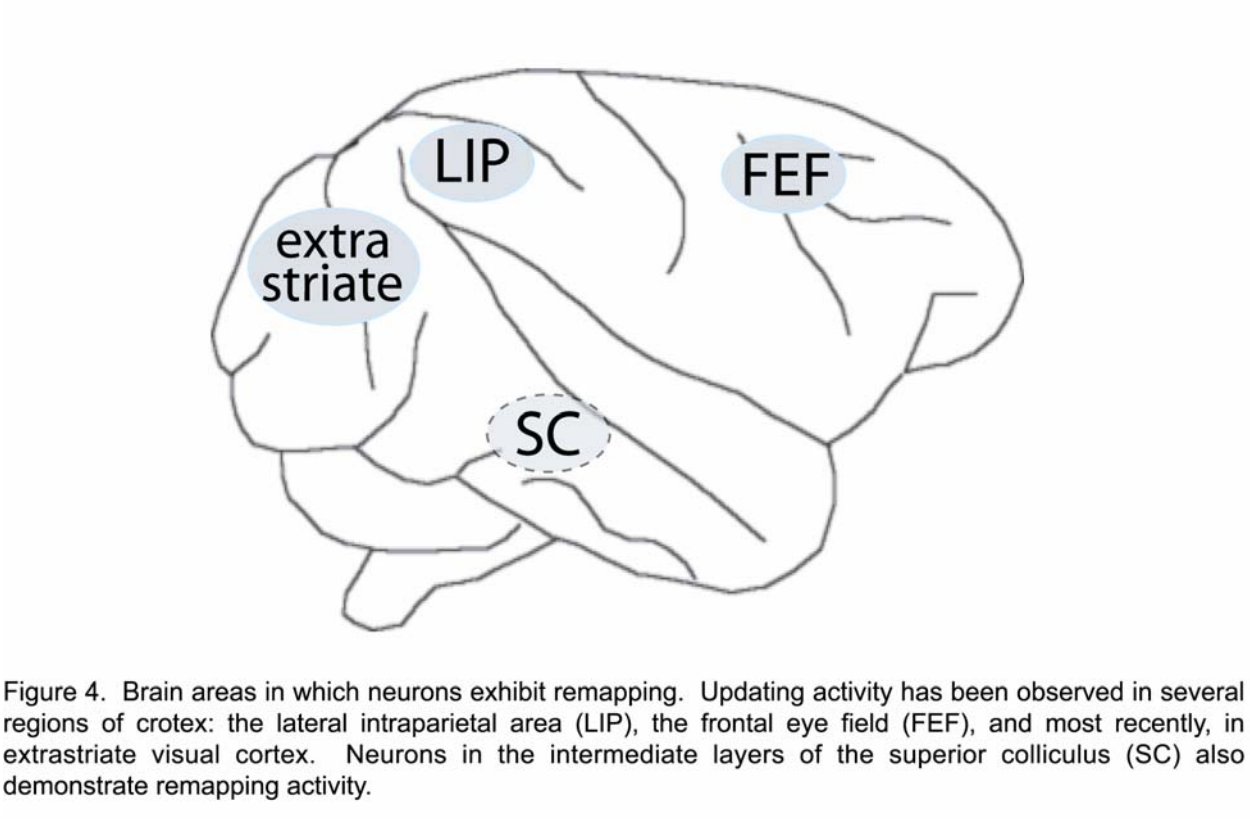


Figure 4. Brain areas in which neurons exhibit remapping. Updating activity has been observed in several regions of crotex: the lateral intraparietal area (LIP), the frontal eye field (FEF), and most recently, in extrastriate visual cortex. Neurons in the intermediate layers of the superior colliculus (SC) also demonstrate remapping activity.

Area LIP is thought to play a central role in spatial updating. The anatomical and physiological properties of this area indicate that it is particularly well-suited for carrying out the computations required to remap visual representations in conjunction with eye movements. Area LIP is situated high in the dorsal stream hierarchy, and receives projections from other association cortices, as well as visual and oculomotor structures (Cavada and Goldman-Rakic, 1989; Lynch 1989; Andersen et al., 1990; Colby and Duhamel, 1991; Clower et al., 2001). The richness of this anatomical connectivity is evident in the response properties of LIP neurons. These neurons exhibit not only visual, memory, and saccade-related activity, but also are modulated by cognitive factors such as attention and anticipation (Gnadt and Andersen, 1988; Colby et al., 1996; Andersen, 1997). Nearly all neurons in area LIP (95%) remap stimulus traces in conjunction with eye movements (Duhamel et al., 1992a). Observations from neuropsychological studies suggest that remapping in area LIP is critical for accurate spatial

behavior. These studies have demonstrated that damage to parietal cortex, but not frontal cortex, causes impaired performance in the double-step task, consistent with failures in spatial updating (Heide et al., 1995; Heide and Kompf, 1998). Taken together, these anatomical, physiological, and neuropsychological findings implicate area LIP as the site for the generation of remapping, where corollary discharge signals from the oculomotor system initiate the updating of visual representations.

Area LIP is strongly and reciprocally connected with the SC and FEF. Three features of the connectivity among these areas may be integral to the processes of spatial updating. First, both LIP and FEF have descending projections to the intermediate layer of the SC, where the majority of neurons are active in relation to saccadic eye movements to visual targets. These descending pathways have been shown to carry a range of visual, mnemonic, and oculomotor signals to the SC (Pare and Wurtz, 1997, 2001; Sommer and Wurtz, 2001). Secondly, there are significant ascending pathways from superior colliculus to cortex. Neurons in the superficial visual layer of the SC project upstream to area LIP, via the pulvinar (Hardy and Lynch, 1992; Clower et al., 2001). Of particular interest is an ascending path from the intermediate layers of the SC to FEF, via the mediodorsal thalamus (Lynch et al., 1994; Sommer and Wurtz, 2002). Recent studies have shown that this pathway transmits corollary discharge signals to cortex (Sommer and Wurtz, 2003, 2004b). Third, area LIP and FEF are also strongly linked (Petrides and Pandya, 1984; Andersen et al., 1990). This pathway may allow for the relay of corollary discharge signals to LIP, via the FEF, and for remapped visual signals to be sent from LIP to FEF. In summary, the connections among these three areas constitute known pathways by which visual and oculomotor signals can be transmitted during spatial updating.

PART III: EXPERIMENTAL AIMS

Aim 1: Pathways for transfer of visual signals during spatial updating

One of the most surprising facets of remapping is that, at the time of the eye movement, neurons are responsive to locations outside their classical receptive fields. An important implication of this finding is that neurons have access to information from throughout the visual field, even from the opposite visual hemifield. Indeed, in the original demonstrations of remapping in area LIP, stimulus representations were updated from one visual hemifield to another (Duhamel et al., 1992a). This across-hemifield updating must require a transfer of information between neurons in opposite hemispheres, as the representation of visual stimuli is highly lateralized (Trevarthen, 1990). As will be described below, the corollary discharge signal must also be communicated between hemispheres (Aim 2).

The first and primary aim of the current investigation was to identify the neural pathways responsible for updating spatial locations across visual hemifields. We hypothesized that the forebrain commissures – the corpus callosum and anterior commissure – provide the primary path for this updating, which is presumed to require an interhemispheric transfer of visual information. The corpus callosum, with roughly half a billion fibers of passage, constitutes the most prominent route for interhemispheric communication (Lamantia and Rakic, 1990; Houzel et al, 2002). In particular, there are extensive callosal connections between parietal cortices in each hemisphere, and between parietal cortex and areas in the frontal lobe (Pandya and Vignolo, 1969; Hedreen and Yin, 1981; Seltzer and Pandya, 1983; Schwartz and Goldman-Rakic, 1984). These connections could support the relay of visual and oculomotor signals required for spatial updating. Neuropsychological studies have demonstrated that the corpus callosum is necessary for integrating a variety of visual stimuli across hemifields, including form and color information as well as complex spatial stimuli (Holtzmann, 1984; Gazzaniga, 1987; Trevarthen, 1990;

Corballis, 1995). We therefore expected that across-hemifield spatial updating would be disrupted, if not abolished, in the absence of these commissures.

We tested this hypothesis by assessing behavioral and neural correlates of spatial updating in two rhesus macaques whose forebrain commissures were surgically transected. We tested spatial behavior using the double-step task. We assessed neural activity by recording from single neurons in area LIP. Using these measures, we evaluated the integrity of spatial updating in two critical conditions, illustrated in Figure 5. In the within-hemifield updating condition, stimuli were updated from one location to another, within the same visual hemifield. In the across-hemifield updating condition, stimuli were updated from one visual hemifield to the other. This condition is also referred to as the "visual-across" condition, to emphasize that the *visual* representation of the stimulus must be updated across hemifields. We predicted that spatial updating would be severely disrupted if not abolished in the visual-across conditions, but not in the within-hemifield condition.

Aim 2: Pathways for transfer of the oculomotor signals that initiate updating

The second aim of the current project was to investigate the pathways that support the transfer of corollary discharge signals that initiate spatial updating. Specifically, we asked whether the forebrain commissures are necessary when stimulus representations are updated within the same hemifield, but when the updating is initiated by a saccade into the opposite hemifield. Oculomotor signals, like visual signals, are highly lateralized. We therefore hypothesized that spatial updating in the split-brain monkey would be disrupted when the initiating saccade was directed into the hemifield opposite the visual stimulus. We evaluated spatial behavior and

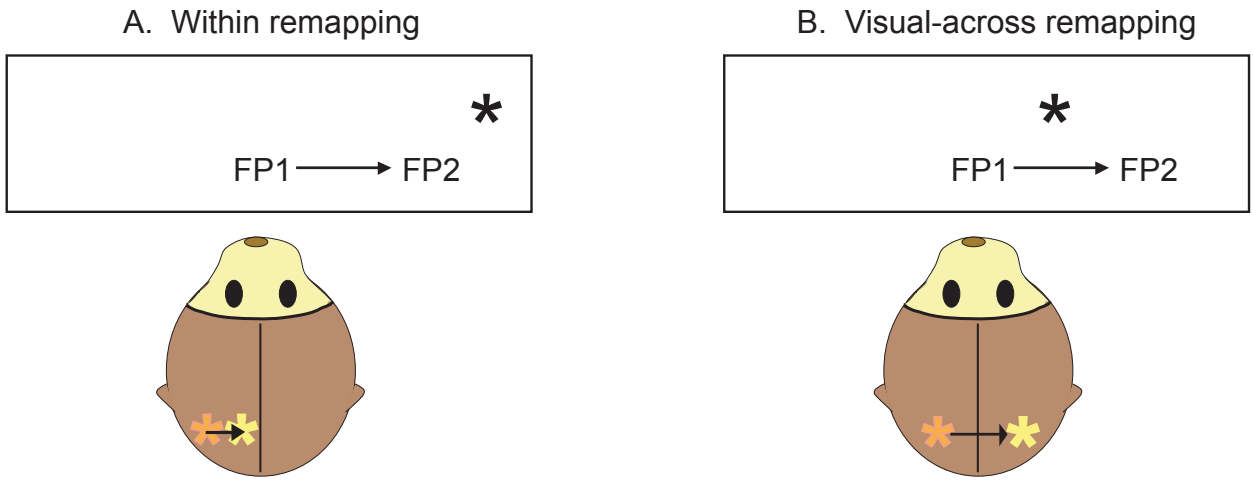


Figure 5. Experimental conditions of Aim 1: comparison of spatial updating when the stimulus location is updated either within or across visual hemifields. In the within condition (panel A), the stimulus is located in the right visual field when the eyes are at FP1. Its retinal location is represented by neurons in the left hemisphere (orange asterisk). When the eyes reach FP2, the location where the stimulus appeared is still in the right visual field, and therefore represented by neurons still within the left hemisphere (yellow asterisk). Updating in this condition involves a transfer of visual signals between sets of neurons located within the same cortical hemisphere. In the visual-across condition (panel B), the stimulus is located in the right visual field when the eyes are at FP1, and therefore represented by neurons in the left hemisphere (orange asterisk). When the eyes reach FP2, however, the location where the stimulus appeared is now in the left visual field. This retinal location is represented by neurons in the right hemisphere (yellow asterisk). Consequently, updating in this condition represents a transfer of visual information between sets of neurons in opposite cortical hemispheres. We expected that visual-across remapping would be impaired in the absence of the forebrain commissures.

remapping activity in area LIP during two conditions, motor-within and motor-across (Figure 6). In both the motor-within and motor-across conditions, stimuli were updated within the same visual hemifield. The critical difference between these conditions was the direction of the saccade that initiated spatial updating. In the motor-within condition, the saccade is directed into the same visual field in which the stimulus is updated. Consequently, the corollary discharge signal is generated by the same hemisphere in which the transfer of visual information occurs. In contrast, in the motor-across condition, the initiating saccade is directed into the opposite hemifield. The corollary discharge signal must therefore be communicated interhemispherically, from the hemisphere generating the saccade command, to the hemisphere in which the visual stimulus is updated. This condition is referred to as the "motor-across" condition, to emphasize the premise that spatial updating requires an interhemispheric transfer of oculomotor signals. The motor-within condition is identical to the within-hemifield condition used in Aim 1; in general, we refer to this simply as the “within” condition.

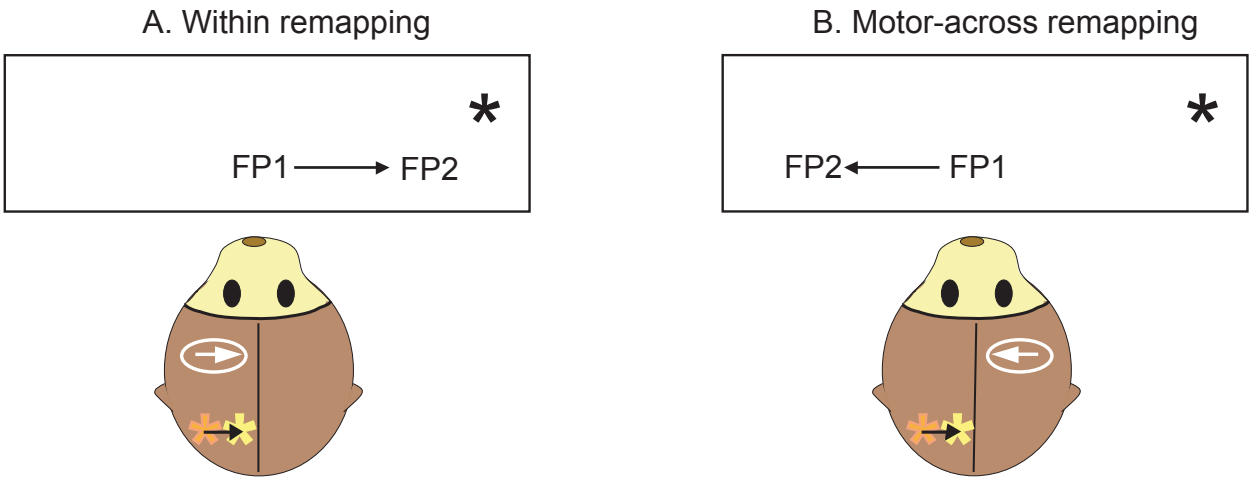


Figure 6. Experimental conditions of Aim 2: comparison of spatial updating when the initiating saccade is made into the same (A) or opposite (B) visual field as the updated stimulus location. In the within condition, the stimulus is located in the right visual field when the eyes are at FP1. When the eyes reach FP2, the location where the stimulus appeared is still in the right visual field. Updating therefore involves a transfer of visual signals between sets of neurons located within the same cortical hemisphere. A rightward saccade initiates the transfer of visual information. This saccade is generated by the left hemisphere. Consequently, the corollary discharge signal (white arrow) and visual signals (orange and yellow asterisks) are housed within the same hemisphere. In the motor-across condition, the stimulus is again located within the right visual field, both before and after the eye movement from FP1 to FP2. As a result, updating in this condition also involves a transfer of visual information within the same hemisphere. In this condition, however, the saccade that initiates updating is directed into the opposite (left) visual field. This saccade is generated by the right hemisphere. Consequently, the corollary discharge signal originates in the hemisphere opposite that in which the visual signals are transferred. We expected that motor-across remapping would be impaired in the absence of the forebrain commissures.

SUMMARY

We have argued that the problem of spatial constancy is a significant one, necessary not only for perceptual stability, but also for the localization of visual targets. The neurophysiological phenomenon of remapping, observed in several cortical and subcortical regions, provides a possible mechanism for achieving spatial constancy. In the current project, we use behavioral and physiological methods to investigate the circuitry that subserves spatial updating. The experiments are founded on the premise that updating requires a transfer of visual signals at the time of the eye movement. This transfer is initiated by a corollary discharge signal, representing the intended eye movement. The following chapters describe three experimental approaches that investigate the communication of these visual and oculomotor signals during spatial updating in the split-brain monkey. In these chapters, we assess spatial updating by measuring its behavioral correlates (Chapter 2), neural correlates (Chapter 3), and by investigating the relationship between neural activity and spatial behavior (Chapter 4).

Chapter 2: Behavioral correlates of spatial updating in the split-brain monkey

OVERVIEW

In Chapter 2, we present a series of behavioral experiments in which we assessed the integrity of spatial updating using the double-step saccade task. We designed specific conditions of the task that required the interhemispheric transfer of either the visual signal ("visual across") or the oculomotor signal ("motor across"). We measured double-step performance for each of these interhemispheric conditions as compared to a strictly intrahemispheric condition, in which both the visual and oculomotor signals remained within the same hemisphere ("within" condition).

We first address the hypothesis that spatial behavior would be impaired when updating required the interhemispheric transfer of visual signals. We assess the monkeys' double-step performance on the visual-across condition, as compared to the within condition. This assessment consists of a total of seven behavioral experiments, which characterize the strengths and weaknesses of updating across visual hemifields in the absence of the forebrain commissures.

We then address the hypothesis that spatial behavior would be impaired when updating required the interhemispheric transfer of motor signals. We assess the monkeys' performance on the motor-across condition as compared to the within condition, and to the visual-across condition. This assessment consists of two experiments, which demonstrate the intact interhemispheric transfer of oculomotor signals in the split-brain monkey.

BACKGROUND

The functional significance of spatial updating is not limited to perceptual stability; spatial constancy is also critical for action. Specifically, it supports the ability to localize targets across intervening eye movements. This ability can be assessed directly using the double-step task. In this task, as described in Figure 3, subjects make consecutive saccades to two briefly appearing targets. The second target is visible only when the eyes are at initial fixation. This introduces a disparity between the retinal coordinates of the target and the motor coordinates required to attain the target after the eye movement. Accurate double-step performance therefore requires that the location of the second target is updated or remapped, in conjunction with the first saccade.

Both humans and monkeys perform the double-step task accurately (Hallett and Lightstone 1976, Mays and Sparks 1980, Gnadt and Andersen 1988, Goldberg and Bruce 1990). Neuropsychological studies have shown that accurate performance depends critically on parietal cortex (Heide et al., 1995; Duhamel et al., 1992b). Patients with damage to parietal cortex are capable of generating slow double-step sequences when both saccades are visually guided. In this case, the trajectory of the second saccade can be computed accurately using retinal information. When the targets are presented in rapid succession, however, the second saccade is not visually-guided. In this case, its accurate computation relies on spatial updating of the second target, to account for the intervening saccade to the first target. Under these circumstances, parietal patients fail to complete the double-step sequence accurately. The role of parietal cortex in performance of the double-step task has been demonstrated further in monkeys. Inactivation of area LIP impairs double-step performance, as evidenced by decreased accuracy and increased latencies for the second eye movement (Li and Andersen, 2001). The necessity of

parietal function for accurate double-step performance underscores the relationship between remapping activity and spatial behavior.

EXPERIMENTAL AIMS

In Aim 1, we hypothesized that the forebrain commissures provide the pathway for the interhemispheric transfer of visual signals required for spatial updating. Our experimental prediction was that, in the absence of these commissures, performance of the double-step task would be impaired selectively on sequences requiring the interhemispheric transfer of this visual information.

We tested this prediction by measuring the double-step performance of split-brain monkeys on two conditions of double-step task: the "within" and "visual-across" conditions. We described the theoretical design of these conditions in Chapter 1 (Figure 5). We now describe the implementation of these conditions in the double-step task, as illustrated in Figure 7. In the within sequence shown in panel A, the second target (T2) appears in the right visual field when the eyes are at central fixation (FP). Its location is therefore encoded by neurons in the left hemisphere. After the disappearance of the central fixation point, the monkey makes a visually-guided saccade to the first target (T1). When the eyes are at T1, the location where T2 appeared is still in the right visual field. Updating in this condition therefore involves a transfer of visual information between sets of neurons within the left hemisphere. In the visual-across sequence shown in panel B, T2 also appears in the right visual field when the eyes are at central fixation. When the eyes reach T1, however, the location where T2 had appeared is now in the left visual field. Its retinal location is represented by neurons in the right hemisphere. Consequently, updating in the visual-across condition presumably involves an interhemispheric transfer of visual information, from neurons in the left hemisphere to neurons in the right hemisphere. Our

expectation was that the split-brain monkeys would exhibit impairment on the visual-across but not the within condition.

In Aim 2, we hypothesized that the forebrain commissures also provide the pathway for the interhemispheric transfer of corollary discharge signals required for spatial updating. Our experimental prediction was that, in the absence of these commissures, performance of the double-step task would be impaired selectively for sequences requiring the interhemispheric transfer of this motor signal.

We tested this prediction by measuring the double-step performance of split-brain monkeys on two conditions of double-step task: the "within" and "motor-across" conditions (Figure 8). The within condition is identical to the one described above for the visual-across experiment. In this condition, the location of the second target is updated within the same (right) visual field. The saccade that initiates spatial updating is also generated into the right visual field. As a result, the oculomotor command is generated by the same hemisphere (left) in which the T2 location is updated. In the motor-across condition, the transfer of visual signals is also within-hemifield: the retinal location of T2 is in the right visual field both before and after the first saccade. The direction of the first saccade, however, is into the left visual field. As a result, the corollary discharge command originates in the right hemisphere, whereas the visual updating occurs within the left hemisphere. We expected that this interhemispheric transfer of oculomotor signals would be disrupted in the split-brain monkey, resulting in impairment of the motor-across but not the within condition.

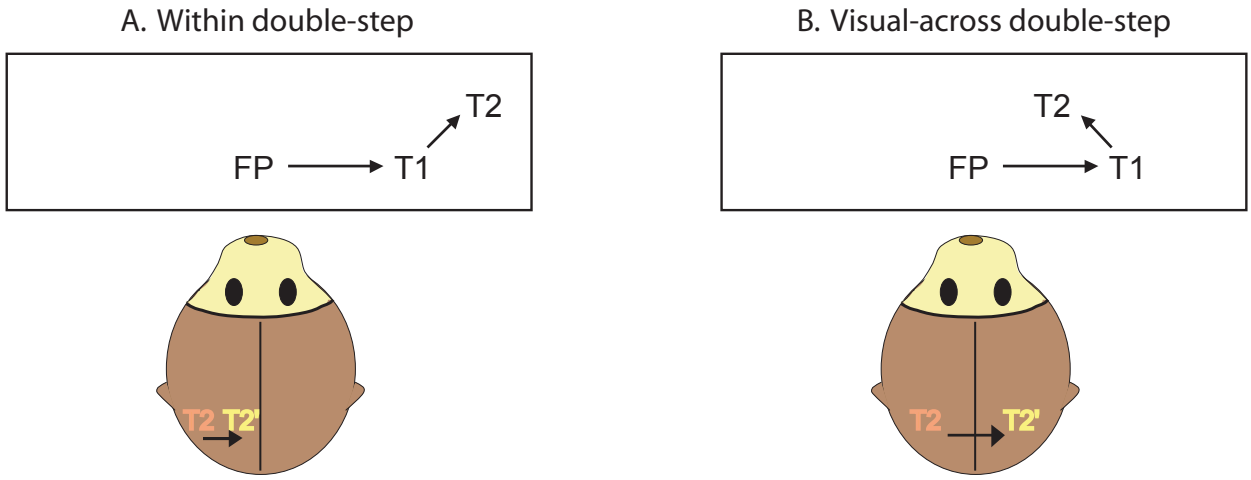


Figure 7. Comparison of double-step saccade conditions that require the second target location to be updated within or across visual hemifields. In each condition, the monkey's task is to make a visually-guided saccade to T1, followed by a memory-guided saccade to T2. In the within condition (panel A), T2 appears in the right visual field when the eyes are at FP. Its retinal location is represented by neurons in the left hemisphere (orange T1). When the eyes reach T1, T2 itself is gone, but a memory trace of T2 is still in the right visual field. This retinal location is encoded by neurons within the left hemisphere (yellow T2'). Updating therefore involves a transfer of visual signals between sets of neurons located within the same cortical hemisphere. In the visual-across condition (panel B), T2 appears in the right visual field when the eyes are at FP, and therefore is initially represented by neurons in the left hemisphere (orange T2). When the eyes reach T1, however, the memory trace of T2 is now located in the left visual field. This retinal location is encoded by neurons in the right hemisphere (yellow T2'). Consequently, updating in this condition involves a transfer of visual information between sets of neurons in opposite cortical hemispheres. We expected that performance of the visual-across condition, but not the within condition, would be impaired in the absence of the forebrain commissures.

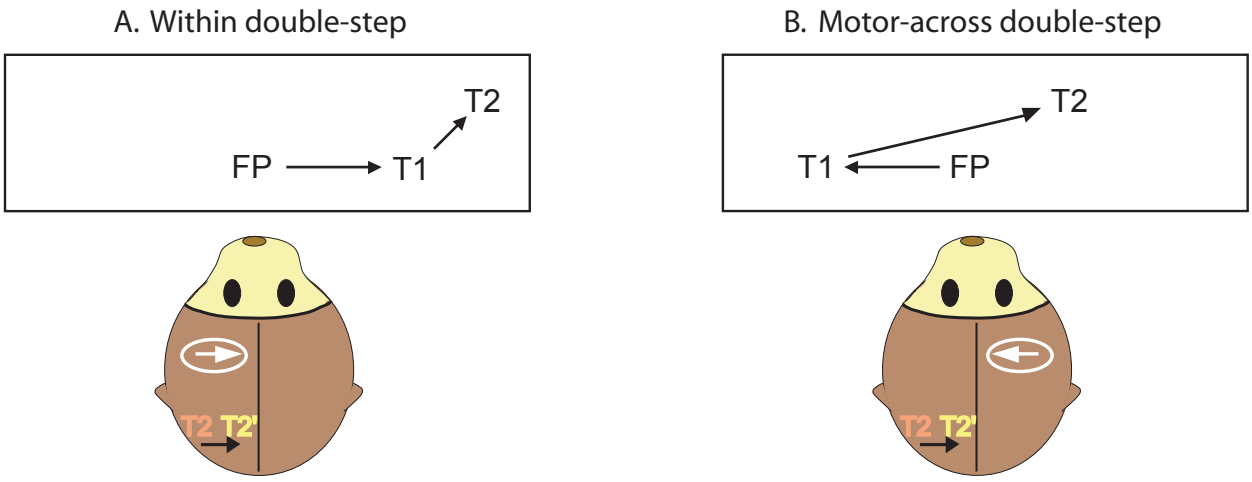


Figure 8. Comparison of double-step conditions in which the initiating saccade is made into the same (A) or opposite (B) visual field as the updated stimulus location. In each condition, the monkey's task is to make a visually-guided saccade to T1, followed by a memory-guided saccade to T2. In both conditions, T2 appears in the right visual field when the eyes are at FP. The memory trace of T2 is still in the right visual field after the eyes have reached T1. Therefore, updating for both conditions involves a transfer of visual signals between sets of neurons located within the same cortical hemisphere (orange T2 and yellow T2' in the left hemisphere). The crucial difference between the two conditions is the direction of the saccade that initiates this transfer of visual information. In the within condition, the first saccade is directed into the same (right) visual field where T2 is updated. This saccade is generated by the left hemisphere. Consequently, the corollary discharge signal (white arrow) and visual signals (orange T2, yellow T2') reside in the same hemisphere. In the motor-across condition, the saccade that initiates updating is directed into the opposite (left) visual field. This saccade is generated by the right hemisphere. Consequently, the corollary discharge signal originates in the hemisphere opposite that in which the visual signals are transferred. We expected that performance of the motor-across condition, but not the within condition, would be impaired in the absence of the forebrain commissures.

APPROACH

Subjects and task

We conducted these studies in two rhesus macaques, designated EM and CH, whose forebrain commissures were surgically transected. As described above, we measured their performance on several conditions of the double-step task. Briefly, this task requires the generation of saccades to two successively appearing targets. In our version of this task, the target for the first saccade remained on the screen until the monkey attained it. This visually-guided saccade allowed us to isolate errors related to generation of the second saccade, which was guided only by spatial memory. Critically, the second target appeared only for 50ms, and therefore was extinguished before the eyes left central fixation. We verified that the monkeys were able to perceive the stimulus only from central fixation, by measuring stimulus decay and psychophysical thresholds. These measures, described in the Appendix, ensured that each monkey's performance of the double-step task relied on updating the memory trace of T2 in conjunction with the saccade to T1. We classified as correct those trials in which the first saccade landed within ~2º of T1 and the second saccade landed within ~2.5º of T2. On correct trials, T2 was re-illuminated and, following a final fixation of T2, the monkey received juice reward. Details of our methodological procedures are found in the Appendix.

Training of the double-step task

Both monkeys were trained to perform the double-step task prior to any behavioral or physiological testing. Training had to meet two objectives in order for subsequent behavioral testing to be effective. First, the monkeys needed to be able to perform multiple double-step sequences in an interleaved fashion. Second, they needed to be able to generalize to new sequences. These objectives required a general understanding of the double-step task, which, in

turn, required lengthy training. Our training protocol consisted of two stages. In both stages, it was critical to train the monkeys without using sequences that required across-hemifield updating. The first stage was designed to impart a general understanding of the double-step task. The second stage served as a transition to behavioral testing.

In the first stage, we used a vertical version of the double-step task (Figure 9B). In the vertical sequences, the first target (T1) was displaced vertically from central fixation, either straight up or straight down. The second target (T2) appeared either in the left or right visual field. For all vertical sequences, the representation of T2 remained in the same visual hemifield when the eyes were at fixation and when the eyes reached T1 (Figure 9A). The monkeys were trained to a criterion of 75% correct for all sequences in the upper and lower visual field (Figure 9B). Both monkeys reached criterion following roughly four months of training.

In the second stage of training, we introduced the horizontal version of the task, which served as the foundation for behavioral testing. In these sequences, the first saccade was directed to the right or left. During training, the monkeys performed only one kind of horizontal sequence, called the central condition (Figure 10B). In central sequences, T1 appeared to the left or right of fixation, and T2 was located directly above T1. In other words, once the eyes reached T1, the stimulus trace of T2 was on the midline and, as such, was represented by both hemispheres (Figure 10A). Central sequences therefore did not require across-hemifield updating. The monkeys were trained to perform central sequences in each of the four visual quadrants (Figure 10B). The second stage of training proceeded fairly rapidly, requiring only a single session for monkey CH to reach criterion, and two sessions for monkey EM.

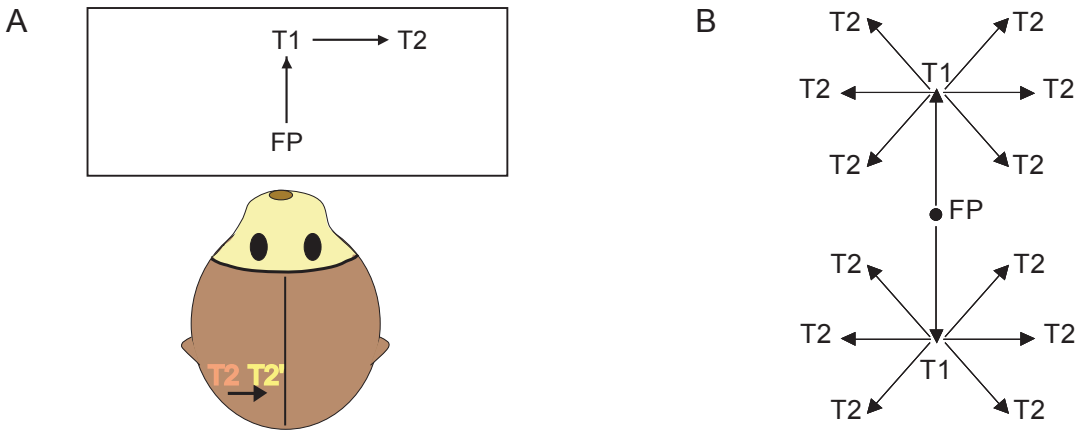


Figure 9. Vertical double-step trials do not require across-hemifield updating. A. The cartoon shows what happens to the representation of T2 when the eyes move vertically. When the eyes are at fixation (FP), T1 appears directly above it, and T2 flashes briefly in the right visual field. The location of T2 is represented in the left hemisphere. When the eyes move to fixate T1, the memory trace of T2 is still in the right visual field. Its new retinal location is still represented in the left hemisphere. In other words, T2 is updated within the same visual hemifield. Updating therefore involves a transfer of information between neurons in the same hemisphere. B. The full set of vertical sequences used during the first stage of double-step training. The first target (T1) appeared either directly above or directly below central fixation (FP). The second target appeared either in the right or left visual field. Saccade metrics were identical to those of the testing configuration (Figure 11). The amplitude of each saccade was 12°. Oblique T2 locations were displaced from the horizontal T2 by 30°. The monkeys first learned to perform a small subset of two vertical sequences, such as "up-right" and "up-left." The remaining sequences were added gradually until the monkeys were able to maintain 75% correct for six sequences interleaved. Upper and lower field sequences were trained in separate blocks until performance reached criterion.

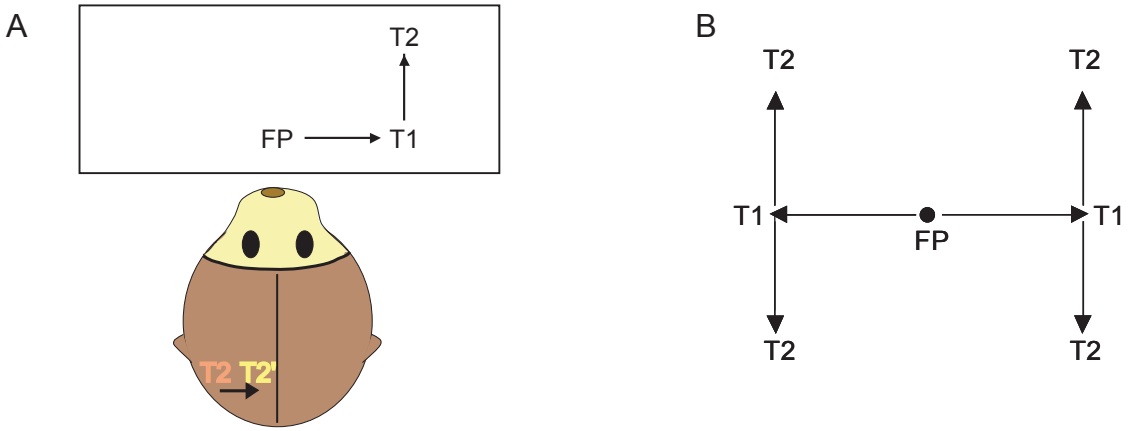


Figure 10. Central double-step trials do not require across-hemifield updating. A. The cartoon shows what happens to the representation of T2 in the central condition. When the eyes are at fixation (FP), T1 appears directly to the right. T2 flashes briefly, directly above T1, in the right visual field. The location of T2 is represented in the left hemisphere. When the eyes move to fixate T1, the memory trace of T2 is located on the vertical meridian. Its new retinal location is therefore represented by both hemispheres. As for the vertical sequences, updating for the central sequences involves a transfer of information between neurons in the same hemisphere. B. The central sequences used during the second stage of double-step training. The first target (T1) appeared either in the right or left visual field. The second target (T2) appeared either directly above or directly below T1. Metrics were identical to those of the testing configuration (Figure 11). Upper and lower field sequences were trained in separate blocks until performance reached criterion.

RESULTS

PART I. CAN SPLIT-BRAIN MONKEYS PERFORM THE VISUAL-ACROSS DOUBLE-STEP TASK?

The first aim of our behavioral experiments was to determine whether performance of visual-across double-step sequences is impaired in the split-brain monkey. In the next three sections, we report our experimental observations that address this aim. In Section 1, we describe the results of two experiments that reveal an initial impairment of the visual-across condition. In Section 2, we describe the evolution and learning of visual-across sequences over multiple testing sessions. In Section 3, we describe three experiments that test the integrity of the double-step performance after the visual-across sequences were learned.

Section 1: Evidence for impaired spatial updating

Experiment 1: Updating across visual hemifields

Behavioral testing began once the monkeys completed the double-step training. At this stage, the monkeys were performing the trained central sequences shown in Figure 10B. We tested both monkeys in the upper visual field first; the lower field was tested the following day. In each session, we introduced four critical test sequences simultaneously. These were the within (green) and visual-across (red) conditions, in each visual field (Figure 11). The new sequences were randomly interleaved with the trained central sequences (black). Visual-across and within sequences were equivalent in novelty, and counterbalanced for the direction of the first and second saccades. The only remaining difference between the two conditions was the difference of interest: accurate double-step performance required either visual-across or within-hemifield spatial updating. Experiment 1 was comprised of four testing sessions, with each monkey (CH and EM) contributing two sessions (upper and lower visual field testings). These initial testing sessions were critical because the monkeys' performance was not confounded by experience with

either the visual-across or the within condition. As such, these sessions provide unique insight into the integrity of spatial updating in the split-brain monkey.

Is performance impaired for visual-across sequences?

The monkeys' first exposures to the within and visual-across conditions revealed a striking and selective impairment for sequences that required updating across visual hemifields. Eye traces from the upper field provide a clear demonstration of the initial double-step deficit (Figure 12A). Traces from the central conditions show that the monkeys were very accurate in the execution of these trained sequences. Likewise, the monkeys were able to perform the within conditions with considerable accuracy, despite the fact that these sequences were entirely novel. In contrast, both monkeys made inaccurate movements on every trial of the first ten visual-across sequences. On these trials, the trajectory of the second saccade deviated only slightly from a straight vertical saccade. These data are consistent with the prediction that performance of visual-across sequences would be impaired in the absence of the forebrain commissures.

Eye traces from the lower field show a similar pattern, but also reveal some surprising dissimilarities (Figure 12B). As in the upper field, both monkeys performed well on central and within conditions. Monkey EM showed a clear impairment for the visual-across sequences: saccade trajectories were predominantly vertical, and were even directed upward on several trials. These data are in keeping with the pattern of impairment in the upper field. Remarkably, however, monkey CH was able to execute the lower-field visual-across sequences with considerable accuracy, even in the first ten trials.

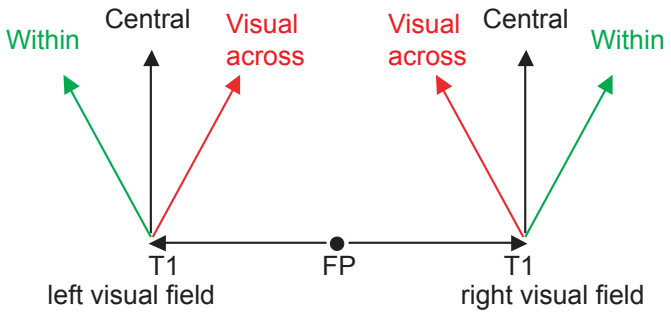


Figure 11. Configuration for testing double-step performance in the visual-across paradigm. The six sequences were randomly interleaved. Testing was conducted separately in the upper visual field (shown) and in the lower visual field. Horizontal arrows represent the first saccade from central fixation (FP) to the first target, T1. In each quadrant, the second saccade (S2) was directed to one of three targets. The central conditions, shown in black, required a vertical S2. These sequences served as the training condition. The within conditions (green) and visual-across conditions (red) were introduced simultaneously. Accurate performance of the within sequences required within-hemifield updating of the T2 location. Accurate performance of the visual-across sequences required across-hemifield updating of the T2 location. For all conditions, the first and second saccades were 12° in amplitude. The within and visual-across S2 trajectories were offset from the central S2 by 30°.

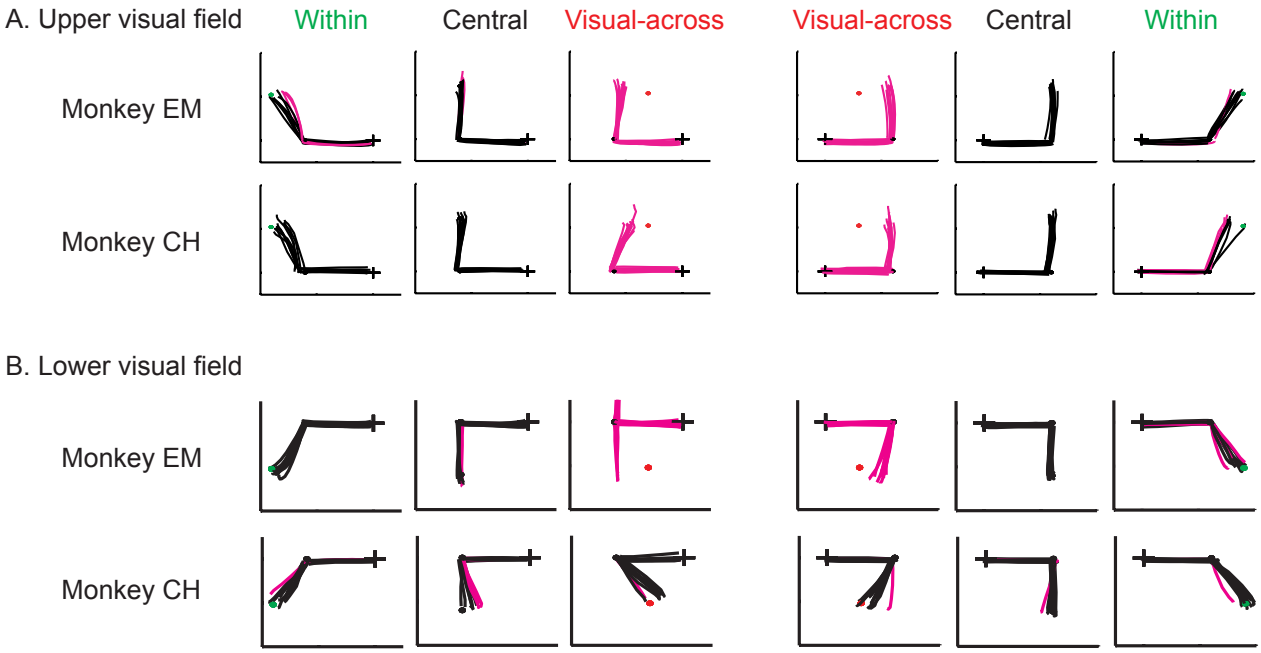


Figure 12. Eye traces reveal an initial impairment for visual-across sequences as compared to within sequences. Individual panels show the eye path, in degrees of visual angle, for the first ten trials of each condition. In each panel, the cross indicates the location of the central fixation point, and small dots indicate the locations of T1 and T2. Black eye traces are from correct trials, pink from incorrect. A) Data from the upper visual field, from monkey EM (top row) and monkey CH (bottom row). B) Data from the lower visual field, from monkey EM (top) and CH (bottom). In each row, panels are arranged by visual field and T2 location, in parallel with Figure 11. Colored labels indicate the condition. For central and within conditions, the trajectory of the second saccade (S2) matched the target trajectory. For visual-across conditions, however, the trajectories were less accurate. In the upper field, S2 deviated only partially toward T2 for both monkeys. In the lower field, the visual-across sequences were similarly impaired in monkey EM. Monkey CH, in contrast, performed the visual-across sequences correctly in both quadrants of the lower visual field.

Double-step saccade endpoints

How representative are these eye traces of performance during the first session? Figure 13 shows the second-saccade endpoints from all valid trials from the first session of testing. For monkey EM, the impairment of the visual-across sequences clearly persisted throughout the first session (Figure 13A). In both the upper and lower visual fields, the endpoints for the central sequences (black) and within sequences (green) were clustered near the correct T2 locations. The endpoints for the visual-across sequences (red) were clustered far from the correct endpoint. For monkey CH, the endpoint data were more variable (Figure 13B). In the upper right field, impairment of the visual-across sequence continued throughout the session. Endpoints for this sequence resembled those for monkey EM. In the upper left quadrant, however, many endpoints for the visual-across sequence were clustered near the correct T2 location. This indicates that performance improved as the monkey gained experience in the first session (about 200 trials of this sequence). In the lower field, monkey CH performed both visual-across sequences with considerable accuracy throughout the session.

The data in Figure 12 and 13 show two contrasting results: in the absence of the forebrain commissures, the performance of visual-across sequences was impaired in most cases, and yet was surprisingly accurate in a few cases. These results are borne out in quantitative analysis, described below. We characterized the monkeys' initial performance in two stages of analysis. First, we classified the trials according to error type. Second, we quantified saccade accuracy and latency and subjected these measures to statistical analyses.

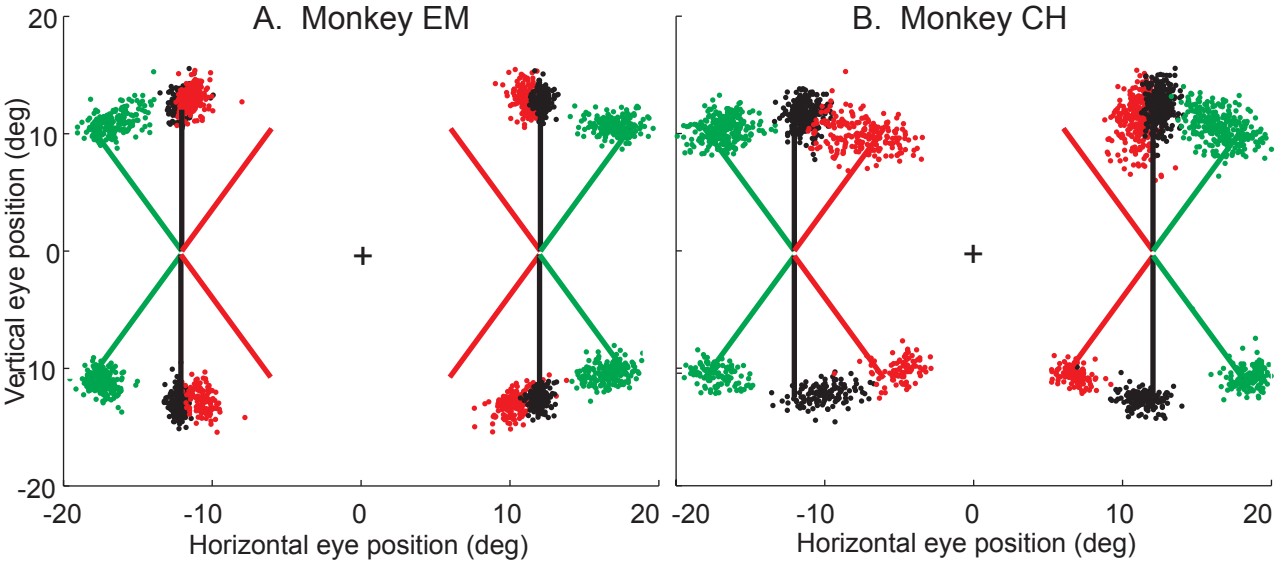


Figure 13. Endpoints of the second saccade from the first session of visual-across testing, for monkey EM (panel A) and monkey CH (panel B). Lines show the target trajectories for the second saccade of each sequence. Lines and endpoints are colored according to condition: central (black), within (green), and visual-across (red). For monkey EM (A), endpoints of the visual-across sequences were clustered near the central target in all four quadrants. For monkey CH (B), endpoints of the visual-across sequences were clustered near the central target in the upper field, particularly in the left quadrant. In the upper right quadrant, endpoints are also clustered correctly near the visual-across target. This reflects the monkey's ability to learn this sequence during the first testing session. In the lower visual field. monkey CH performed the visual-across sequences with considerable accuracy in both quadrants.

Percentage of correct and incorrect trials in the first session

In the first stage of analysis, we determined the percentage of trials belonging to each of three categories: 1) correct trials, 2) S2 errors, in which the monkey made an accurate saccade to T1 but not to T2, and 3) reversal errors, in which the monkey's first saccade went directly to T2 (see Methods for details of classification). The percentage of trials in each of these categories are shown in Figure 14, for upper and lower visual field testing in each monkey. Percent correct (filled columns) typically was high for central (black) and within conditions (green) for both monkeys. The percent correct for across conditions (red) varied according to monkey and visual quadrant. For monkey EM, percent correct was 0, regardless of visual quadrant. For monkey CH, it ranged from 0% (upper RVF) to 80% (lower RVF).

We found that the two monkeys exhibited distinct behavior, not only in terms of the percent correct for visual-across trials, but also in terms of the kinds of errors committed. For monkey EM, all of the error trials were S2 errors, in which the monkey reached T1 but not T2 (open columns). For monkey CH, error trials also included reversal errors, in which the first saccade went directly to T2 (hatched columns). These reversals occurred almost exclusively for the visual-across sequences, constituting up to 20% of trials. This reinforces the possibility that the monkeys employed different strategies in response to the visual-across conditions. Overall, the classification of trials provides a coarse quantitative description of the basic observations depicted in Figure 13: monkey EM demonstrated impaired visual-across performance in all quadrants, while monkey CH demonstrated variable impairment, depending on visual quadrant.

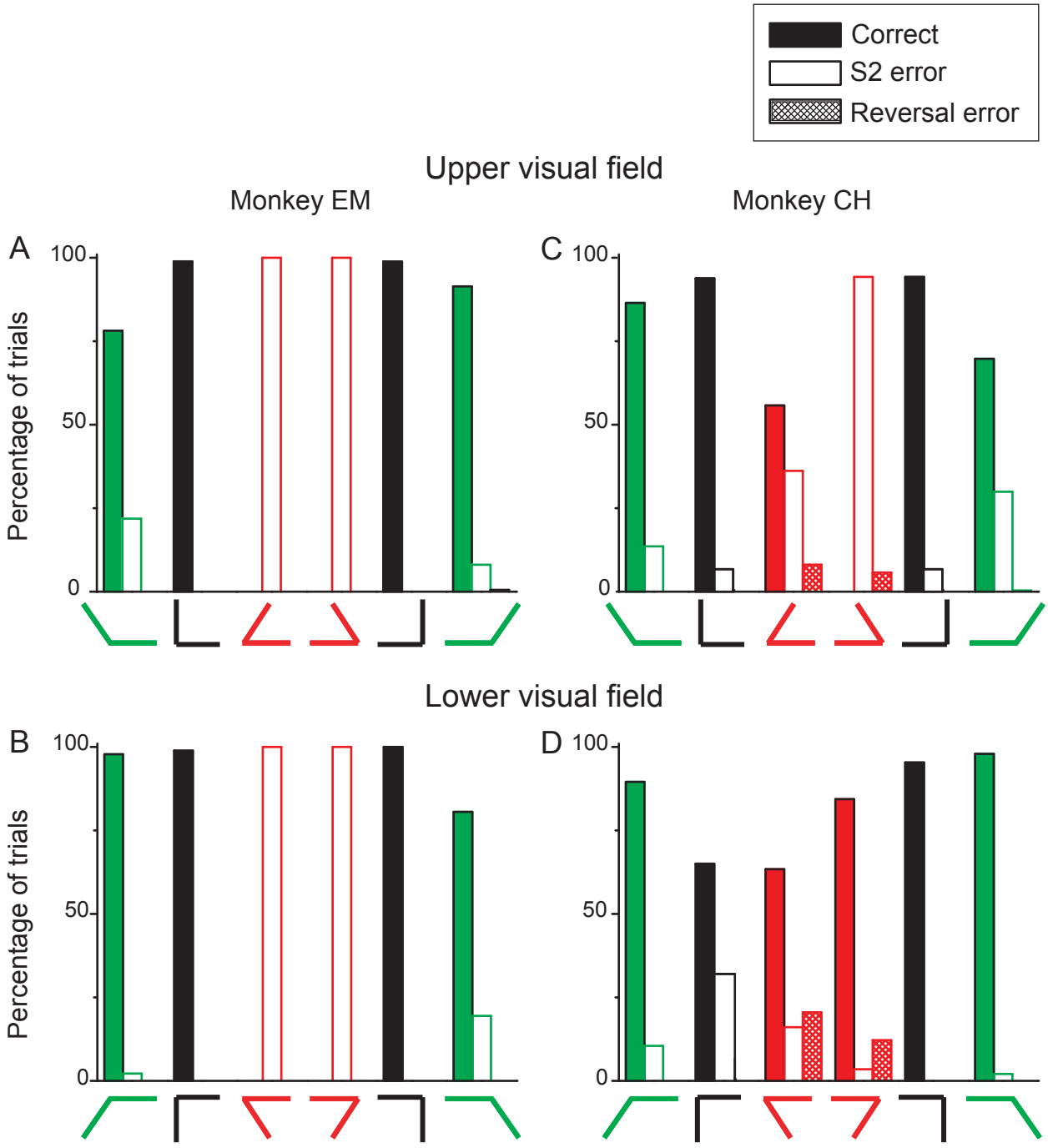


Figure 14. Percentage of correct and incorrect trials for double-step performance in the first session of testing. Percentages are shown separately for monkey EM (A, upper field; B, lower field) and monkey CH (C, upper field; D, lower field). Each panel shows percentages from six sequences. Sequences are indicated by the icons along the x axis. Central conditions are shown in black, within in green, and visual-across in red. Solid bars represent the percentage of correct trials. Open bars indicate incorrect trials in which the first saccade went to T1 but the second saccade did not reach T2 (S2 errors). Hatched bars indicate incorrect trials when the monkey made the first saccade directly to T2.

Quantification of saccade accuracy and latency

In the second stage of analysis, we used saccade metrics to evaluate the monkeys' performance of the double-step task. We measured the accuracy of the second saccade, and the latency of both saccades. For this analysis, we used only those trials where the monkey reached T1 successfully and directed the second saccade into the correct vertical visual field. We focused on two measures of accuracy: angular error and distance error (Appendix, Figure A1). These provide complementary information about saccade accuracy. Angular error refers to the angular difference between the saccade trajectory and the target trajectory. This indicates how well the direction of the saccade matched the direction of the target, though it gives no information about final endpoint accuracy. We report the results using unsigned angular error; information about the signed measure can be found in the Appendix. Distance error refers to the absolute vector distance between the saccade endpoint and the target. As such, it captures the absolute accuracy of the endpoint, but says nothing about the directional trajectory of the saccade. We anticipated that a failure to update locations across visual hemifields would cause decreased accuracy of the second saccade, manifest in both angular and distance error.

For each measure of interest, we conducted a univariate analysis of variance (ANOVA) to determine the significance of three independent factors on double-step performance: updating condition (central, within or across), direction of the first saccade ('S1 direction,' right or left), and vertical visual field (upper or lower). ANOVAs were conducted separately for each monkey. When we observed significant interactions, we conducted post-hoc analyses to determine the significance of differences in performance between specific sequences. We corrected for all possible pairwise comparisons between the sequences (Tukey's HSD, calculated at α=05 for 66 pairs), but focused on the comparison of each of the visual-across sequences to three 'matched' sequences. 1) The central sequence in the same quadrant was matched for the

direction of the first saccade, though not for novelty. 2) The within sequence in the *same* visual quadrant was matched for novelty and for the direction of the *first* saccade. 3) The within sequence in the *opposite* quadrant was matched for novelty and for the direction of the *second* saccade. We considered an individual visual-across sequence to be significantly impaired when it was significantly worse than each of the matched sequences ($p<.05$, Tukey's HSD). If all three pairwise comparisons were significant, we inferred that there was an impairment in spatial updating, rather than an impairment related to novelty or saccade direction. Throughout the description of behavioral results, we refer to individual sequences as being significantly impaired only if they met this criterion.

How is accuracy of the second saccade affected?

We found that the accuracy of the second saccade was significantly decreased for the visual-across condition, in most but not all cases. We first report the significant main effects, which provide a broad sense of the results. We then focus on the interactions, which show that the magnitude of visual-across impairment varied, depending on visual quadrant.

The ANOVA revealed significant main effects of updating condition on both the angular error and distance error of the second saccade (all $p<.0001$). These main effects reflect the fact that we obtain significant differences between conditions by collapsing the data over all four quadrants of the visual field (Figure 15). For both monkeys, average angular and average distance error were increased for the visual-across condition (red) as compared to both the within condition (green) and the well-trained central condition (black). We found a significant main effect of vertical visual field in both monkeys, for both angular and distance measures of accuracy. Monkey EM showed increased error in the lower field, whereas monkey CH showed increased error in the upper field ($p<.0001$ for all measures). In monkey EM, there were no

differences in angular error according to S1 direction ($p>.3$), though distance error was slightly worse in the left visual field ($p<.05$). In monkey CH, we observed a main effect for S1 direction in both accuracy measures, with increased error in the right visual field ($p<.0001$ for both measures).

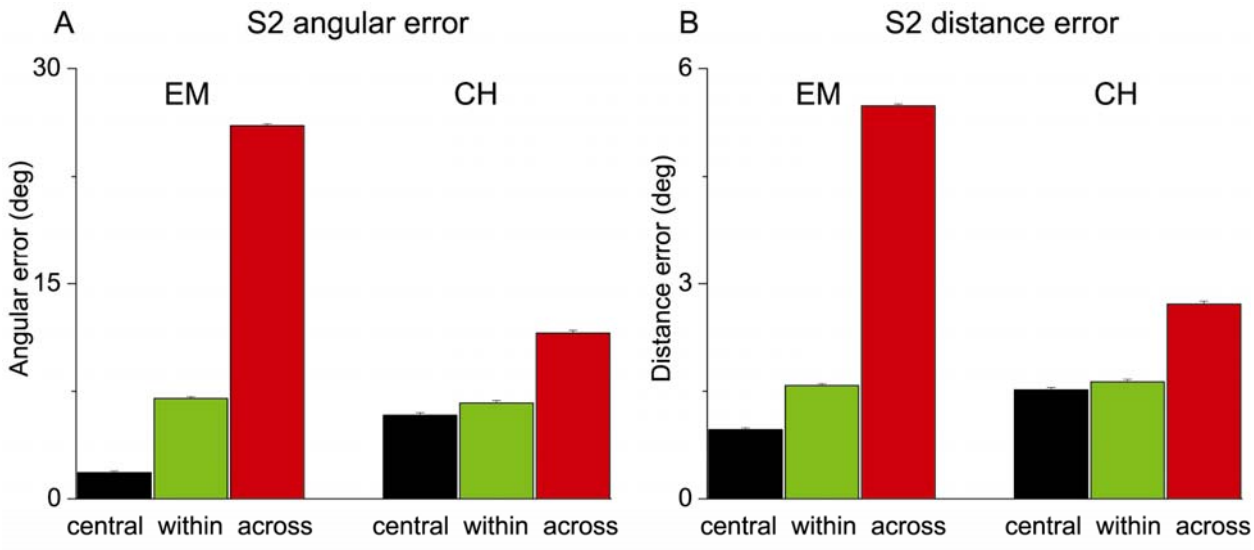


Figure 15. Average angular error (A) and distance error (B) for central (black), within (green) and visual-across (red) conditions of the double step task. In each panel, data from monkey EM are on the left, and data from monkey CH are on the right. For each condition, data were collapsed over sequences in all four quadrants; data from individual sequences are shown in Figure 16. Errors bars represent standard error of the mean. Both monkeys show increased overall error for the visual-across condition as compared to central and within conditions. This increase was observed for both angular (A) and distance error (B) .

These main effects provide a cursory understanding of the data. The core results, however, are revealed in the significant interactions. We focused on the three-way interaction between updating condition, S1 direction, and vertical visual field, which indicates variability in the magnitude of visual-across impairment, depending on the visual quadrant of the individual sequence. Such variability was plainly evident in the raw data of monkey CH (Figure 13). The average angular and distance errors for each sequence are shown for both monkeys in Figure 16. Panels A and C show data from the upper field, panels B and D from the lower field. In each

panel, the data from monkey EM are on the left, and data from monkey CH are on the right. At a glance, it is clear that error values were increased for most of the visual-across sequences (red) in relation to central (black) and within sequences (green). In monkey CH, however, error for the three conditions did not adhere to this pattern, especially in the lower visual field.

We found a significant interaction between updating condition, S1 direction, and vertical visual field for both monkeys, for both measures of accuracy (all $p<.0001$). In monkey EM, all four visual-across sequences were significantly impaired in both angular and distance error ($p<.05$, Tukey's HSD, compared to matched central and within conditions; procedure described above). In monkey CH, two of the visual-across sequences were significantly impaired. Angular error was significantly increased for the visual-across sequence in the upper right quadrant (Figure 16A). Distance error was significantly increased for the visual-across sequences in both upper field quadrants (panel C). We conclude that double-step performance was generally – but not always – less accurate for visual-across than, as compared to matched central and within sequences.

Is saccade latency affected?

We hypothesized that saccade initiation would be slower for visual-across conditions, given the absence of the most direct interhemispheric path, the forebrain commissures. We anticipated that this slowing would be evident in the initiation of the second saccade of the double-step task. We expected that the latency of the first saccade, which is visually-guided, would be unaffected.

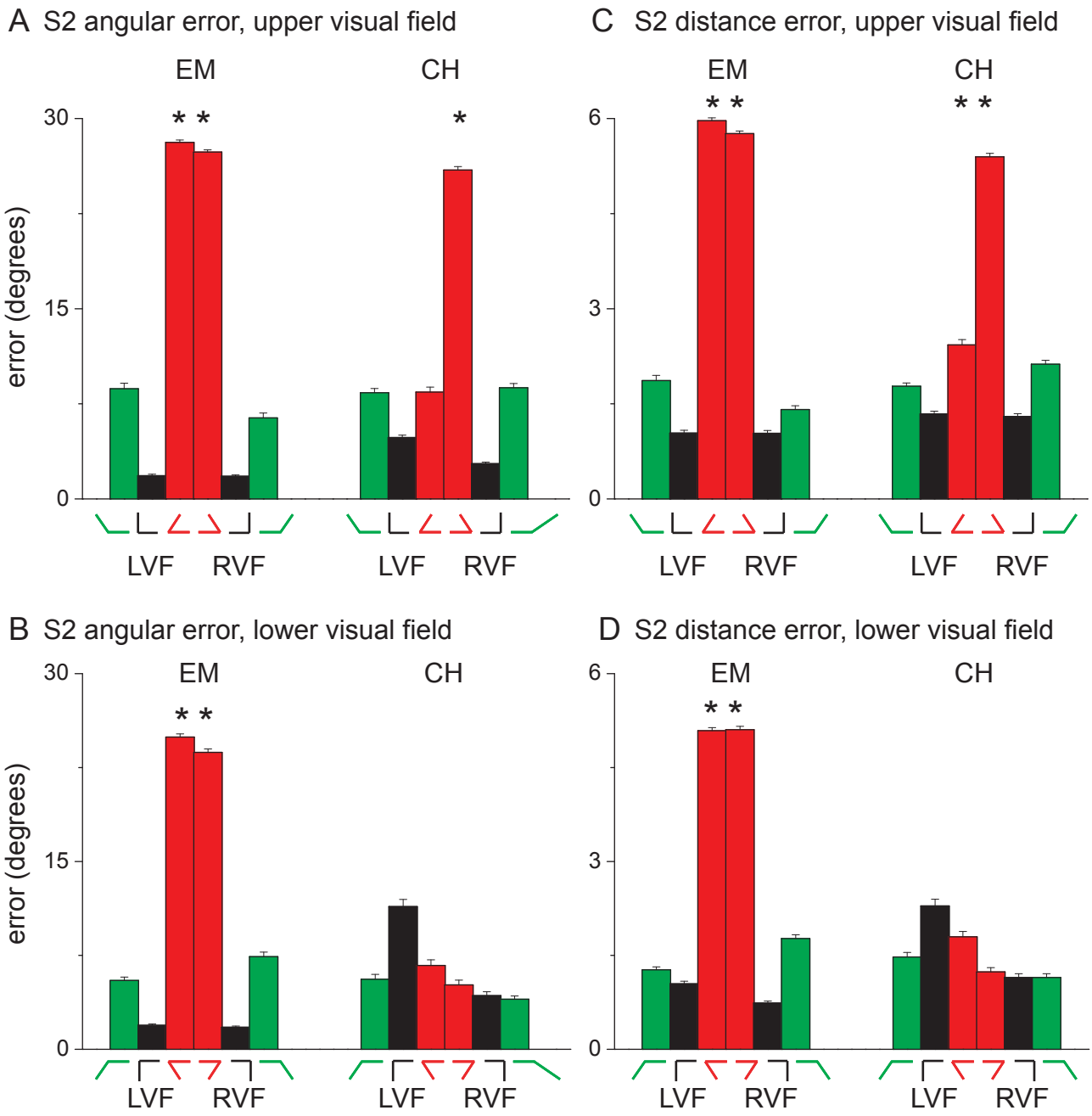


Figure 16. Measures of accuracy of double-step performance for each sequence; the same data are shown collapsed over quadrants in Figure 15. A,B: Angular error (mean +/-SE) for each sequence in the upper field (A) and lower field (B). In each panel, the first six columns show data from monkey EM, and the second six show data from monkey CH. Icons below each column indicate the sequence. Colors indicate the condition: black = central, green = within, red = visual-across. C, D. Distance error (mean+/-SE) for each sequence in the upper field (C) and lower field (D). Conventions as in A, B. For monkey EM, angular and distance errors were significantly increased for the visual-across sequences, as compared to within sequences, in all quadrants. For monkey CH, angular error was significantly increased for visual-across, relative to within, in the upper right quadrant. Distance error was significantly increased for visual-across, relative to within, in all quadrants except the lower left. Performance of baseline central conditions was equivalent or better than performance of within conditions, except in the lower left quadrant for monkey CH. Asterisks indicate visual-across sequences in which error was significantly increased as compared to corresponding central and within sequences ($p<.05$, Tukey's HSD).

On average, the latency of both the first and the second saccade was prolonged for the visual-across as compared to the within and central conditions. The ANOVA revealed a significant main effect of updating condition for both saccades (all $p<.0001$). These main effects can be readily observed when the data are collapsed over all quadrants (Figure 17). The monkeys showed similar overall patterns in their reaction times. For the first saccade (panel A), average reaction time was longest for the visual-across condition (red bars), and shortest for the within condition (green bars). Average reaction time for the central condition fell between these values (black bars). For the second saccade (panel B), average reaction time was again longest for the visual-across condition (red), but was shortest for the well-trained central condition (black). Mean reaction time for the within condition was between these values (green).

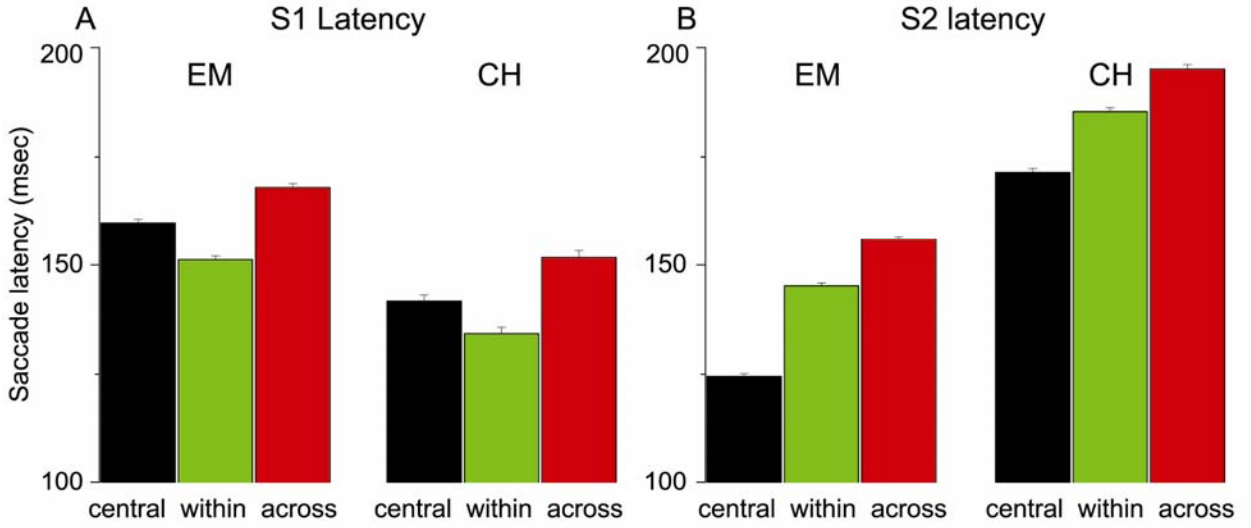


Figure 17. Average latencies for the first and second saccade, for each condition of the double step task. Conventions as in Figure 15; latencies for individual sequences are shown in FIgure 18. For both monkeys, reaction times for the first saccade (panel A) as well as the second saccade (panel B) were prolonged for the visual-across condition (red) as compared to both the central (black) and within (green) conditions. These data suggest that initiation of the double-step sequence was delayed when across-hemifield updating was required.

The latency of both the first and second saccades depended significantly on the interaction between updating condition, S1 direction, and vertical field (S1 latency, $p<.0001$ for monkey EM, $p<.05$ for monkey CH; S2 latency, $p<.0001$ for both monkeys). Figure 18 shows the latencies for the first saccade (panels A, B) and second saccade (panels C,D) for each sequence. As with the accuracy data, we asked whether the latencies of specific visual-across sequences were significantly increased relative to the matched central and within sequences. For both monkeys, reaction times for the first saccade were significantly prolonged in only one quadrant. By contrast, reaction times for the second saccade were significantly prolonged in three of four quadrants, for both monkeys. This indicates that initiation of the first, visually-guided saccade was minimally affected in sequences requiring across-hemifield updating, whereas initiation of the second, memory-guided saccade was slowed for these sequences.

In summary, quantitative analysis showed that performance was significantly impaired when the double-step sequence required T2 to be updated from one visual hemifield to the other. The visual-across impairment was evident in both decreased accuracy and increased reaction times for the second saccade. Analysis also indicated plain departures from this impairment. The accuracy and latency differences depended significantly on S1 direction and vertical visual field. These departures were most apparent in the learning and lack of initial impairment in the visual-across performance of monkey CH. We characterize the successful performance of the visual-across condition in the latter parts of this chapter (Sections 2 and 3). In the following paragraphs, we examine and rule out alternative explanations for the initial impairment of visual-across double-step performance.

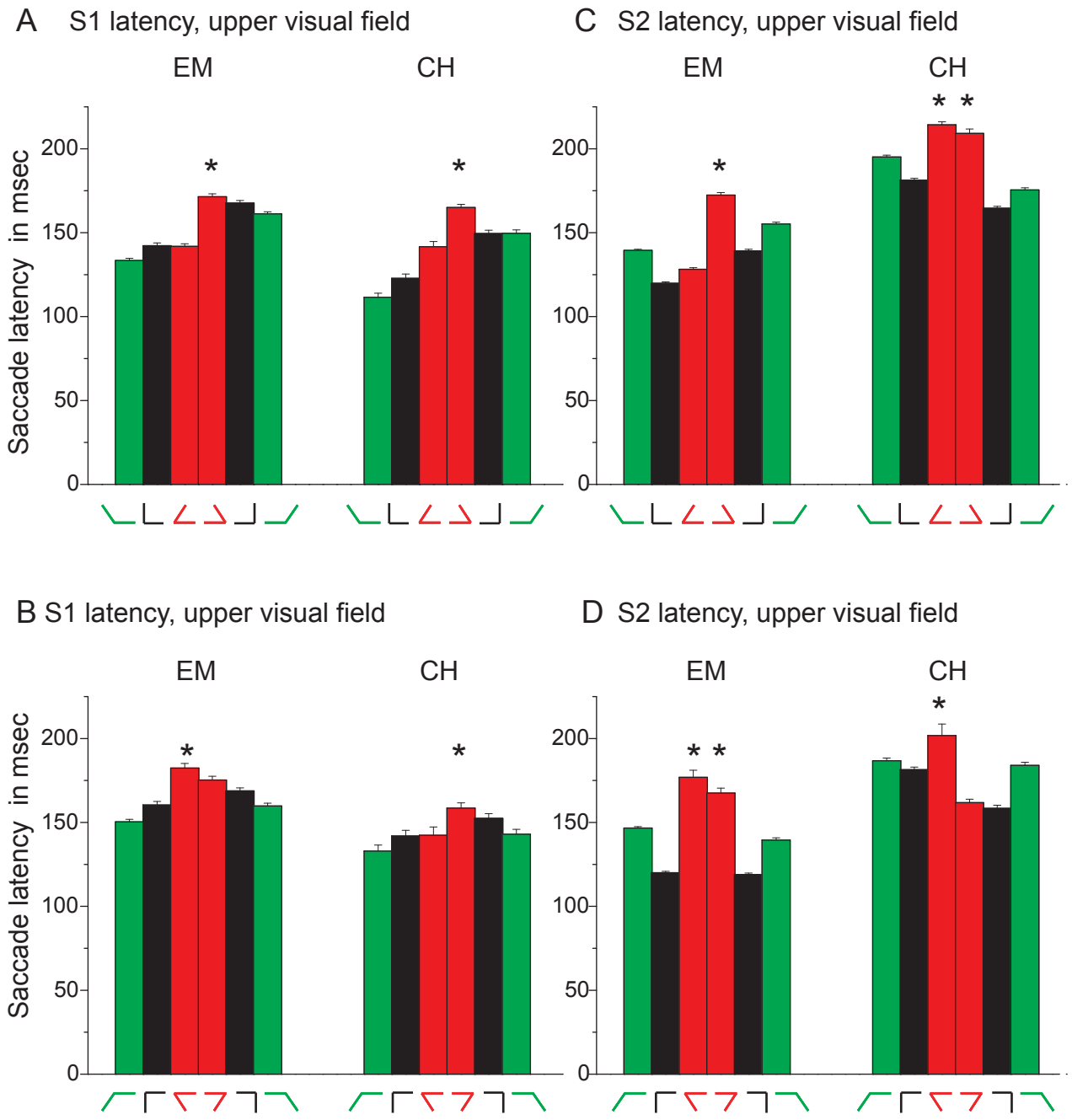


Figure 18. Measures of latency for the first and second saccades for each double-step sequence, from the first session of testing. These are the same data shown in Figure 17, now separated by quadrant. A,B: Latency of the first saccade (mean +/-SE) for each sequence in the upper field (A) and lower field (B). C, D. Latency of the second saccade (mean+/-SE) for each sequence in the upper field (C) and lower field (D). All conventions as in Figure 16. Both monkeys initiated the visual-across sequences (red) more slowly than central (black) or within (green) sequences. Prolonged visual-across latencies were observed for the first saccade (A,B) as well as the second saccade (C,D). Asterisks indicate visual-across sequences with latencies significantly longer than those of corresponding within and central sequences ($p<.05$, Tukey's HSD).

Is accuracy of the first saccade affected?

We first addressed the possibility that inaccuracy of the second saccade was due to inaccuracy of the first saccade. We minimized the variability in first saccade accuracy by making that saccade visually-guided. Furthermore, the accuracy and latency measures described above were computed only from those trials where the monkey's first saccade fell within two degrees of T1. At a glance, the data (Figure 19) confirm that saccades to T1 were very accurate for both monkeys; axes are matched to those of S2 error (Figure 16) so as to allow direct visual comparison.

The ANOVA nevertheless revealed main effects of updating condition on the accuracy of S1. Angular error differed significantly by updating condition only in monkey EM ($p<.0001$; monkey CH, $p>.7$). Distance error differed significantly by condition in both monkeys ($p<.0001$). Differences between conditions were very small, however. For monkey EM, average angular error in the visual-across condition (red) was increased by 0.201° relative to the central condition (black), and by 0.295° relative to the within condition (green). Distance error was 0.084° greater than central and 0.051° greater than within. For monkey CH, the visual-across distance error was 0.102° greater than the central error, and 0.163° greater than within. These observations confirm that the magnitude of conditional differences in the first saccade were exceedingly small, and cannot account for those observed in the second saccade.

Can the monkeys perform visually-guided and memory-guided saccades?

We next considered whether the monkeys' performance of the visual-across condition reflected a sensorimotor or mnemonic impairment, rather than an impairment in spatial updating. We tested these possibilities by having the monkeys perform visually-guided and memory-guided saccades

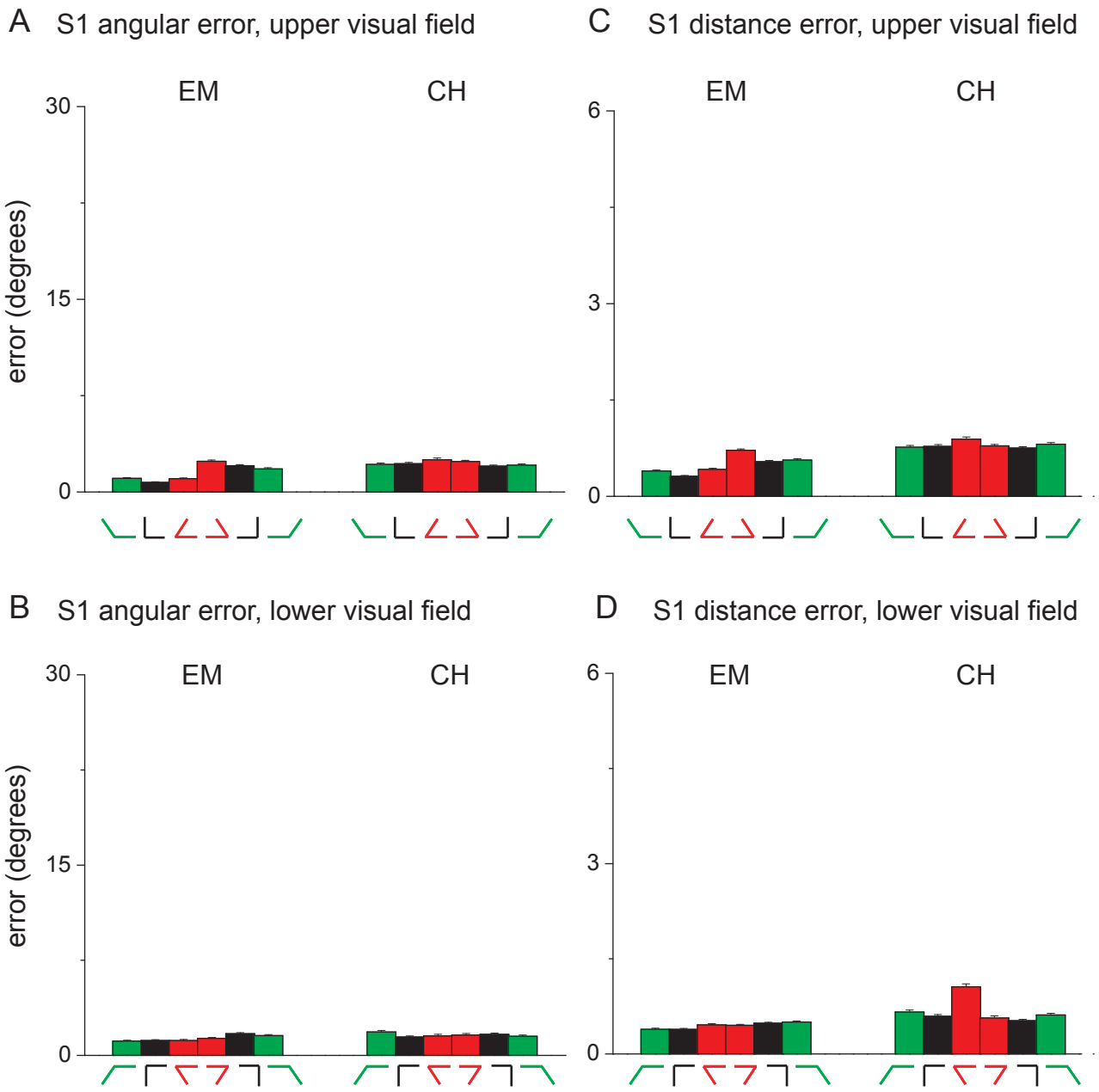


Figure 19. Measures of accuracy for the first saccade of the double-step task, from the first session of testing. A,B: Angular error (mean +/-SE) for each sequence in the upper field (A) and lower field (B). C, D: Distance error (mean+/-SE) for each sequence in the upper field (C) and lower field (D). Conventions as in Figure 16. Axes are matched to those used in Figure 16, to allow direct comparison of accuracy for the first saccade and accuracy of the second saccade. Accuracy differences between the visual-across and within conditions were too small to account for the accuracy differences observed for the second saccade.

to the T2 locations of double-step task. We used two paradigms. In the first paradigm, the monkeys made saccades from central fixation (FP) to the T2 locations. This tested the monkeys' ability to encode and remember T2 locations relative to the initial position of the eyes. In the second paradigm, the monkeys made saccades from T1 to T2. This tested the monkeys' ability to encode and remember the T2 locations relative to the position of the eyes at T1. At the end of each double-step testing session, we evaluated the monkeys' VGS and MGS performance in both paradigms to determine whether impairment in the double-step task reflected a deficit in either of these sensorimotor processes.

Neither monkey showed a selective impairment for attaining the visual-across T2 location, regardless of paradigm. Figure 20 shows the eyetraces from the monkeys' first ten trials of the visually-guided (A,B) and memory-guided tasks (C,D). Rows A and C show saccades from central fixation, and rows B and D show saccades from T1. Performance was less accurate for memory-guided as compared to visually-guided saccades, as observed in previous studies in normal monkeys (Barash et al., 1991). The accuracy and latency measures for visually-guided and memory-guided saccades in each paradigm are shown in Figures 21 and 22, respectively. Analysis of variance revealed small but significant differences by updating condition, for all four sensorimotor tasks. These conditional differences, however, were opposite those observed in the double-step task: namely, overall error and latency values were increased for the within as compared to the across conditions. These differences likely reflect the tendency for saccade performance to decline for more peripheral targets (Kalesnyka and Hallett, 1994; Li and Andersen, 2001). We conclude that the visual-across impairment in the double-step task cannot be attributed to a deficit in encoding, remembering, or generating eye movements to the visual-across T2 locations.

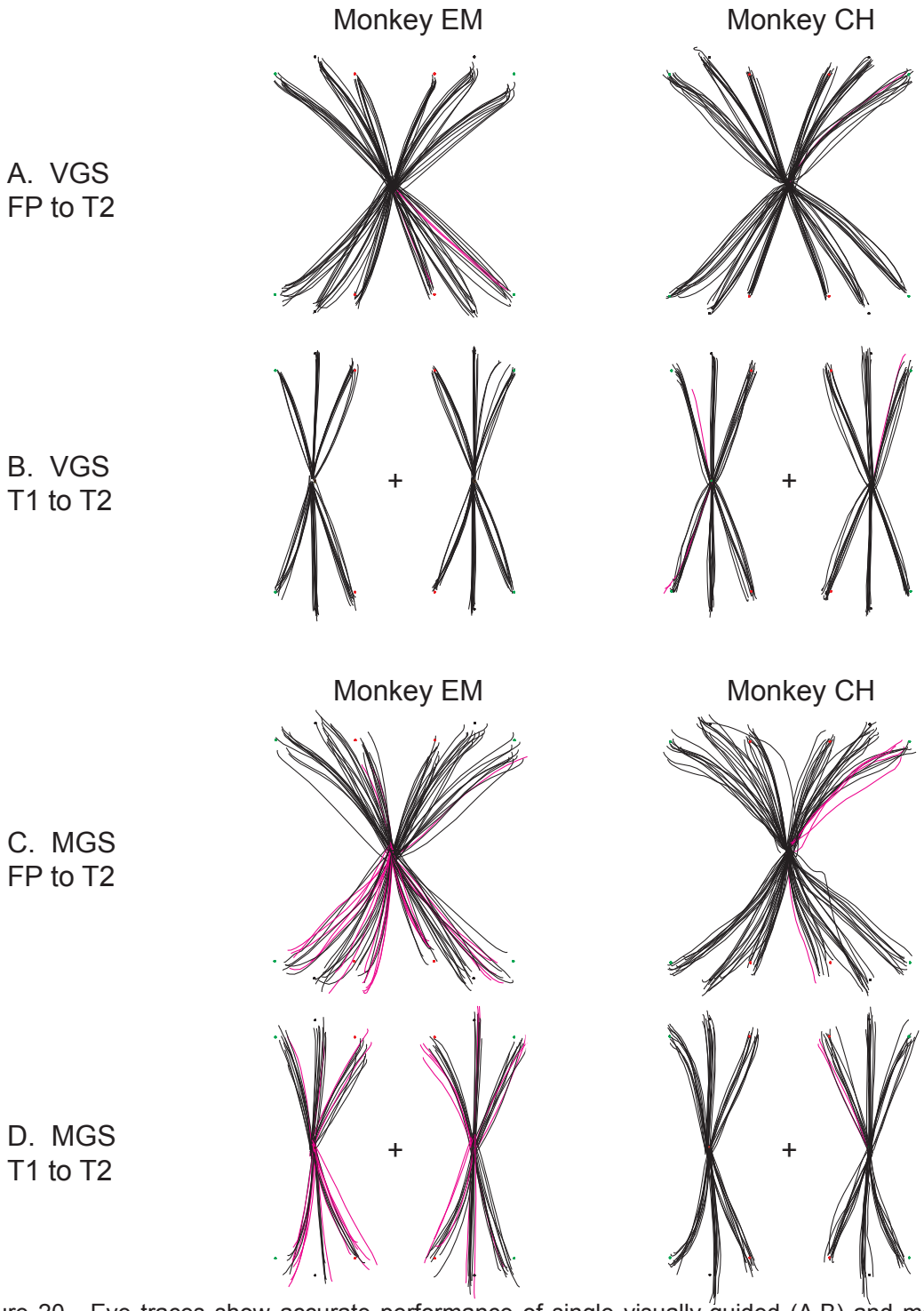


Figure 20. Eye traces show accurate performance of single visually-guided (A,B) and memory-guided (C,D) saccades to T2 locations of the double-step task. A) Visually-guided saccades from central fixation to the T2 locations. B) Visually-guided saccades from T1 to T2 locations. C) Memory-guided saccades from fixation to the T2 locations. D) Memory-guided saccades from T1 to T2 locations. Colored dots indicate target locations, coded by their condition in the double-step task (black=central, green=within, red=visual-across). Data are from the first ten trials. Axes indicate horizontal (x) and vertical (y) degrees of visual angle. These data indicate that the monkey was capable of making accurate saccade to the locations tested, both under visual guidance and when the target location had to be remembered.

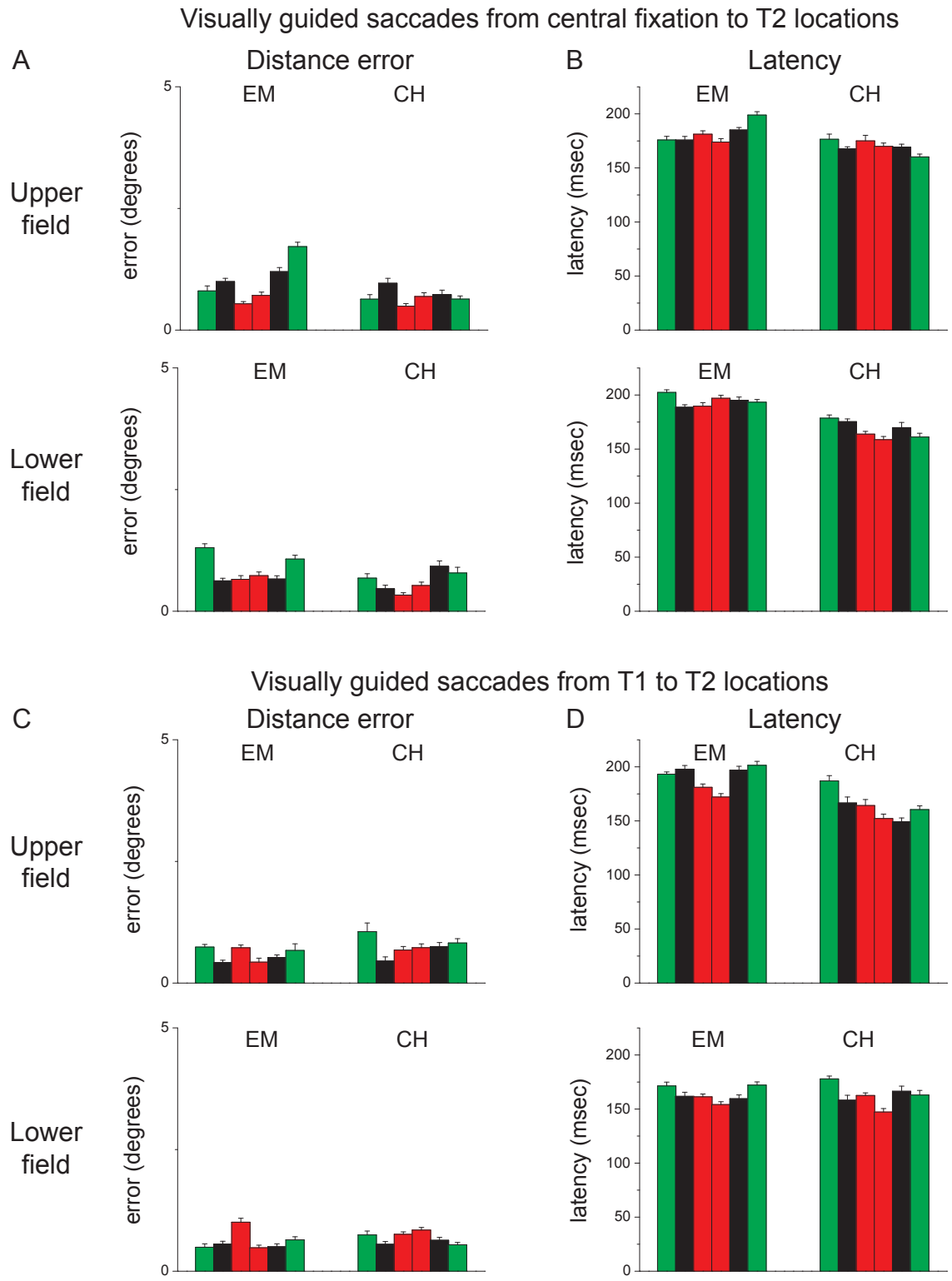


FIgure 21. Accuracy and latency measures for visually-guided saccade (VGS) performance. Panels A-B show distance error and latency of VGS made from central fixation to the T2 locations used the double-step task. Panels C-D show the same measures for VGS from T1 to T2. In each panel, VGS conditions are arranged and labeled according to the corresponding double-step conditions (see Figure 16). Upper field data are in the top row, lower field in the bottom row. Saccades to the visual-across T2 locations (red bars) are not impaired relative saccades to central (black) and within (green) T2 locations.

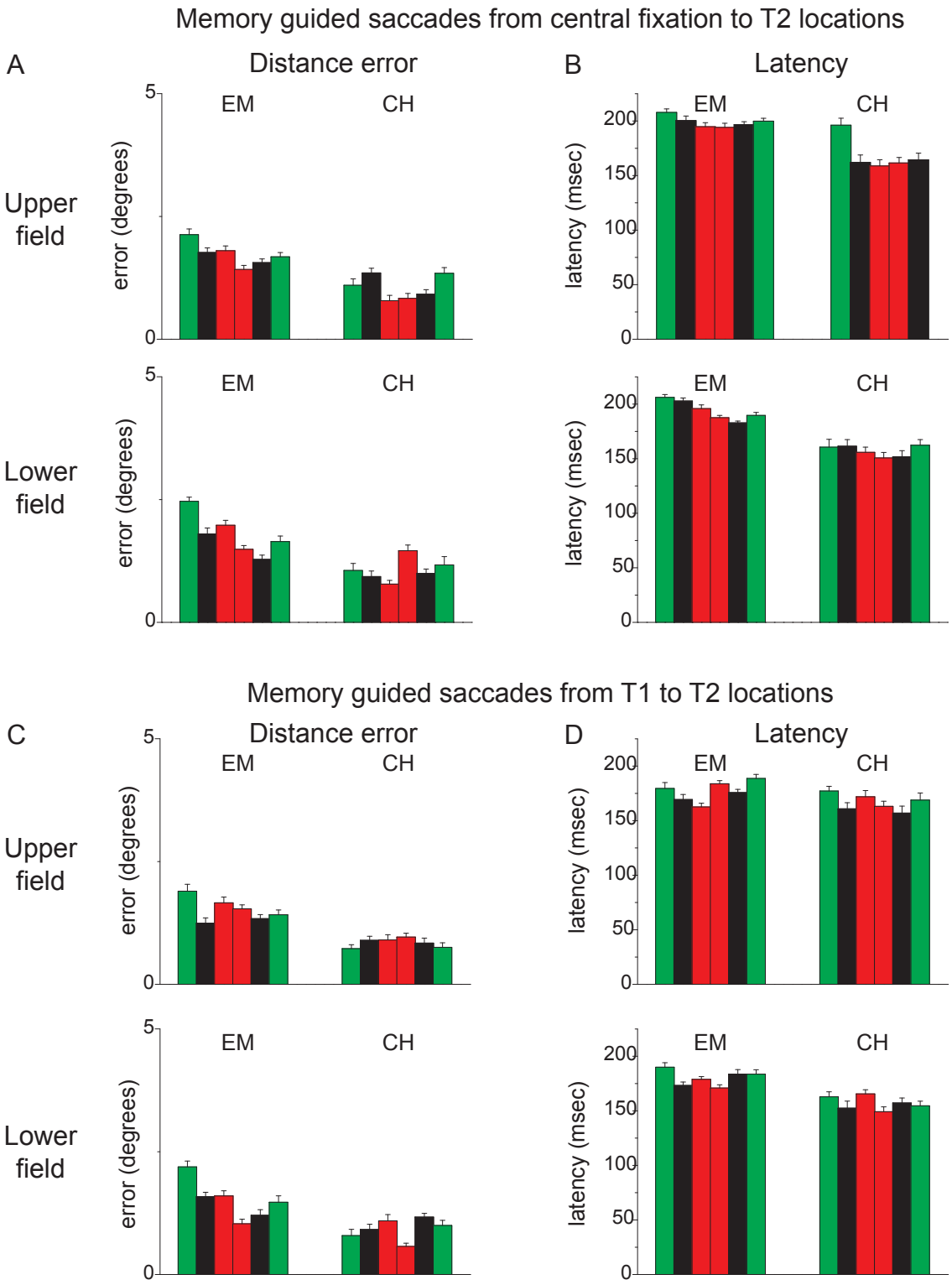


FIgure 22. Accuracy and latency measures for memory-guided saccade (MGS) performance. Panels A-B show distance error and latency of MGS made from central fixation to the T2 locations used the double-step task. Panels C-D show the same measures for MGS from T1 to T2. In each panel, MGS conditions are arranged and labeled according to the corresponding double-step conditions. Upper field data are in the top row, lower field in the bottom row. MGS to the visual-across T2 locations (red bars) are not impaired relative to MGS to central (black) and within (green) T2 locations.

Summary of findings for Experiment 1

In Experiment 1, we found strong evidence of impairment of visual-across updating in the absence of the forebrain commissures. We also obtained clear evidence that visual-across updating was not completely abolished, and could recover quickly for some sequences. In Experiment 2, we investigate the spatial bounds of the visual-across impairment. We then turn our focus toward the successful performance of the visual-across condition, which is addressed in Sections 2 and 3.

Experiment 2: Ipsilateral representation for use in spatial updating

The impairment observed in visual-across performance prompted us to investigate the representation of visual space available for accurate updating in the split-brain monkey. Physiological studies in normal monkeys have shown that visual receptive fields in lateral intraparietal cortex can extend approximately three degrees into the ipsilateral visual field, but rarely extend more than five degrees (Ben Hamed et al., 2001). For the standard visual-across sequences used in Experiment 1, T2 was located six degrees from the vertical midline. This configuration was designed to ensure that T2 was represented only in the contralateral hemisphere.

In Experiment 2, we asked whether the visual-across impairment could be mitigated by placing the second target closer to the vertical midline. We measured the monkeys' performance of the double-step task using three different spatial configurations. The first configuration was the standard visual-across paradigm used in Experiment 1. We refer to this configuration as the six-degree paradigm, to emphasize that the visual-across T2 was located six degrees from the midline. In the second configuration, the visual-across T2 was located three degrees from the midline ("three-degree" paradigm). Finally, in the third configuration, T2 was located directly

on the midline ("zero-degree" paradigm). This configuration does not require across-hemifield updating, because each cortical hemisphere contains a representation of the vertical meridian. Even so, we use the term "visual-across" for the midline sequences, to underscore the parametric comparison of the three configurations. In each paradigm, saccade metrics were equivalent for all three conditions (central, within, and visual-across). For the three- and zero-degree paradigms, we trained the monkeys on the new central condition, and then introduced the new within and visual-across conditions simultaneously. We tested each new paradigm in separate sessions.

Performance of the standard visual-across sequences remained impaired in this experiment. We measured performance of the standard six-degree paradigm in every session in which the new configurations were tested. The monkeys' performance of the standard sequences did not vary between sessions. Figure 23A shows endpoint data from the 11th session of testing for monkey EM, whose visual-across impairment persisted in all four quadrants.

We asked whether this impairment would disappear when the visual-across T2 was located only three degrees from the midline. We hypothesized that a single hemisphere might have access to visual representations of this T2 location, both before and after the eye movement. If so, the monkeys would be able to perform the visual-across sequences accurately in the three-degree paradigm. Alternatively, ipsilateral spatial representations might be degraded in the absence of the forebrain commissures (Gross et al., 1977).

We found that performance of the visual-across sequences did not improve when T2 was placed three degrees from the midline. To the contrary, performance worsened in all quadrants. Figure 23B shows the endpoint data from monkey EM. The striking deterioration in

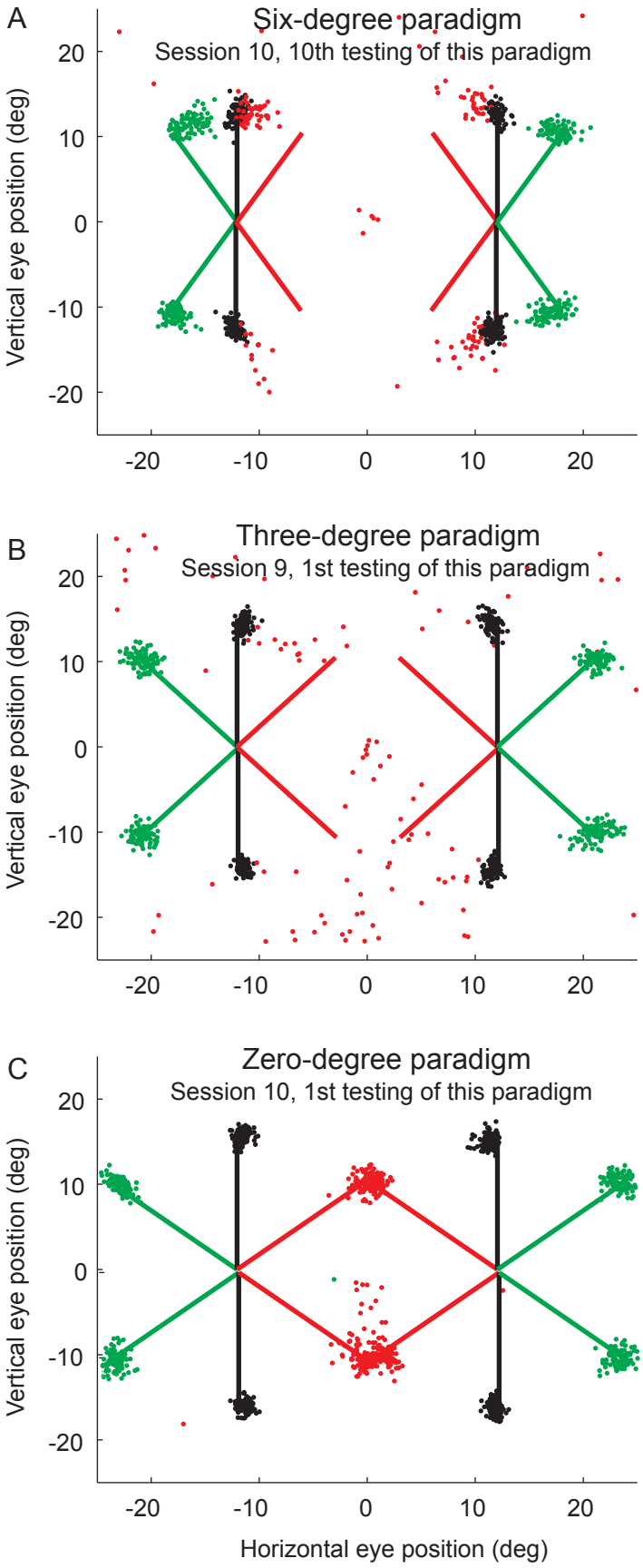


FIgure 23. Endpoints from double-step performance of the standard six-degree paradigm (A), the three-degree paradigm (B), and the zero-degree paradigm (C). Data are from monkey EM. In each panel, lines represent the target trajectories for central (black), within (green), and visual-across (red) sequences. Colored dots show the landing points of the second saccade.

Panel A shows the endpoints from the standard six-degree paradigm, from the tenth testing session. Impairment of the visual-across condition is evident in all four quadrants. Some of the visual-across endpoints are scattered in the periphery or near central fixation. These reflect the fact that the monkey's performance in session 10 had worsened relative to initial testing in Experiment 1.

Panel B shows the endpoints from the three-degree paradigm. Performance continued to be accurate for the central and within sequences, but was wildly inaccurate for the visual-across sequences. The endpoints are scattered even more erratically than for the six-degree paradigm. This suggests that the unfamiliar T2 location was particularly disruptive for visual-across performance.

Panel C shows the endpoints from the zero-degree paradigm. The landing points are accurately clustered at the target locations, for all three conditions. This indicates that updating is intact for locations on the vertical meridian.

performance was likely in response to the unfamiliarity of this sequence, which exacerbated the existing visual-across impairment.

Finally, we asked whether the monkeys could perform the visual-across sequences if T2 were placed directly on the midline. We expected the monkeys to perform these sequences without difficulty. We considered, however, an alternate hypothesis, which challenges our original interpretation of the visual-across impairment. This impairment may not reflect a disruption of across-hemifield updating in the split-brain monkey. Instead, it may reflect a general difficulty in performing sequences in which the direction of the second saccade is opposite that of the first saccade. Under this hypothesis, the monkeys would be unable to perform the midline sequences. The zero-degree paradigm allowed us to distinguish between these two hypotheses.

We found that performance of the midline sequences was very accurate. Figure 23C shows the endpoints from first session of testing the zero-degree paradigm. The visual-across endpoints, shown in red, are accurately clustered at the midline location of T2.

We assessed the relationship between T2 location and visual-across performance by comparing the accuracy of trials from the three configurations described thus far. Figure 24 shows the effect of configuration on the accuracy of each condition. Panels A and B show angular error, panels C and D show distance error. Each panel shows average error for each of the configurations, grouped by condition (central = black, within = green, visual-across). For each configuration, error is collapsed over all four quadrants. Visual-across performance was worse for the three-degree configuration than for the standard, and improved substantially when T2 was located on the midline. For the within and central conditions, performance changed very

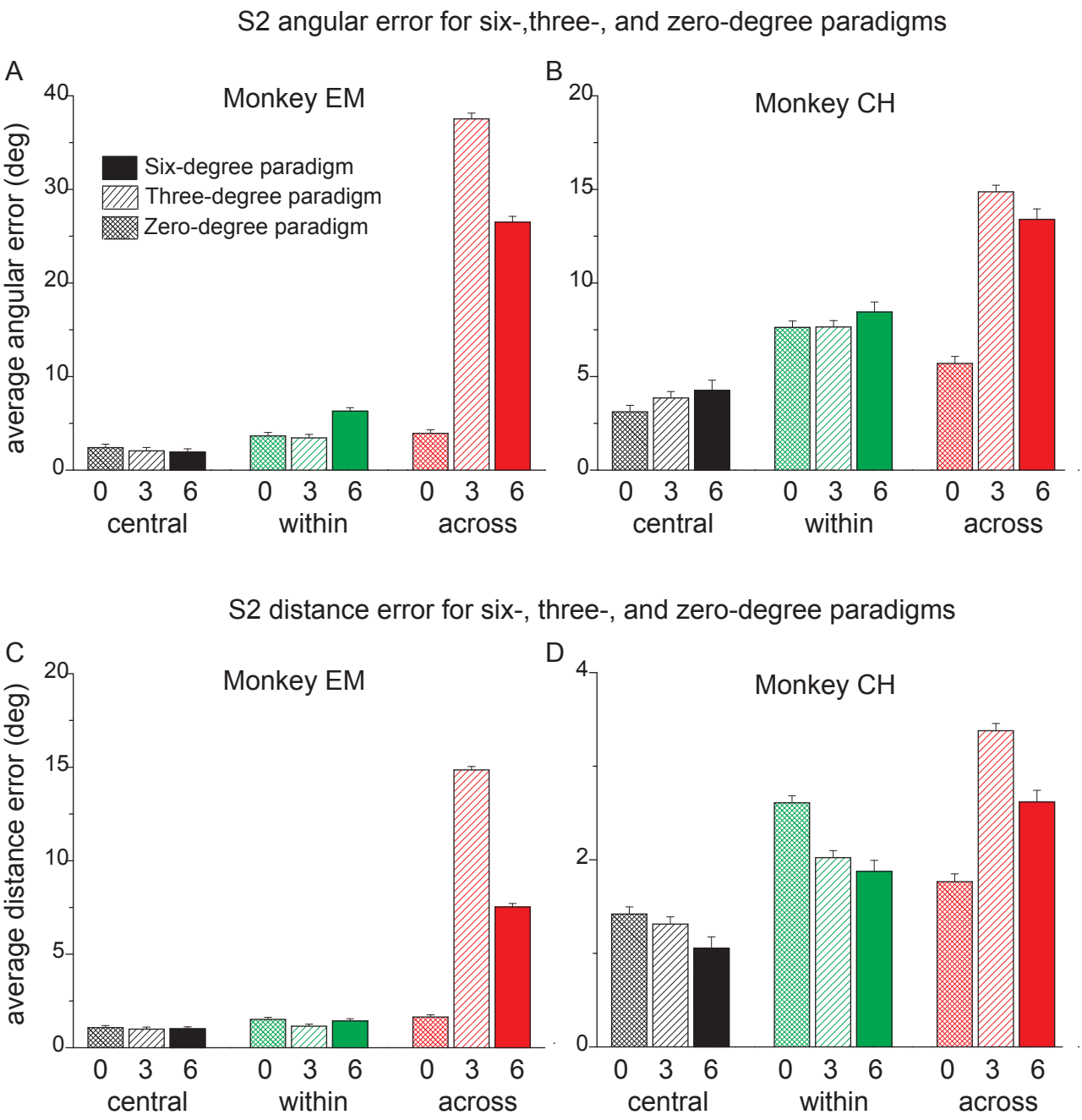


Figure 24. Impairment of the visual-across condition was abolished when T2 was located on the midline, but persisted when T2 was located three degrees from the midline. Panels A and B show the average angular error for monkey EM (A) and monkey CH (B). Panels C and D show the average distance error. In each panel, error is grouped by condition, with central conditions in black, within in green, and across in red. For each condition, there are three average error values, one from each of the three paradigms; values represent the average from all four quadrants. Hatched bars represent error from the zero-degree paradigm, diagonal bars represent error from the three-degree paradigm, and solid bars represent error from the six-degree paradigm. In the six-degree (standard) paradigm, the visual-across condition was selectively impaired relative to within and central sequences (compare solid red bars to solid green and black bars). This impairment was exaggerated in the three-degree paradigm (diagonal bars), and disappeared entirely in the zero-degree paradigm (hatched bars).

little by configuration, and in some cases showed patterns opposite those observed for the visual-across condition.

We conducted an ANOVA to determine the significance of these effects. The ANOVA had four factors: updating condition (central, within, or visual-across), S1 direction (right or left), vertical visual field (upper or lower), and of configuration (visual-across T2 at 0°, 3°, or 6°). This analysis revealed significant main effects of updating condition and configuration for angular error and distance error in both monkeys (all $p<.0001$). Importantly, it also revealed a significant interaction between updating condition and configuration (all $p<.0001$). *Post hoc* analyses confirmed that visual-across accuracy improved significantly for the midline configuration as compared to the three-degree and six-degree configurations, for both monkeys ($p<.05$, Bonferroni correction). In contrast, the accuracy of within sequences was either unchanged or decreased for the midline as compared to the three-degree and six-degree configuration. The decline in performance on the within condition likely occurred because the T2 locations were farther in the periphery (21° and 24°).

The data from Experiment 2 indicate that stimuli presented three degrees from the midline cannot be updated across visual hemifields in the absence of the forebrain commissures. Locations along the midline, however, are updated readily. The monkeys' ability to perform the midline sequence also rules out the possibility that the visual-across impairment reflects a simpler deficit in generating a second saccade in the opposite direction of the first saccade.

Summary of Section 1

Initial impairment of double-step sequences that require across-hemifield updating

In Experiment 1, we found that the performance of the double-step task was selectively impaired for sequences that required a location to be updated from one visual hemifield to the other. This

impairment was evidenced by significant increases in both error and reaction time for the visual-across sequences in six of eight cases (all four visual quadrants in monkey EM, and the two upper quadrants in monkey CH). This impairment was not attributable to errors in the first saccade of the double-step sequence, nor to any general impairment in visually-guided or memory-guided saccades. In Experiment 2, we learned that inaccurate performance of the visual-across condition was not ameliorated when the second target was placed closer to the midline. When the second target was placed directly on the midline, however, the monkeys performed the double-step task very accurately. Overall, the findings from these two experiments indicate that the updating of spatial locations from one visual hemifield to another – even locations near to the vertical meridian – is disrupted in the split-brain monkey.

Visual-across sequences can be performed accurately

There were two surprising exceptions to the initial impairment of the visual-across sequences. First, monkey CH was effectively unimpaired in the lower visual field. Second, we found that performance of the visual-across sequences improved with experience, even for sequences showing initial impairment. We continued to test the monkeys on the standard sequences until performance was stable. In Section 2, we characterize the evolution of accurate visual-across performance. In Section 3, we describe three experiments that tested the soundness of visual-across updating after learning had taken place.

Section 2: Evolution of visual-across performance

In this section, we describe the observations gained from monitoring the monkeys' performance of the standard double-step sequences over multiple testing sessions. We characterized learning of the visual-across sequence by estimating the number of trials to criterion, and by measuring

saccade accuracy and latency as the monkeys gained experience. We made five basic observations. 1) Learning of the visual-across sequences was initiated at different times, depending on the monkey and the quadrant of the visual field. 2) Once initiated, learning usually proceeded in rapid steps. 3) Reaction times decreased as accuracy improved. 4) Visual feedback likely facilitated learning. 5) After multiple sessions of testing, overall performance of the visual-across condition was no longer significantly worse than performance of the within condition. The visual-across impairment nevertheless persisted for one visual-across sequence in each monkey.

1. General timecourse of visual-across learning

We monitored the monkeys' performance of the standard sequence over multiple sessions, in order to characterize the acquisition of successful visual-across performance. For each monkey, we tested the upper and lower visual fields until performance of the visual-across sequences reached asymptote. For each visual-across sequence, we obtained an estimate of the number of trials required for learning. To do this, we established a learning criterion, which was based on the accuracy of central and within sequences (angular error < 15°, distance error < 3.5°). The approximate number of trials to criterion for each visual-across sequence is shown in Table 1. As we saw in the initial testing session (Experiment 1), improvement in the visual-across sequences was heterogeneous. Learning varied by monkey and by quadrant of the visual field. Monkey EM learned to perform the visual-across sequences first in the lower right quadrant then in the upper right. For this monkey, learning occurred more slowly in the left visual field, and was slowest in the lower left quadrant. In contrast, monkey CH reached criterion very rapidly in both quadrants of the lower visual field. Here, initial visual-across performance was unimpaired relative to performance of central and within conditions (Figure 16). In the upper left quadrant,

	Monkey EM		Monkey CH	
	Left	Right	Left	Right
Upper field	2471 (44)	1667 (20)	70 (1)	918 (27)
Lower field	2710 (49)	1336 (15)	10 (1)	10 (1)

Table 1. Number of trials to criterion for the visual-across sequences; number in parentheses indicates the session in which criterion was met. To reach criterion, average angular error had to be less than 15° and average distance error had to be less than 3.5°, for three consecutive ten-trial bins. For sequences that reached criterion during the first session of testing (in less than 200 trials), the listed number indicates the first of these three bins. For sequences that reached criterion after the first session of testing, the listed number indicates the total number of trials performed, up to and including the session in which criterion was met.

monkey CH learned to perform the visual-across sequence during the first session of testing. In the upper right quadrant, learning took place far more slowly.

2. Rapid changes in accuracy

How did visual-across learning progress? Did accuracy improve gradually before reaching criterion, or did it improve in a rapid, stepwise fashion? We characterized the evolution of learning by plotting the mean accuracy of double-step performance in each testing session. Figures 25 and 26 show the angular error (A,B) and distance error (C,D) as a function of session, for each monkey. We focus on those quadrants where visual-across performance was impaired beyond the first testing session (monkey EM, all quadrants: panels A-D; monkey CH, upper right quadrant: dotted red line of panels A,C). In these five quadrants, both measures of error were initially increased for the visual-across sequences (red lines), as compared to central (black) and within (green). After several sessions, monkey EM's performance of the visual-across sequences became considerably less accurate. At this stage, the monkey seemed to abandon its efforts to perform the visual-across sequences. The monkey often made erratic saccades into the periphery, rather than attempting a second eye movement toward the target location.

For monkey EM, visual-across accuracy eventually improved in rapid, discrete steps. This is evident in the visual-across sequence in the lower right quadrant (Figure 25, B and D, dotted red line). Between sessions 14 and 15, angular error suddenly dropped from 25° to 3°,

and distance error dropped from 13° to 2°. Visual-across performance in the upper field began to improve at about the same time (panels A, C). In the upper right quadrant, accuracy improved quickly, reaching criterion at session 20 (dotted red line in panels A, C). In the upper left quadrant, errors decreased sharply at session 20 (solid red line in panels A, C). Visual-across accuracy improved last in the lower left quadrant, but still improved sharply (dotted red line in B and D; session 46). Monkey CH learned to perform the visual-across sequence in three of four quadrants during the first session of testing. In the remaining quadrant, visual-across learning took place gradually (Figure 26, dotted red line in panels A and C). Performance of this sequence improved in more gradual increments than those observed in monkey EM.

3. Changes in latency parallel changes in accuracy

For both monkeys, saccadic reaction times changed over the course of the testing sessions. Figures 27 and 28 show the average latency of the first and second saccades for each testing session. Overall, latencies decreased as the sessions proceeded, regardless of condition. This trend was most apparent for S2 latency in monkey CH (Figure 28, panels C,D). With few exceptions, changes in saccade latency corresponded with changes in accuracy. For some

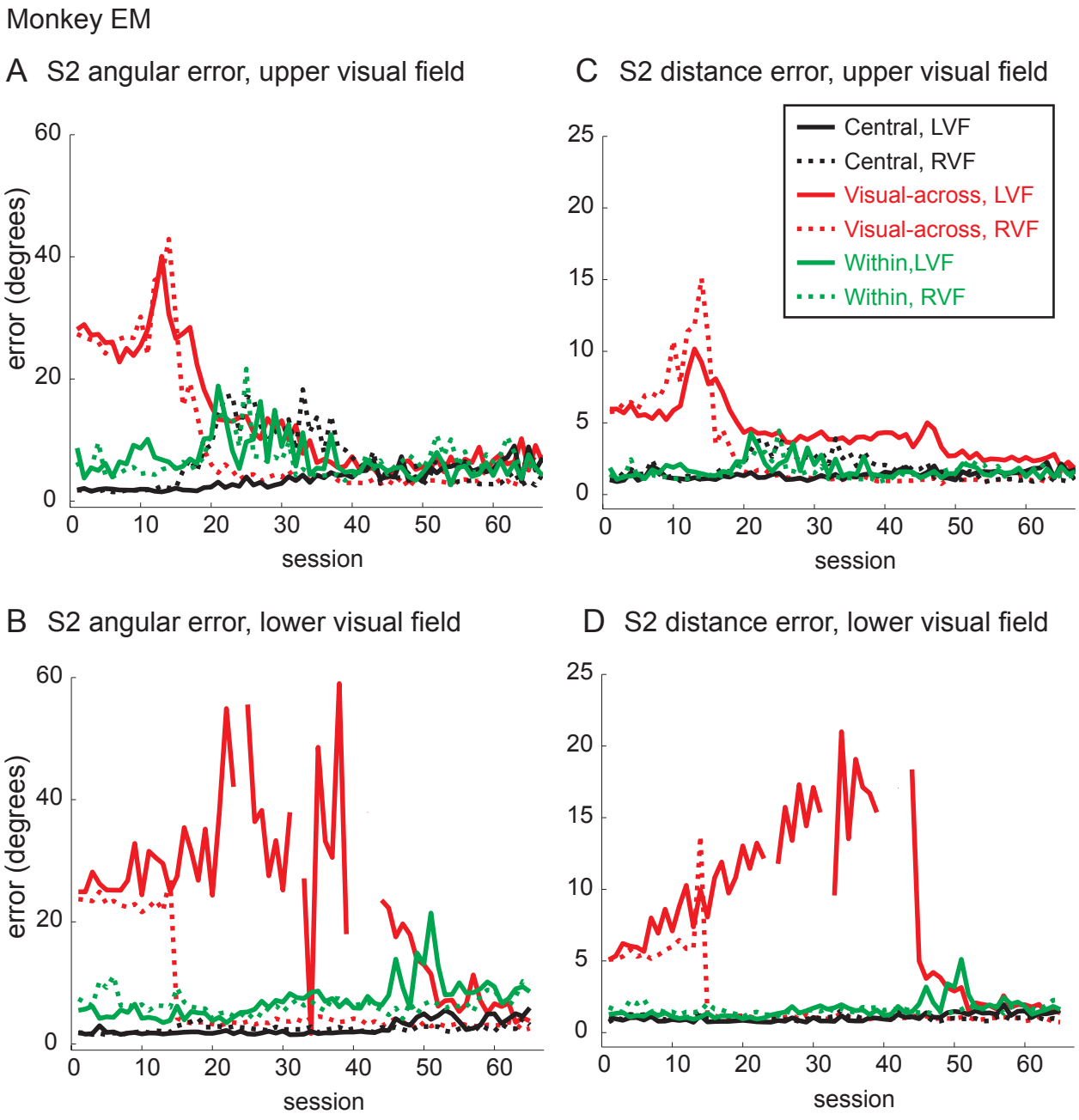


Figure 25. Accuracy of double-step performance for monkey EM, over multiple sessions. Angular error is shown in the panels on the left, for the upper visual field (A) and lower visual field (B). Distance error is shown in the panels on the right, for the upper (C) and lower (D) visual fields. In each panel, each line represents one of the six sequences. The y axis represents error in degrees; the x axis indicates the session number of testing. In the upper visual field (panels A,C), performance of visual-across sequences (red lines) became less accurate in the first several sessions: increased error values are seen for both angular error (panel A) and distance error (panel C). The visual-across performance improved considerably by session 20. In the lower field (panels B, D), performance of the visual-across sequence in the right quadrant (dotted red line) improved sharply at session 14. In the lower left quadrant, performance of the visual-across sequence remained inaccurate for more than 40 session (B,D, solid red lines). For this sequence, the monkey sometimes directed all second saccades into the upper field, rather than into the lower field. Breaks in the solid red line indicate sessions where no data were available due to removal of these highly erratic trials.

Monkey CH

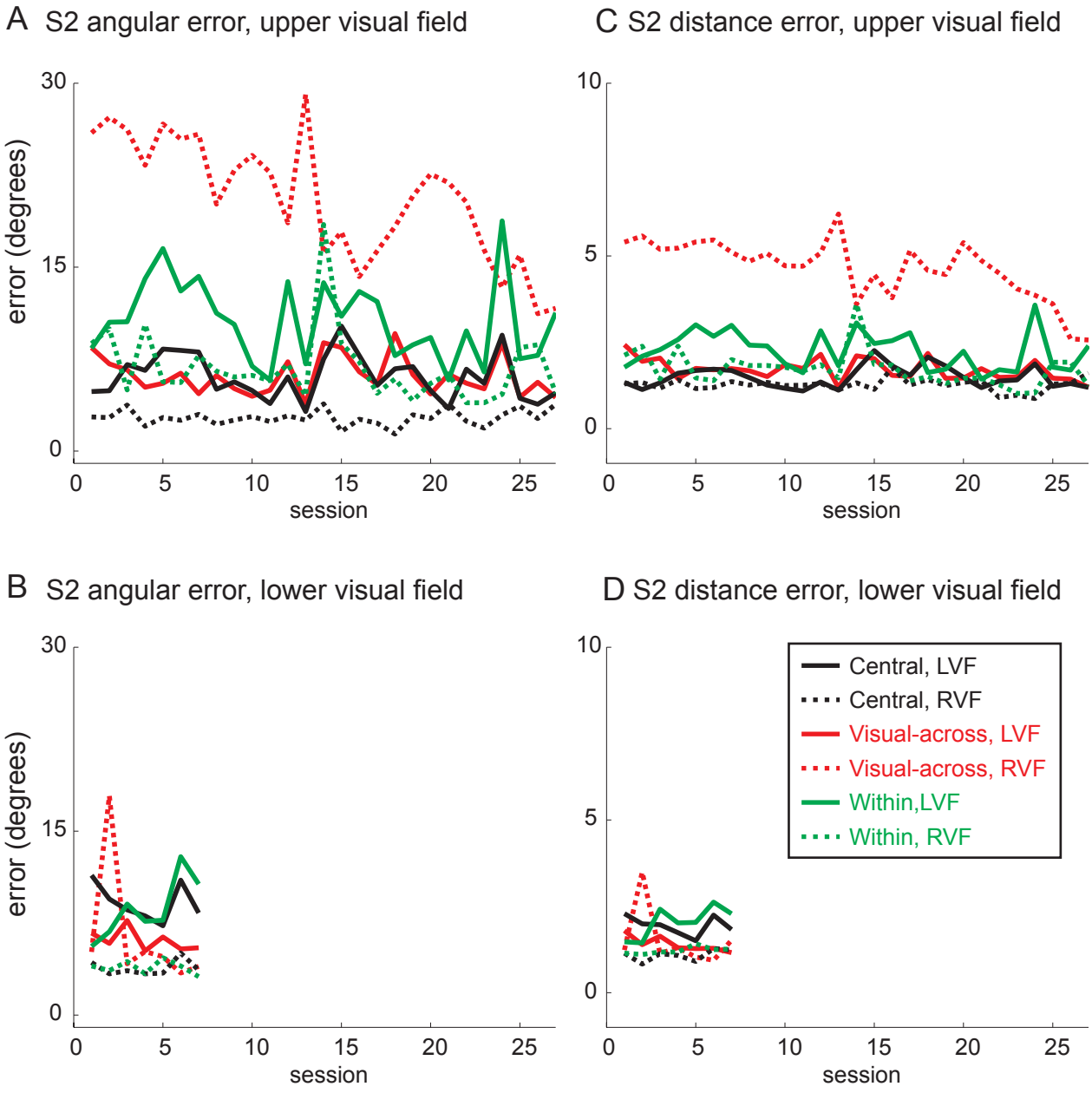


Figure 26. Accuracy of double-step performance for monkey CH, over multiple sessions. Panels on the left show angular error for the upper (A) and lower (B) visual fields. Panels on the right show distance error for the upper (C) and lower (D) visual fields. Testing of the standard sequences continued until performance on the visual-across condition was stable. In the upper visual field (panels A and C), performance of visual-across sequences reached criterion for learning in 27 sessions of testing. Throughout these sessions, the monkey was impaired on the visual-across sequence in the upper right quadrant (dotted red line). In the lower field, performance of the visual-across sequences was accurate in the first session of testing and changed very little in subsequent sessions;standard testing was therefore complete at session 7.

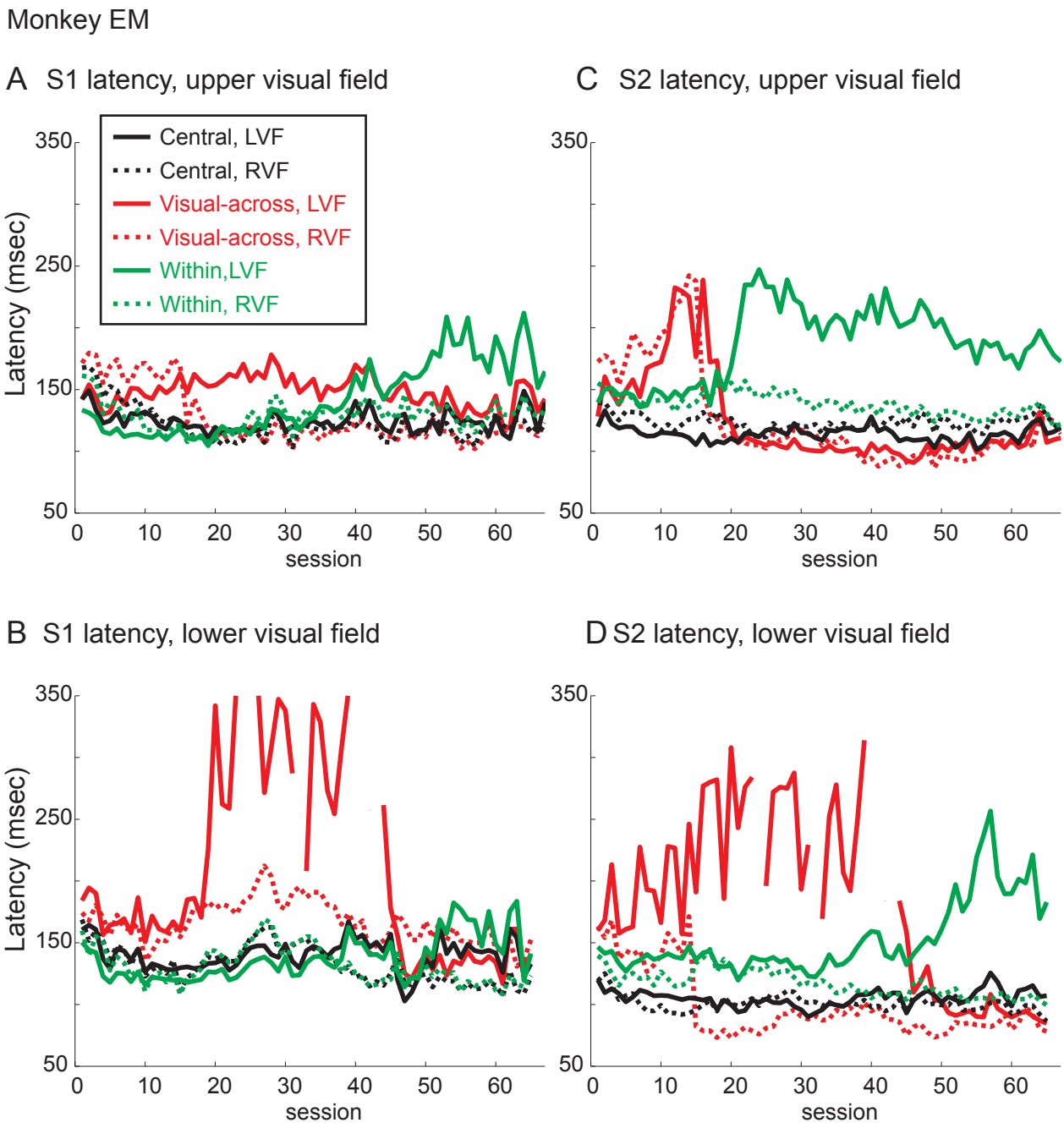


Figure 27. Latencies of the first and second saccades of double-step performance over multiple sessions, monkey EM. A,B: S1 latency in upper (A) and lower (B) visual fields. C,D: S2 latency in upper (C) and lower (D) visual fields. For the first saccade (panels A and B), latencies were only slightly prolonged in the visual-across sequences in initial testing, but increased during the middle sessions (red lines). By the final sessions, however, S1 latencies for the visual-across sequences were similiar to those for the central and within sequences. For the second saccade (panels C and D), latencies were prolonged for the visual-across condition in initial testing, and became even slower in subsequent sessions. The S2 latency decreased rapidly as accuracy improved (Figure 25). This improvement was marked between sessions 15 and 20 for sequences in the upper field (panel C) and lower right quadrant (panel D, dotted red line). The missing sections of the solid red line (panels B and D) reflect the fact that the monkey made highly erratic saccades in all trials in this visual-across sequence (lower left); these were removed from analysis.

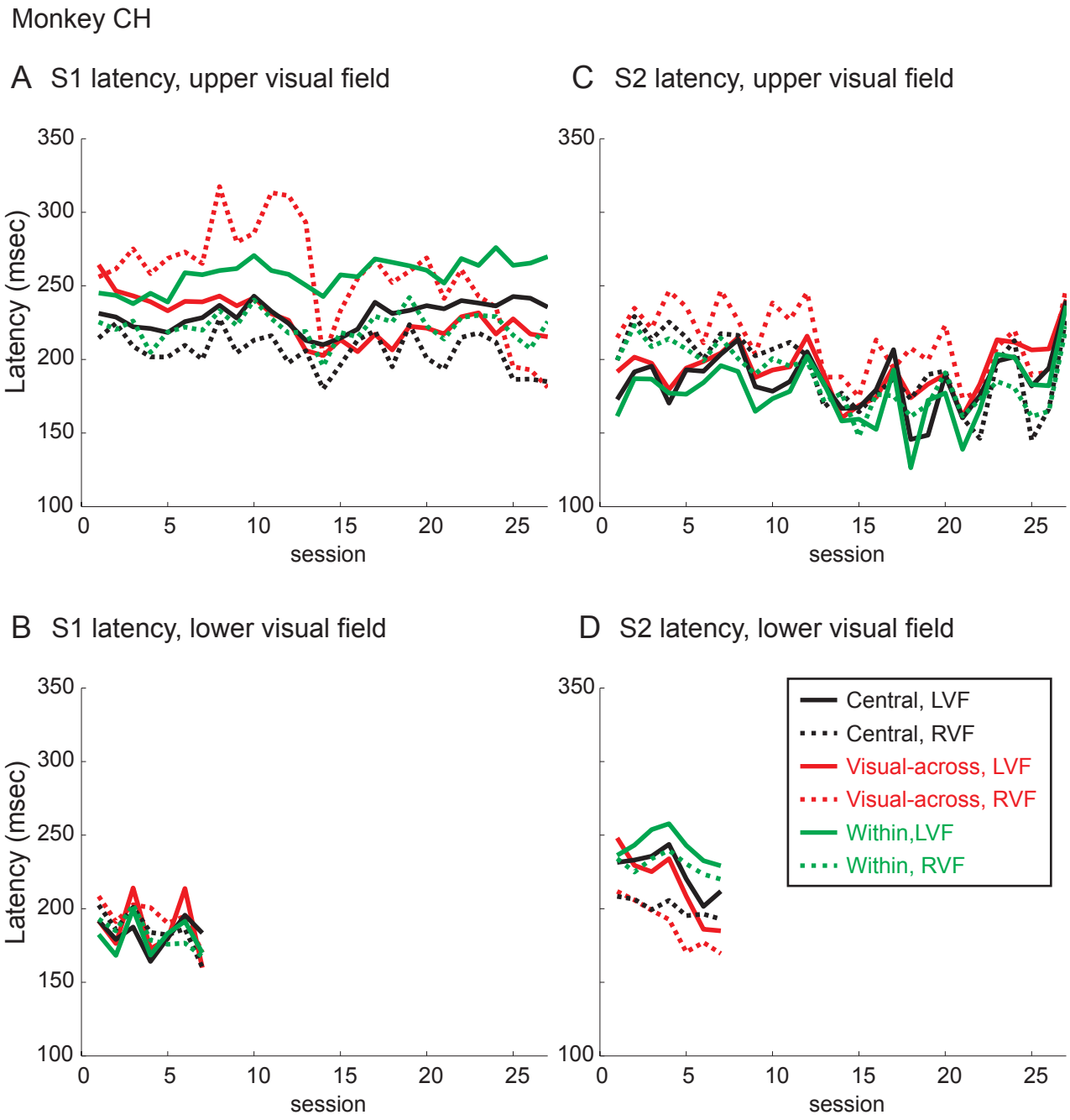


Figure 28. Latencies of the first and second saccades of double-step performance for monkey CH, over multiple sessions. Panels on the left show latency for the first saccade, for the upper (A) and lower (B) visual fields. Panels on the right show latency for the second saccade, for the upper (C) and lower (D) visual fields. Saccadic reaction times showed minimal variablity over multiple testing sessions. The notable exception is seen in the visual-across condition in the upper right quadrant, for first saccade latency (panel, dotted red line). The latency for this sequence increased temporarily after several testing sessions, similar to observations in monkey EM (Figure 27).

sequences, accuracy improved in parallel with decreases in S1 latency (Figure 27, panel B, red lines; Figure 28, panel A, dotted red line). For other sequences, accuracy varied with S2 latency (Figure 27, panel C, red lines). There were no obvious patterns that explained these different accuracy-latency relationships. The essential observation, however, is that the monkeys were able to initiate the visual-across sequences more rapidly as learning progressed.

4. Factors contributing to the initiation of learning

What elicited the improvement in visual-across performance? In some cases, there were identifiable factors that contributed to the animal's learning. For monkey EM, visual-across performance improved in most quadrants after the testing of midline sequences described in Experiment 2. We first tested the midline sequences in session 10. We then continued to test both the midline and three-degree paradigms in subsequent sessions. During this time, successful performance at the midline seemed to generalize to a recovery of visual-across performance. Improvement occurred first for sequences in the three-degree paradigm, and then extended to the standard paradigm in which T2 was located six degrees from the midline.

Visual feedback was likely an important factor in learning. Whenever the monkey performed a trial correctly, the T2 target reappeared and the monkey was required to refixate its location. This feedback provided additional reinforcement of visual-across performance. The presence of visual feedback likely accounted for the discrete and rapid decreases in accuracy. Typically, the monkey spontaneously initiated a change in behavior that allowed it to perform some trials correctly. The resulting visual feedback may have helped to maintain correct performance. There was one exception to this self-initiated learning. In the lower left field, monkey EM was unable to perform the visual-across sequences even after 40 sessions (Figure 25, solid red line in panels B, D). The monkey's performance of this sequence was so erratic in

several sessions that no valid trials were available (breaks in solid red line). In session 45, we expanded the size of the electronic eye window at T2, in order to determine whether this visual-across sequence could be learned under any circumstances. This allowed the monkey to receive visual feedback even for inaccurate saccades. The monkey reached the learning criteria for this visual-across sequence at session 49. Visual feedback therefore appears to be sufficient to instigate learning. It is not strictly necessary, however. In the upper left quadrant, monkey EM did not receive consistent visual feedback for the visual-across sequence until session 49. Nonetheless, accuracy improved substantially at session 15 (Figure 25, solid red line in panels A, C). This shows that performance of visual-across condition can improve without dependence on visual feedback.

5. What does learned performance look like?

Data from the final testing sessions show remarkable improvement in the performance of visual-across sequences, in all quadrants and for both monkeys (Figure 29). The endpoint data are shown for monkey EM (panel A) and monkey CH (panel B) from a final testing session when performance of the visual-across sequence had met criterion for learning in all four quadrants. The improvement in visual-across performance is appreciable for both monkeys, compared to Figure 13. In quadrants where the visual-across endpoints had initially clustered near the central trajectory, the endpoints now are clustered more closely to the accurate visual-across trajectory.

The monkeys' improved performance in the visual-across condition was supported by statistical analysis of data from the final testing session. We conducted univariate ANOVAs to evaluate the effects of updating condition, direction of the first saccade, and vertical visual field, just as we had in Experiment 1. For data from this final testing session, we still observed a significant main effect for updating condition for both measures of accuracy, in both monkeys.

These effects are illustrated in Figure 30. For both monkeys, error values were considerably smaller for the central as compared to the within and visual-across conditions. On average, monkey EM was least accurate in the visual-across condition, whereas monkey CH was least accurate in the within condition.

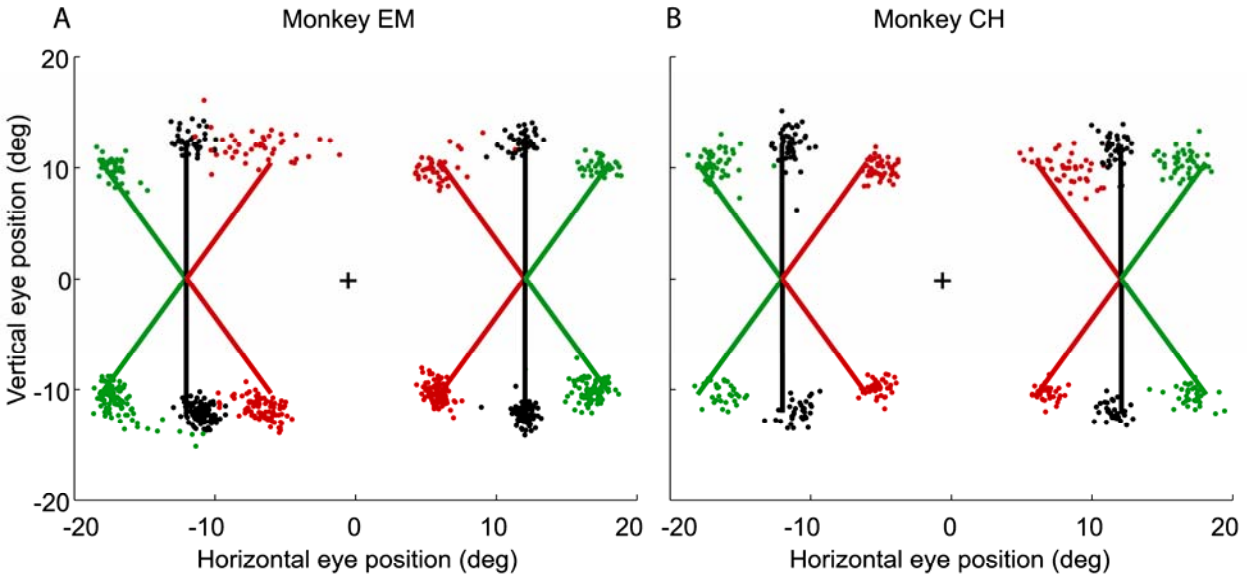


Figure 29. Endpoints of the second saccade from the final session of visual-across testing. A) Performance of monkey EM. B) Performance of monkey CH. Lines show the target trajectories for the second saccade of each sequence. Lines and endpoints are colored according to condition: central (black), within (green), and visual-across (red). For both monkeys, endpoints of the visual-across sequences are clustered near the appropriate target in all four quadrants. Persistence of visual-across impairment is evident in the upper left quadrant for monkey EM (panel A), and in the upper right quadrant for monkey CH (panel B).

We were ultimately interested in determining whether, in this final testing session, the monkeys continued to be impaired on individual sequences of the visual-across condition. We used the same *post hoc* procedure employed in Experiment 1 to assess whether each visual-across sequence was significantly impaired relative to the matched central and within sequences (Tukey's HSD, α=.05. We found that visual-across performance was significantly less accurate

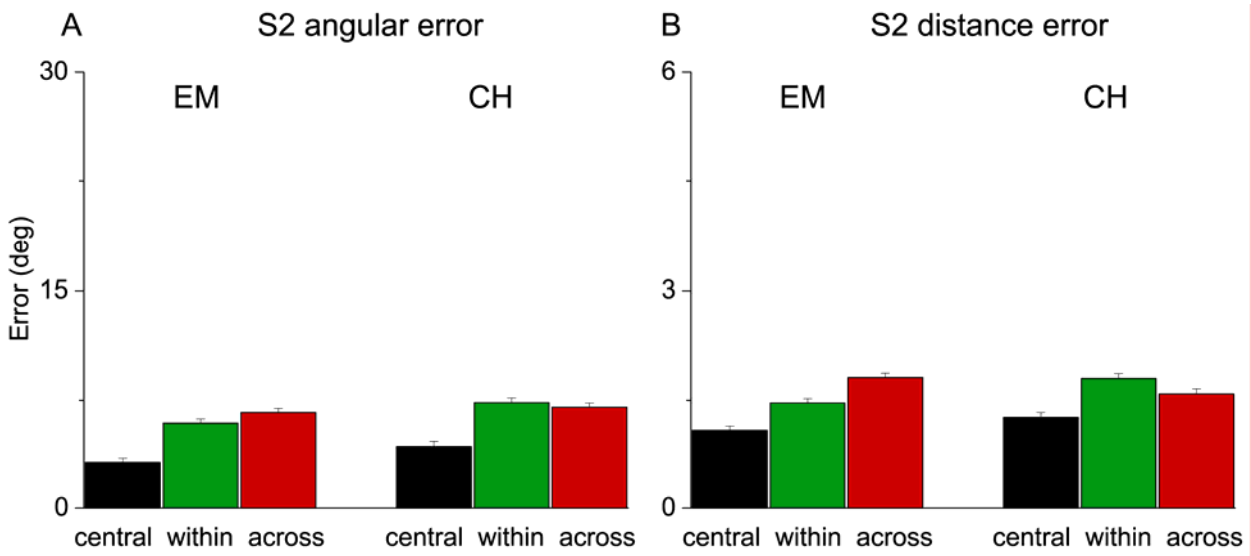


Figure 30. Average angular error (A) and distance error (B) for central (black), within (green) and visual-across (red) conditions of the double step task, from the final testing session. In each panel, data from monkey EM are on the left, and data from monkey CH are on the right. For each condition, data were collapsed over sequences in all four quadrants. Errors bars represent standard error of the mean. For both monkeys, accuracy of the visual-across condition was similar to accuracy for the within condition.

than central or within performance in only two quadrants (one in each monkey); in Experiment 1, this impairment was significant in six quadrants (all four in monkey EM, and two in monkey CH). Monkey EM continued to show increased visual-across errors in the upper left visual field, monkey CH in the upper right field (Figure 31, panels A and C). The magnitude of this impairment, however, is far less than the impairment observed in the first session of testing (Figure 16, same scale).

Finally, we investigated the monkeys' reaction times for the learned visual-across sequences. We considered the possibility that accurate performance of the visual-across sequence might require slow, deliberate eye movements. In the final behavioral testing session, however, we found that overall reaction times of both monkeys were no longer systematically increased for the visual-across condition. The ANOVA revealed significant main effects of updating condition on the reaction times for both saccades, in both monkeys (all $p<.001$). These

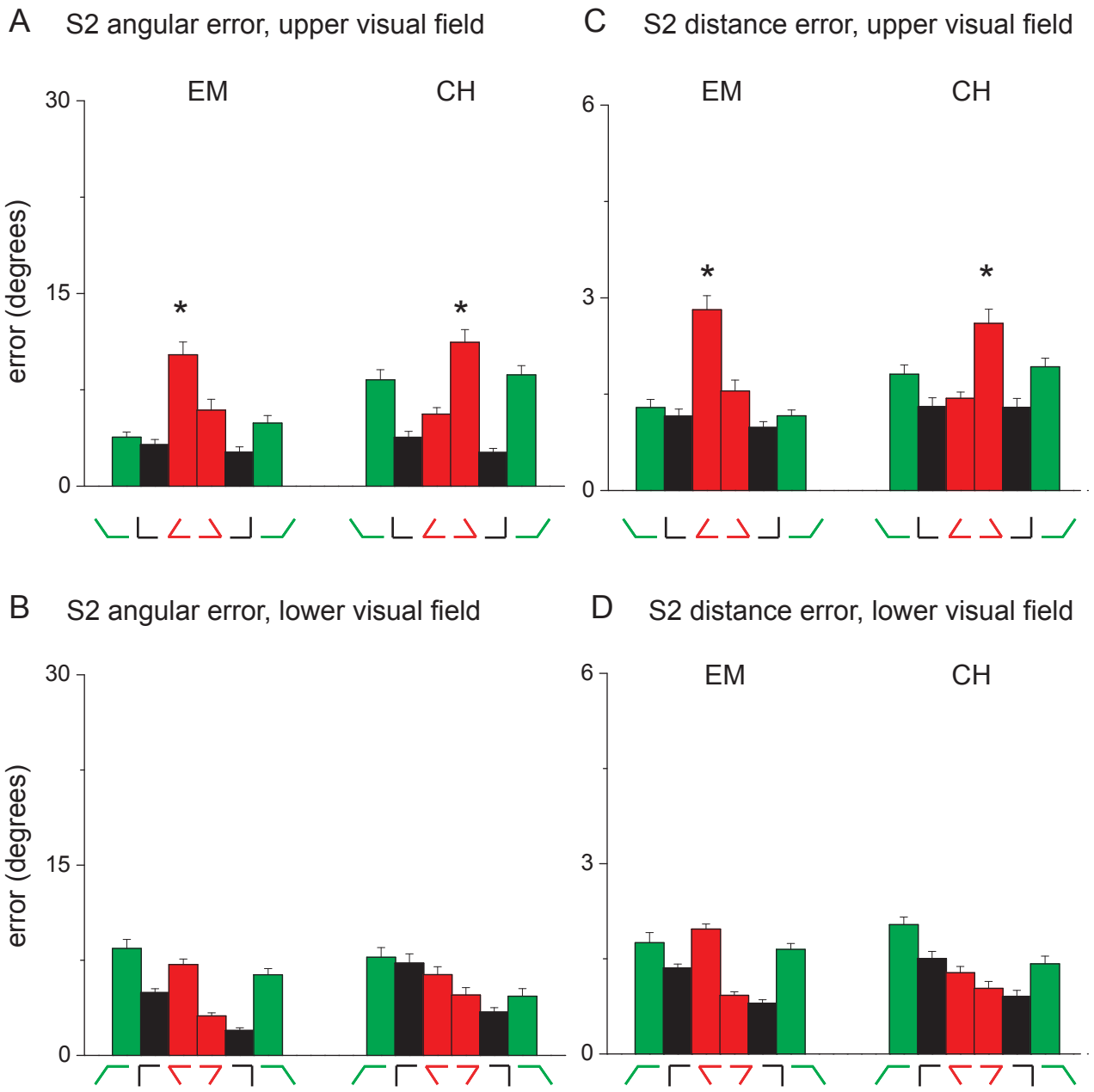


Figure 31. Measures of accuracy of double-step performance from final sessions of testing, showing improved visual-across performance. A,B: Angular error (mean +/-SE) for each sequence in the upper field (A) and lower field (B). C, D. Distance error (mean+/-SE) for each sequence in the upper field (C) and lower field (D). Axes match those of Figure 16 to allow direct visual comparison. For monkey EM, angular and distance error for the visual-across condition remains significantly increased in the left visual field (upper and lower), as compared to within and central. For monkey CH, angular and distance error for the visual-across condition remains significantly increased only in the upper right quadrant. Asterisks indicate the visual-across sequences with significant impairment relative to matched central and within conditions. Even in these quadrants, errors are considerably smaller than those observed in initial testing.

effects are illustrated in Figure 32. On average, monkey EM initiated the first saccade more quickly for the visual-across condition as compared to the within condition (panel A). Monkey CH, in contrast, continued to show a prolonged reaction time for the visual-across condition. The pattern of latencies for the second saccade were similar for the two monkeys. Both were now *fastest* for the visual-across condition, and slowest for the within condition (panel B).

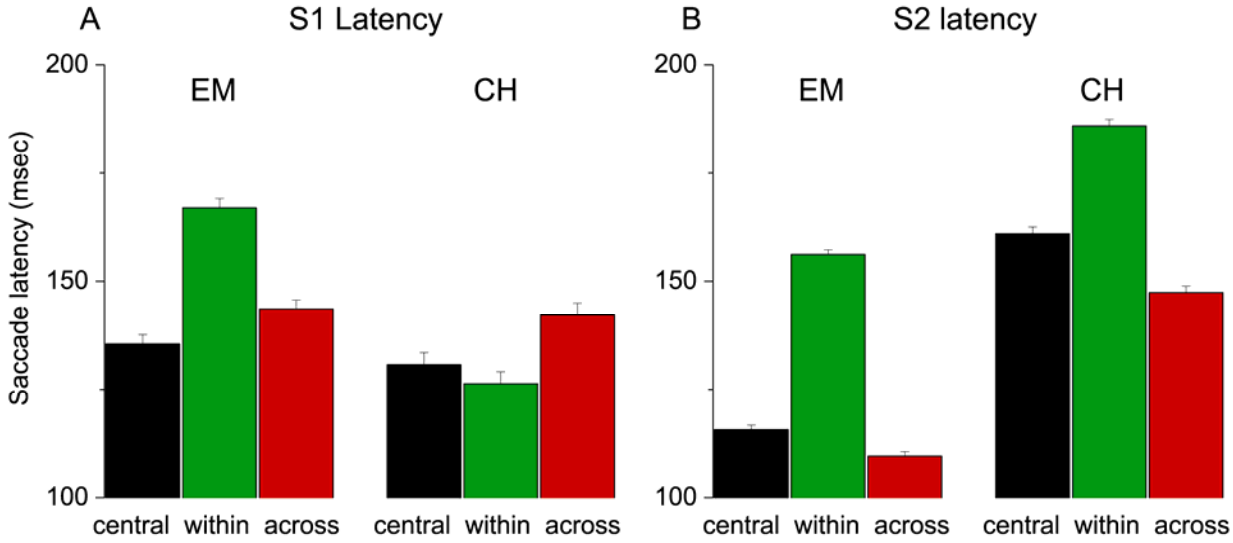


Figure 32. Average latencies for the first (A) and second (B) saccades for each condition of the double step task, after multiple sessions of testing. Conventions as in Figure 30. For the first saccade (panel A), both monkeys showed longer latencies for the visual-across condition as compared to the central condition. For monkey EM, S1 latency was most prolonged for the within condition. For the second saccade, latencies had similar patterns for the two monkeys. S2 latency was slowest for the within conditions, and fastest for the visual-across conditions. These data indicate that, following extensive experience with the standard sequences, reaction times were not selectively delayed when across-hemifield updating was required.

Reaction times were variably dependent on the interactions between updating condition, S1 direction, and vertical visual field. The latency measures for each sequence are shown in Figure 33. The ANOVA revealed significant three-way interactions for first saccade latency in monkey EM ($p<.0001$), and for second saccade latency in both monkeys ($p<.01$). We conducted *post hoc* analyses to determine the significance of impairment for each visual-across sequence, as

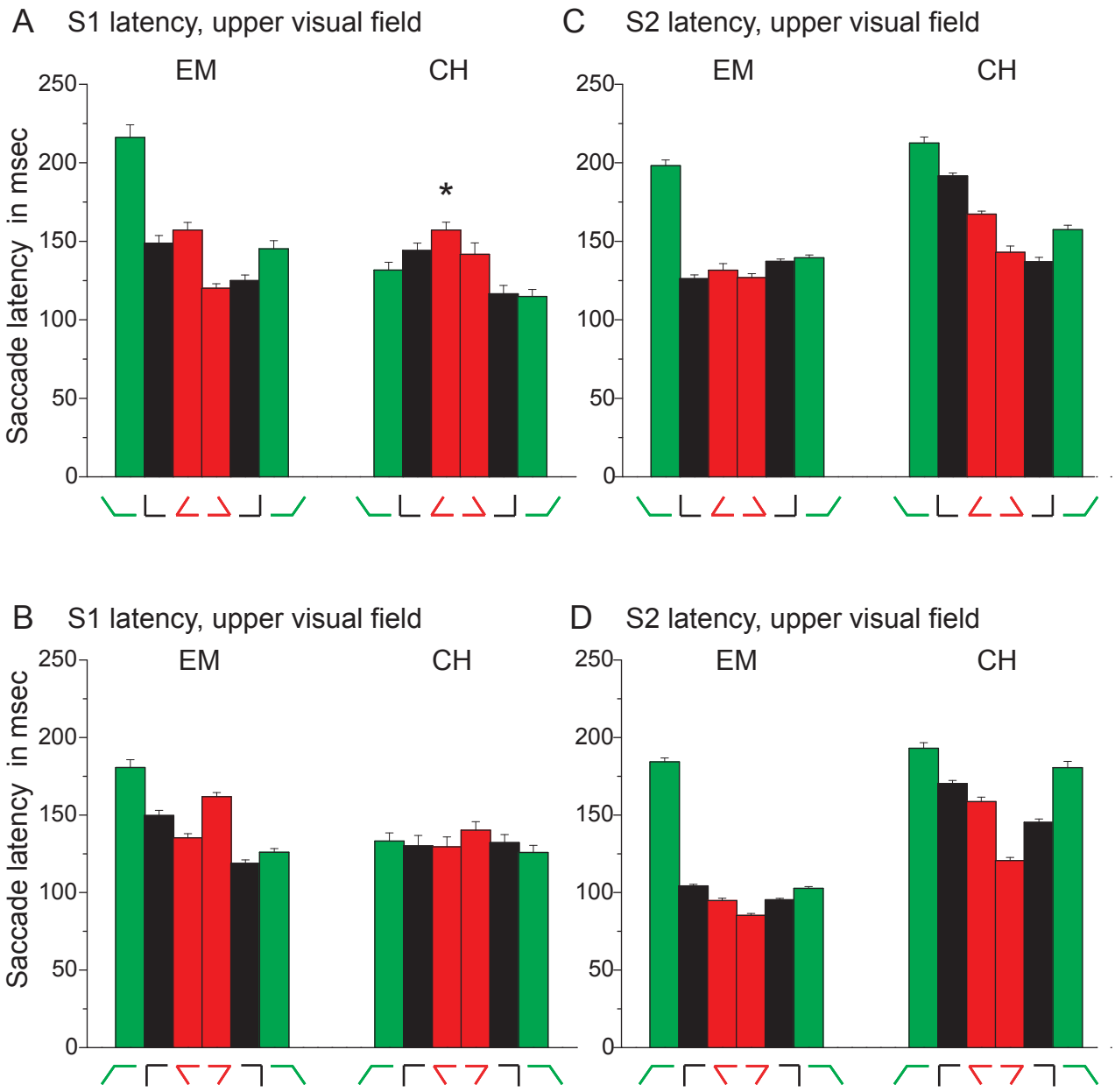


Figure 33 Measures of latency for the first and second saccades of the double-step, following multiple sessions of testing. A,B: Latency of the first saccade (mean +/-SE) for each sequence in the upper field (A) and lower field (B). C, D. Latency of the second saccade (mean+/-SE) for each sequence in the upper field (C) and lower field (D). Visual-across latency is significantly increased relative to both of the matched within latencies in only one quadrant: monkey CH, upper left visual field, S1 latency only (panel A; asterisk indicates significant slowing relative to matched central and within conditions). In many quadrants, latencies were longest for the within sequences, particularly for the second saccade. These data indicate that accurate performance of the visual-across sequences did not require a concomitant slowing of reaction times.

compared to the matched central and within sequences. We found that reaction time in the visual-across sequence was significantly slowed in only one quadrant, in only one monkey, and only for the first saccade (panel A: monkey CH, upper left). In all other cases, initiation of the visual-across sequence was equivalent to, or even faster than, the matched central and within sequences. These data indicate that the monkeys did not have to perform the double-step task more slowly in order to successfully complete the visual-across sequences.

In summary, we made five observations regarding the monkeys' performance of the visual-across sequences over time. 1) Improvement in the visual-across condition took place over a range of timescales, varying by monkey and by visual quadrant. 2) The accuracy of visual-across sequences typically improved in rapid steps, once learning was initiated. 3) Saccade latencies also changed abruptly as the visual-across sequence was learned, often in parallel with changes in accuracy. 4) Visual feedback was likely sufficient, though not necessary, to bring about improved performance of visual-across sequences. 5) Both monkeys showed minimal impairment of visual-across sequences in the final testing session, although significant inaccuracies persisted in one quadrant in each monkey.

Section 3: Testing the integrity of the learned visual-across sequences

The monkeys' ability to learn the visual-across sequences led us to ask three experimental questions. First, is performance of the learned sequences under sensory control (Experiment 3)? Second, does learning generalize to new sequences (Experiment 4)? Finally, are the learned visual-across sequences susceptible to increased memory demands (Experiment 5)?

Experiment 3: Is visual-across performance under sensory control?

What kind of information do the monkeys use to perform the visual-across sequences correctly? One possibility is that the monkeys learned to apply a motor rule, such as "if the first saccade is leftward and the second saccade is unknown, then direct the second saccade up and to the right." In this scenario, the monkeys would not be using sensory information about the actual target location. We tested this possibility by introducing a small shift of the T2 locations for within and across trials. (Figure 34). The shift, or *phi*, was small enough to allow the monkey to perform the trials correctly without taking sensory information into account. In other words, the monkey would continue to receive reward if they executed the same 'learned' saccade to the original T2, even on offset trials. If the monkeys were using a motor rule, we expected that the trajectory of S2 would not change systematically with the location of T2. If, however, the monkeys had access to sensory information about the precise location of T2, even on visual-across sequences, then the trajectory of S2 would vary according to the position of T2.

We tested the phi configuration when the monkeys' performance of the visual-across sequences had reached asymptote in at least two quadrants of the visual field. We chose these testing times in order to capture the monkeys' performance at a relatively early stage of successful visual-across performance. This strategy had the further benefit of allowing us to determine whether there were any indications of sensory control for sequences that were not yet fully learned.

Both monkeys generated the double-step sequences according to the actual location of the second target. This spatial precision was observed not only for the within conditions, as expected, but also for the visual-across conditions. Figure 35 shows the endpoint data from monkey EM. Endpoints for the standard within and visual-across conditions (green or red) are

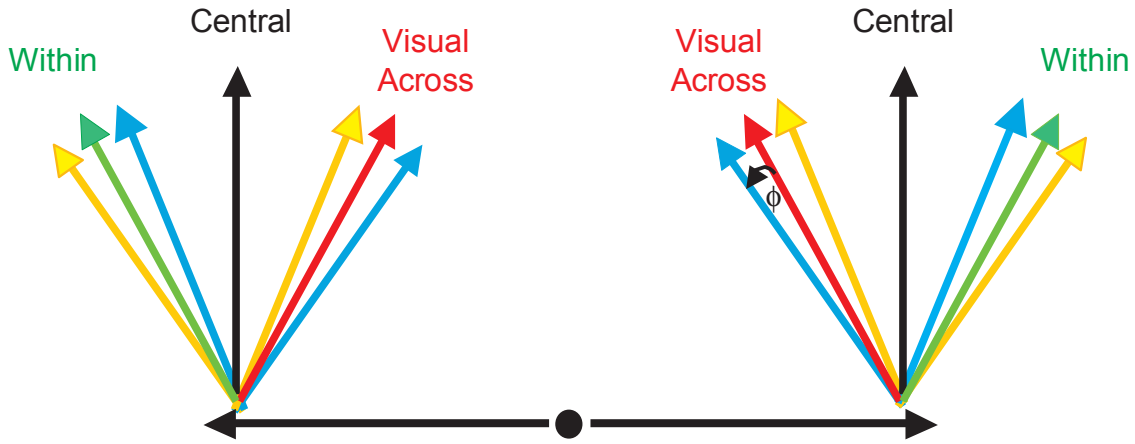


Figure 34. Configuration of upper-field sequences for testing whether updating is under sensory control. The six standard sequences were interleaved with a total of eight new sequences in which the position of T2 was shifted slightly. Central sequences are shown in black, within in green, and visual-across in red. There were two shifted sequences for each standard within and across sequence. In these sequences, T2 was displaced by five angular degrees (ϕ) from the standard. The displacement was either toward (cyan) or away from (yellow) the vertical meridian. This shift was small in relation to the electronic eye window at T2. This allowed the monkeys to receive reward on shifted trials, even if they made saccades to the standard T2 location. The same configuration was tested in the lower visual field.

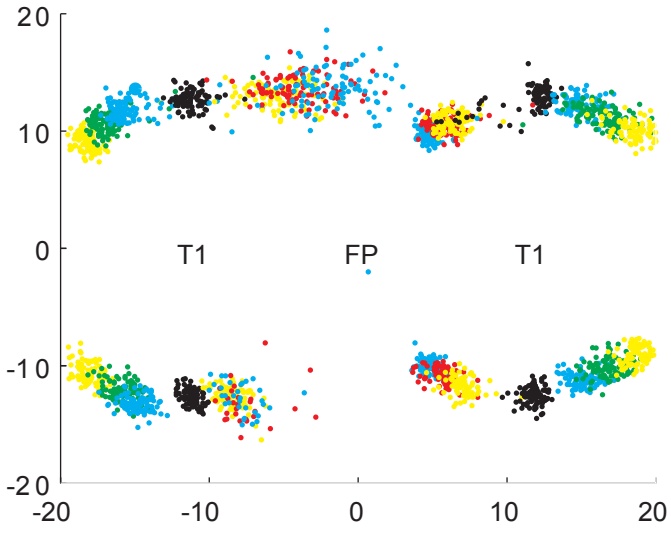


Figure 35. Double-step saccade endpoints reflect target positions; example data from monkey EM. Endpoints for the standard conditions are represented in black (central), green (within), and red (visual-across). Endpoints for the shifted within and visual-across sequences are shown in yellow (offset toward periphery) and cyan (offset toward midline). Endpoints were clustered according to target location for all the within sequences. This same pattern is observed for the learned visual-across sequences (upper and lower right quadrants). The endpoints for the upper left visual-across sequence, where some impairment remained, also showed evidence of the accurate shift. These data demonstrate that double-step performance is under sensory control, even when locations must be updated across visual hemifields.

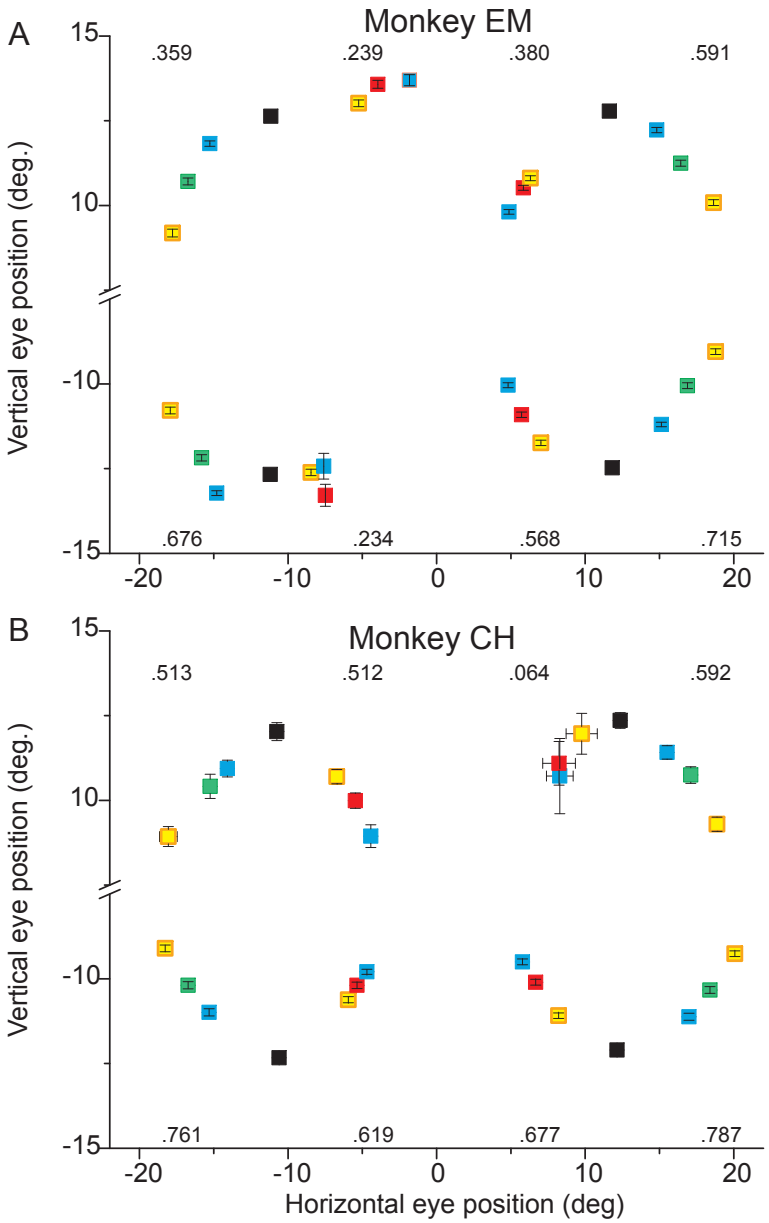


Figure 36. Spatial updating is under sensory control, even for visual-across conditions. Colored squares show the mean endpoint of the second saccade for each sequence, for monkey EM (A) and monkey CH (B). Error bars show standard error. Endpoints are from testing in the upper field (above Y axis break) and lower visual field (below Y axis break). Colors correspond to the labeling of sequences in Figure 34 (cyan = target shifted toward vertical meridian; yellow = target shifted toward periphery). We conducted regression analyses on data from each standard within (green) and visual-across (red) sequence and its two shifted sequences (yellow and cyan). We asked whether the angular trajectory of the ideal saccade was predicted by the angular trajectory of the monkey's saccade. The R^2 value for each set is shown in small print above the datapoints (for upper field sequences) or below them (for lower field sequences). We found highly significant R^2 values ($p<.0001$) for all but two visual-across sequences, where performance of this condition remained impaired: for monkey EM, the R^2 value for the visual-across sequence in the lower left quadrant was significant at $p<.05$, though the displacement of the monkey's endpoints does not match target locations; for monkey CH, the R^2 value for the visual-across sequence in the upper right field was insignificant ($p=.06$). Remarkably, we did observe significant displacement for visual-across sequences that were not fully learned (monkey EM, upper left quadrant). These data show that the second saccade was guided by sensory information about actual target location, even for the visual-across condition.

flanked by endpoints for the phi conditions (pink and cyan). This pattern is apparent not only for the within sequences, but also for the visual-across sequences where learning has occurred (right visual field). In Figure 36, we have plotted the mean endpoints for each sequence for monkey EM (panel A) and monkey CH (panel B). For both monkeys, the endpoints of the second saccade vary according to T2 location. In some cases, this was evident even when the visual-across sequence was still impaired. In monkey EM (panel A) visual-across endpoints in the upper left quadrant are inaccurate relative to the target locations. Nevertheless, the endpoints are offset from one another.

These data indicate that the average trajectory of the monkey's saccade reflected the location of the target. We assessed the significance of this relationship by conducting a regression analysis, asking whether the angular trajectory of the monkey's saccade was related to that of the ideal saccade. We conducted the regression separately on the data from each standard sequence with its associated shifted sequences. We found highly significant R^2 values ($p<.0001$, see Figure 36) for all but two sequences: the visual-across sequence in the lower left for monkey EM (panel A), and in the upper right for monkey CH (panel B); these were sequences for which learning had not yet taken place. We conclude that the monkeys were not using a motor rule to perform the visual-across sequences, but were in fact basing their behavior on the sensory location of T2.

We have shown that the monkeys were able to learn the visual-across sequences and execute them under sensory control. We next considered that the performance of these visual-across sequences might be particularly susceptible to increases in task difficulty. The following two experiments address this possibility by asking whether visual-across performance is robust in response to novel spatial configurations (Experiment 4) and increased mnemonic load (Experiment 5).

Experiment 4: New spatial configurations disrupt visual-across performance

In Experiment 4, we asked whether the learning of the standard visual-across sequence would generalize to a novel configuration of the double-step task. We changed the amplitude of both the first and second saccades, and altered the angular displacement of the second saccade. In this new configuration, the amplitudes of the first and second saccades were 8° and 15°, respectively, and angular displacement was 45°; in the standard sequences, saccade amplitudes were both 12°, with a displacement of 30°. Once again we introduced the within and visual-across sequences simultaneously, following brief training to criterion on the new central conditions. Testing was conducted in Session 53 for monkey EM and in Session 7 for monkey CH. Data from the standard configuration were obtained at the end of each session. At the time of testing, both monkeys had learned the visual-across sequence in at least two quadrants, but continued to show impairment in others (monkey EM, lower left, monkey CH, upper right).

We found that both monkeys performed the new sequences fairly well, though with more inaccuracy than for the standard sequences. The question of greatest interest was whether this discrepancy between new and standard sequences was greater for the visual-across sequences than for the central or within sequences. Accuracy measures for the standard and new paradigms are plotted in Figure 37. The data are organized as in Figure 16, but now there are two sets of sequences for each monkey. Data from the standard paradigm are shown in the bottom of each panel, with data from the novel paradigm above.

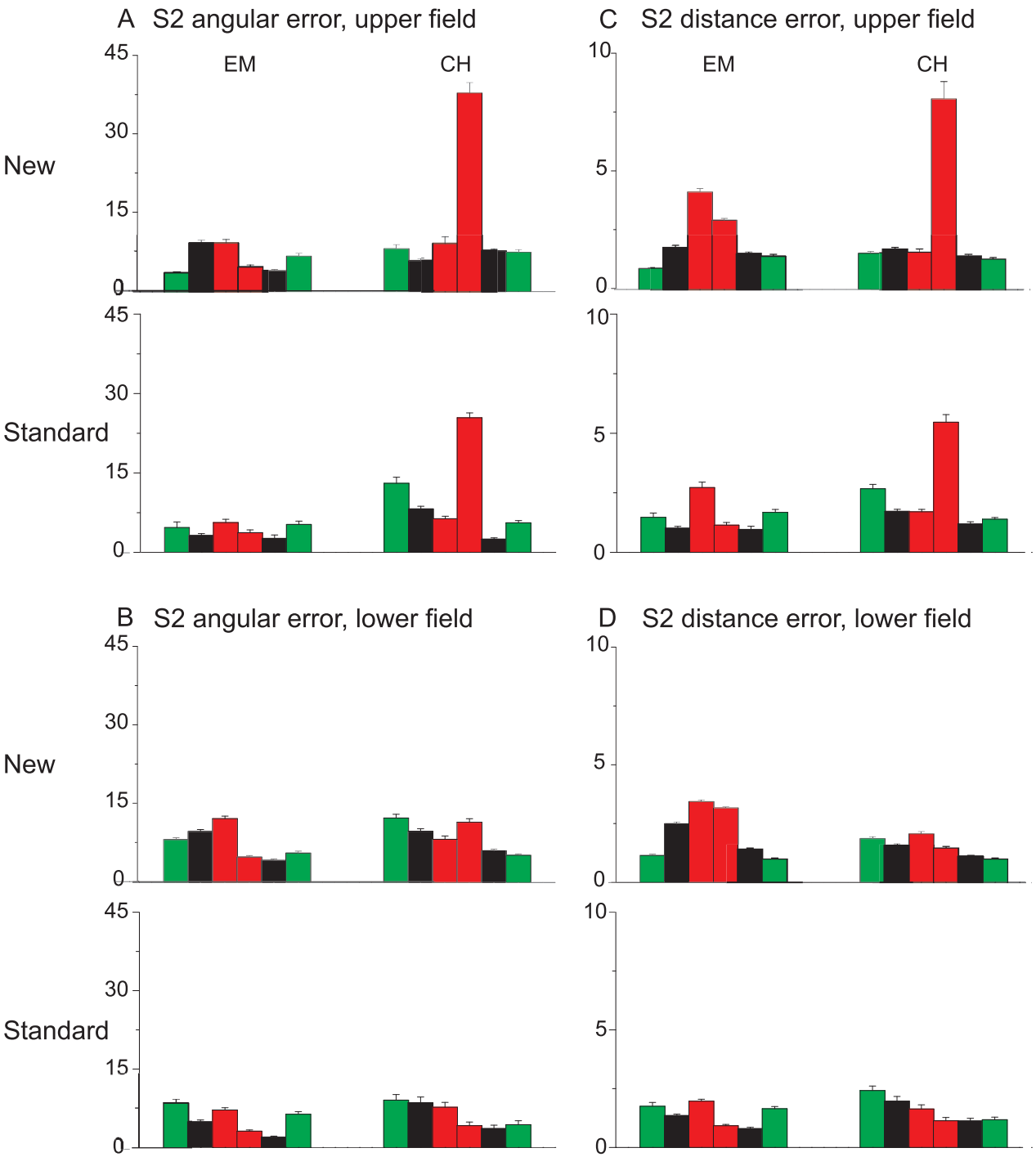


Figure 37. Measures of accuracy for double-step performance for standard and new configurations. General conventions as in Figure 16. Panels A and B show angular error from the upper and lower visual fields. Panels C and D show distance error. In each panel, there are two sets of accuracy measures for each monkey. The upper set of bars represents the accuracy for the six new sequences. Below these, the solid bars represent the accuracy for the six standard sequences. Angular error increased for most of the new sequences as compared to standard, regardless of condition. The magnitude of this increase, however, was greatest for the visual-across sequences. Distance error was also increased for the new sequences, but primarily for the visual-across condition (red bars). These data suggest that generalization to new sequences was less robust for visual-across as compared to within conditions.

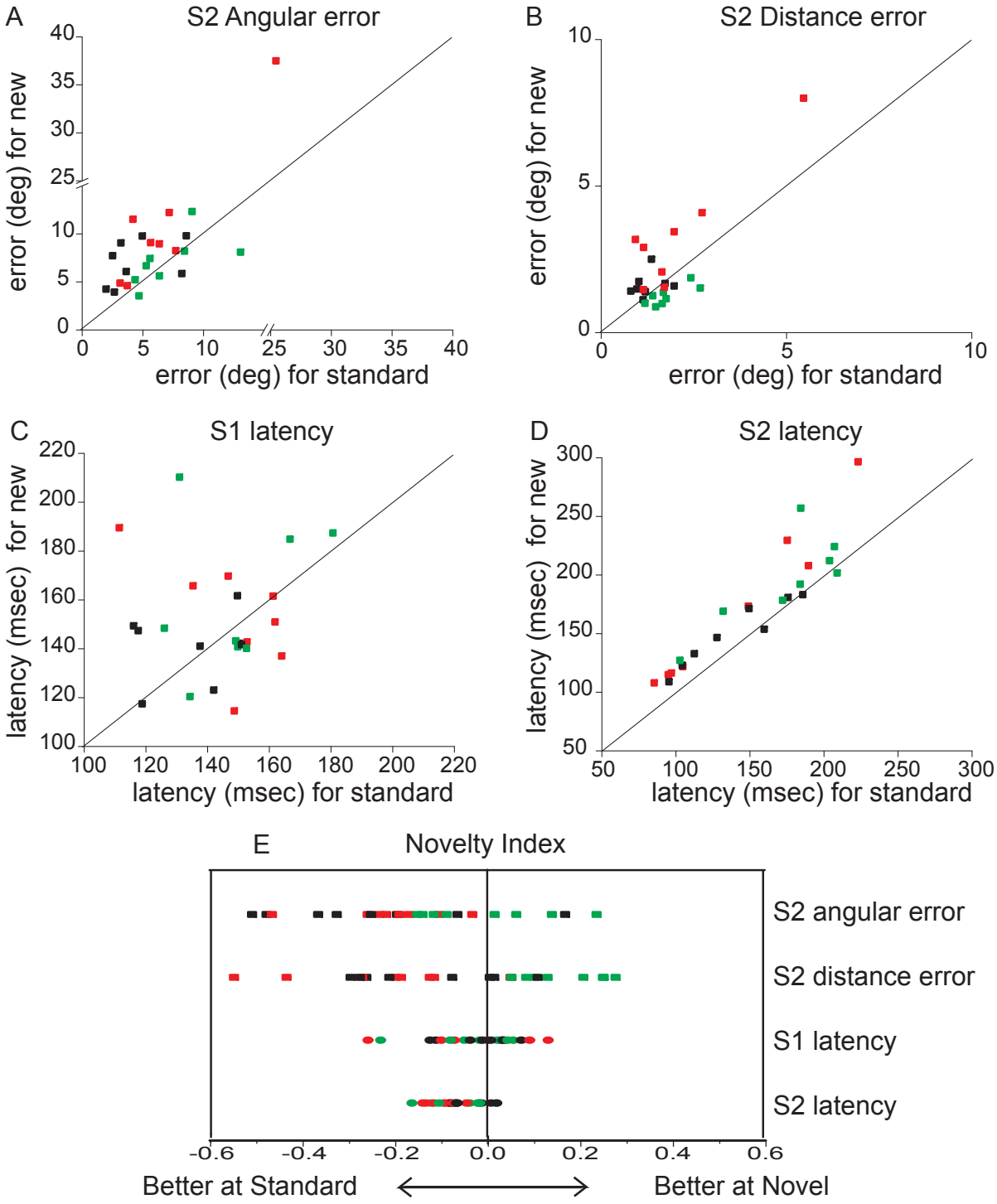


Figure 38. Panels A-D plot the accuracy and latency from the new configuration (y axis) compared to the standard configuration (x axis). Each point represents mean values from a single condition in a single quadrant. Conditions are labeled by color: central=black, within=green, visual-across=red. Each monkey contributes 12 points (3 conditions x 4 quadrants). Points falling above the unity line indicate that performance was worse for the new sequence (increased error or prolonged latency). Panel E shows the index values for each measure, for each of the sequences. The majority of the points fall to the left of zero, indicating better performance for standard as compared to new sequences. This tendency is particularly evident for the accuracy of the visual-across sequences (red).

We can visualize the effect of novelty more directly in Figure 38. Here, we have plotted error for the standard sequence against error for the novel sequence. Each point represents performance for a given sequence (central, within, or across) in a given quadrant of the visual field. Points along the unity line indicate equivalent performance of the old and new sequences. Points falling above the line indicate that performance was worse for the new sequence. In panel A, we see that angular error was increased for new compared to old sequences for most pairs, particularly for central and visual-across conditions. In panel B, we see that distance error was more equivalent for new and old sequences, though primarily for the central and within conditions. The visual-across condition showed more striking increases in distance error for the new sequences (red points above the line).

We next asked whether the monkeys performed the new sequences more slowly than the standard sequences. We used the same approach as for the accuracy measures. Figure 38 shows the latency of the standard sequences plotted against latency of the new sequences, for the first saccade (panel C) and second saccade (panel D). Saccadic reaction times were not differentially affected by updating condition. For the first saccade, the points for all conditions are equally distributed above and below the line. For the second saccade, nearly all the points fall above the line. This indicates that the monkeys were slower to initiate the second saccade for the new sequence, regardless of condition.

The data in the scatterplots are summarized in panel E of Figure 38. We normalized the data by computing a Novelty Index for each accuracy and latency measure ((New–Old) / (New + Old)). Negative index values, to the left of zero, indicate that performance worsened on the new sequences. The index values indicate that novel sequences led to greater inaccuracy for the visual-across (red) than for central (black) or within (green) conditions. For reaction time, however, novelty had an equivalent effect for all three conditions. These data suggest that the

monkeys' experience with the visual-across condition provided some benefit when they encountered a new spatial configuration of the task. Generalization to new sequences of the visual-across condition is still less robust, however, than that of the within and central conditions. The implication is that accurate performance in the double-step task remains more difficult when updating requires a transfer of visual information across hemifields.

Experiment 5: Visual-across updating is intact in a delayed double-step task

Performance in the double-step task depends on remapping of an evanescent memory trace. We hypothesized that performance of the visual-across condition might deteriorate if the monkey had to hold the T2 stimulus trace in mind during a delay period. We tested this by introducing a delay period (300-500ms) between the time of T2 appearance and the monkey's cue to initiate the double-step sequence. This experiment was conducted in monkey CH, at a point when visual-across performance was accurate in most quadrants. We used a training procedure similar to the original one: the monkey first learned to perform a vertical version of the delay task, which did not require across-hemifield updating. The monkey performed these sequences to criterion (75% correct) following 18 sessions of training. The monkey was then trained on the central conditions of the horizontal version of the task, reaching criterion within 2 sessions. Finally, we introduced the visual-across and within delay conditions simultaneously, to determine whether the monkey's performance was affected by the imposed delay.

We found that the monkey's performance of the visual-across sequences was not selectively impaired in the delay paradigm. The scatterplots of saccade endpoints suggest that performance was less precise for all three conditions in the delayed version, as compared to the standard version of the double-step task (Figure 39, compare to Figure 29). Visual-across performance was not selectively worse, however, relative to performance of the central or within

conditions. Accuracy and latency measures are shown in Figure 40. We conducted ANOVAs of these accuracy and latency measures to quantify the monkey's performance of the delay double-step, as a function of updating condition, S1 direction, and vertical field. We found that angular error depended significantly on updating condition ($p<.05$). However, this effect was due to decreased error for the central condition (8.0°) as compared to visual-across (10.5°) and within (9.9°; both comparisons $p<.05$, Tukey's HSD). Angular error was not significantly different for the visual-across as compared to the within condition. Distance error and reaction times did not vary significantly by updating condition.

The effect of updating condition varied by quadrant in the delay task, yielding a significant three-way interaction for both accuracy measures. Using the same *post hoc* procedure described for earlier experiments, we found that visual-across performance was significantly less accurate in the upper right quadrant. The monkey had shown persistent impairment for this sequence in the standard, non-delay version of the double-step task. For example, even in final testing session of the standard task, performance of this sequence was less accurate than that of the matched within conditions (Figure 31, panels A and C). Therefore, the increased error for this sequence in the delay task is likely unrelated to the additional mnemonic requirements of this paradigm. We conclude that visual-across performance does not selectively deteriorate when the monkey is required to withhold its response during a delay period. This suggests that the circuitry supporting visual-across updating in the split-brain is not disrupted by increased working memory demands.

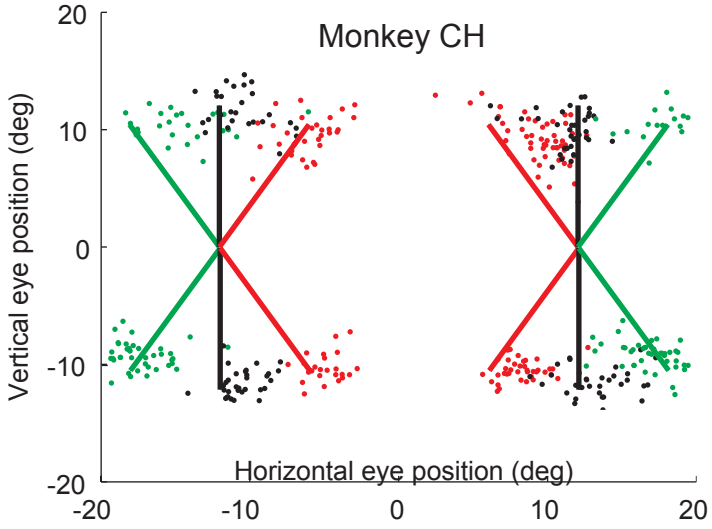


Figure 39. Endpoints of the second saccade in the delayed double-step task, which was tested in monkey CH. Conventions as in Figure 13. Upper visual field and lower visual field were tested in separate sessions. Endpoints were generally less accurate than for the non-delay version of the task, but importantly, performance of the visual-across condition was not selectively impaired.

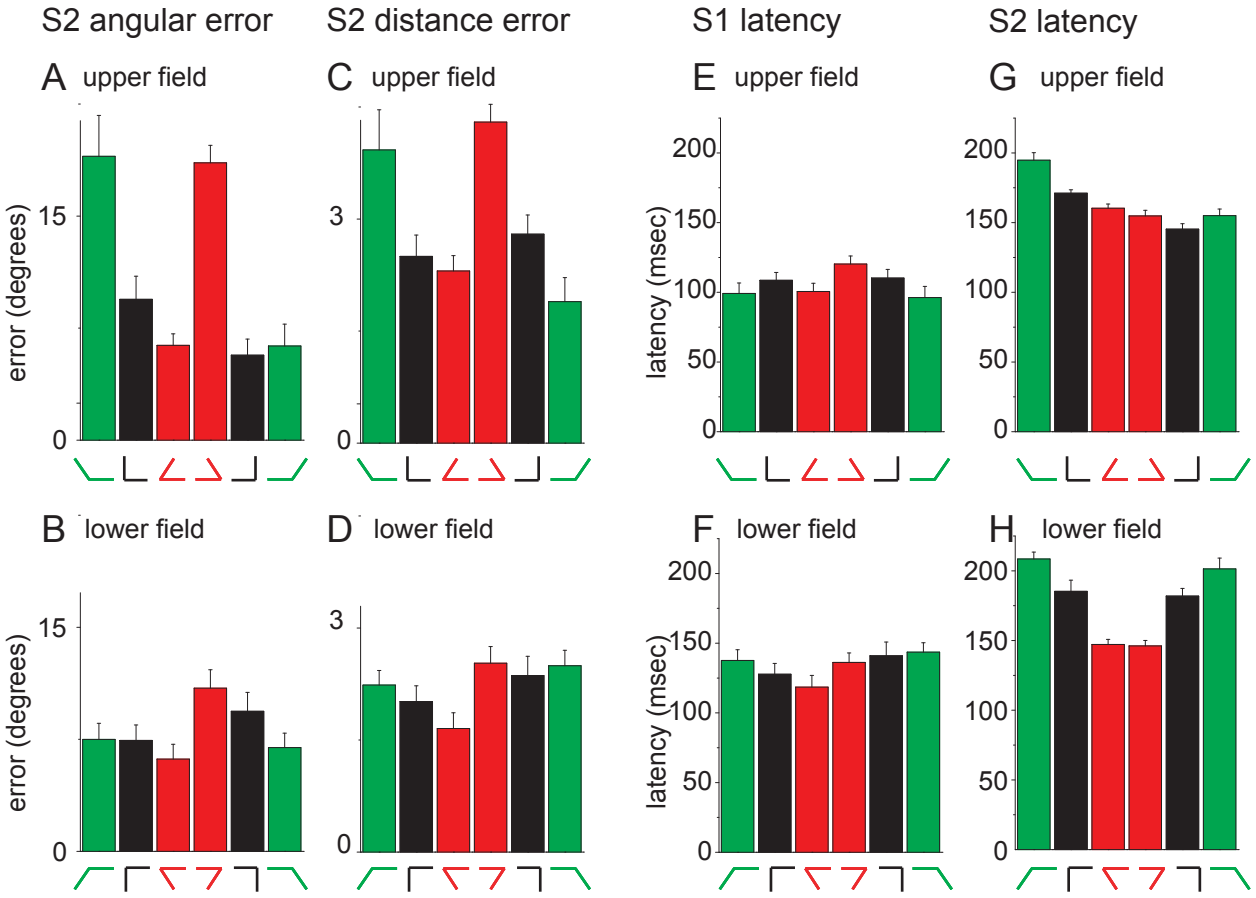


Figure 40. Measures of accuracy and latency for the delayed double-step task. A,B: Angular error (mean +/-SE) for each sequence in the upper field (A) and lower field (B). C, D. Distance error (mean+/-SE) in the upper (C) and lower field (D). Performance of the visual-across sequences was not significantly impaired in any quadrant, relative to matched central and within sequences. E,F: Initiation of the first saccade was not significantly different for any of the visual-across sequences as compared to the matched sequences. In the lower visual field, S2 latency (H) was significantly faster for the visual-across sequences, but did not differ by condition in the upper field. These data indicate that the monkey was not selectively impaired on the visual-across condition when working memory demands increased.

Summary, Part I.

In the last three experiments, we evaluated the integrity of learned visual-across performance. In Experiment 3, we found that performance of the double-step task was under sensory control, both for within and for visual-across conditions. In Experiment 4, we learned that the monkeys performed the double-step sequences less accurately when the spatial configuration was unfamiliar. This deterioration in accuracy was most apparent for the visual-across condition, and least apparent for the within condition. In Experiment 5, we found that performance of the visual-across condition was unaffected by increased working memory.

PART II. CAN SPLIT-BRAIN MONKEYS PERFORM THE MOTOR-ACROSS DOUBLE-STEP TASK?

Accurate performance of the double-step task requires that the location of the second target is updated in conjunction with the first saccade. This updating of spatial representations is thought to be initiated by a copy of the motor command to make the saccade to the first target. Eye movement commands may arise from any number of cortical and subcortical structures. The cortical eye fields and the superior colliculus all encode contraversive saccades. Hence, the command for a rightward eye movement arises from left brain structures. In the within and visual-across conditions, the eye movement command is generated in the same hemisphere that represents the memory trace of the stimulus. We realized that we could construct a situation in which the eye movement command was generated in the opposite hemisphere. We asked whether, in this situation, performance of the double-step task was disrupted in the absence of the forebrain commissures.

Experiment 6: Transfer of corollory discharge signals is largely intact

The initial impairment for visual-across conditions suggests that the forebrain commissures indeed serve as the primary route for transferring visual signals between the cortical hemispheres at the time of an eye movement. Are these same commissures also the primary route for relaying information about the impending eye movement, in order to initiate visuospatial updating? We addressed this question by testing the monkeys on a configuration that allowed us to compare performance of the within condition to a "motor-across" condition (Figure 41). In the motor-across condition, the representation of T2 is updated within the same hemifield, and thus the transfer of visual information is within-hemisphere. The corollary signal that initiates the updating, however, is thought to arise in the opposite hemisphere. As in previous experiments, the monkeys first performed the central sequences alone, to verify that baseline performance was above the criterion of 75% correct. The conditions of interest, motor-across and within, were then introduced and interleaved randomly with the central condition. The motor-across and within sequences were matched in saccade amplitude and in novelty. We asked whether monkeys were impaired selectively on the motor-across sequences.

We found that performance of the motor-across sequences was relatively unimpaired, as shown by the eye traces from the first ten trials (Figure 42). Both monkeys performed this sequence effortlessly in the upper and lower visual field (A-D), with one exception. Monkey EM made large errors in the first few motor-across trials in the upper right field. The monkey nevertheless learned this sequence rapidly, as indicated by Figure 43. The endpoints from the entire session are clustered near the correct T2 location for all sequences, suggesting that both animals were readily capable of performing the visual-across sequences as well as the within sequences.

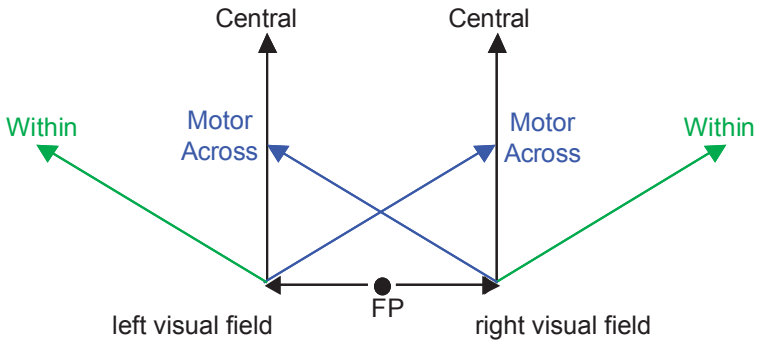


Figure 41. Configuration for testing double-step performance in the motor-across paradigm. Six sequences were randomly interleaved. Testing was conducted separately in the upper visual field (shown) and in the lower visual field. Horizontal arrows represent the first saccade from central fixation (FP) to the first target, T1. In each quadrant, the second saccade (S2) was directed to one of three targets. The central conditions, shown in black, required a vertical S2. The within conditions (green) and motor-across conditions (blue) were introduced simultaneously. The within and motor-across condition both require within-hemifield updating of the T2 location. In the within condition however, updating is presumably initiated by an oculomotor command that is generated in the same hemisphere in which the visual locations are represented. In contrast, in the motor-across condition, updating is presumably initiated by an oculomotor command that is transferred from one hemisphere to the other. For all conditions, the first saccade was 6 degrees in amplitude, and the second saccade was 13 degrees. The within and visual-across S2 trajectories were offset from the central S2 by 65 degrees.

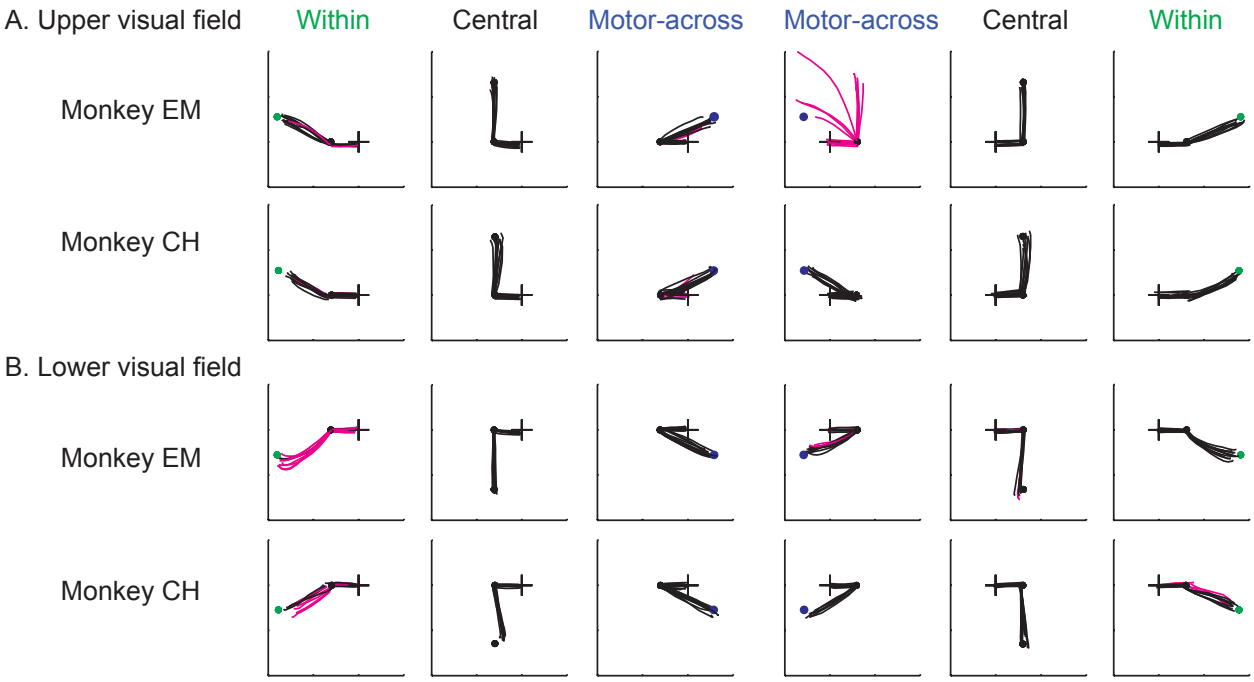


Figure 42. Eye traces show that performance of motor-across sequences was relatively unimpaired as compared to within sequences. Individual panels show the eye path, in degrees of visual angle, for the first ten trials of each condition. Conventions as in Figure 12. Colored labels indicate the condition. For central and within conditions, the trajectory of the second saccade (S2) matched the target trajectory. Remarkably, the monkeys also performed the motor-across sequences accurately in these first ten trials, with one exception. Monkey EM made initial errors in this condition in the upper right visual field, but began to adjust the trajectory toward the target as the trials progressed. These data show a relative lack of impairment for sequences requiring an interhemispheric transfer of corollary discharge signals.

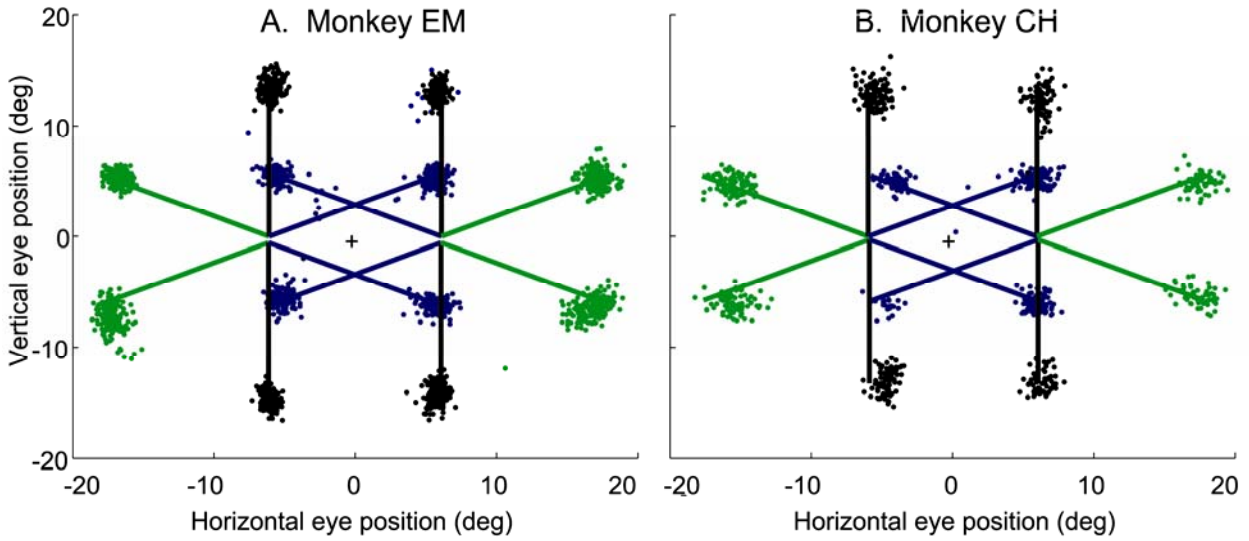


Figure 43. Endpoints of the second saccade from the first session of motor-across testing. A) Initial performance of monkey EM. B) Initial performance of monkey CH. Lines show the target trajectories for the second saccade of each sequence. Lines and endpoints are colored according to condition: central (black), within (green), and motor-across (blue). For both monkeys, endpoints for the motor-across condition are clustered accurately near the T2 location.

The monkeys' overall success in performing the motor-across condition is evident in the accuracy measures of Figure 44. ANOVAs revealed a significant effect of updating condition for both monkeys, for both measures of accuracy (all $p<.001$). The pattern of conditional differences, however, did not reflect an overall impairment of the motor-across sequence. Rather, overall error values were increased for the within condition relative to both the central and motor-across conditions. Accuracy also depended significantly on the interaction between updating condition, S1 direction, and vertical visual field (angular error, significant in monkey EM only, $p<.001$; distance error, significant in monkey EM at $p<.05$, in monkey CH at $p<.01$). We conducted *post hoc* analyses as we had for the visual-across experiments. Specifically, we asked whether the accuracy of each motor-across sequence was significantly worse than the accuracy of the matched central and within sequences. Only one of the motor-across sequences

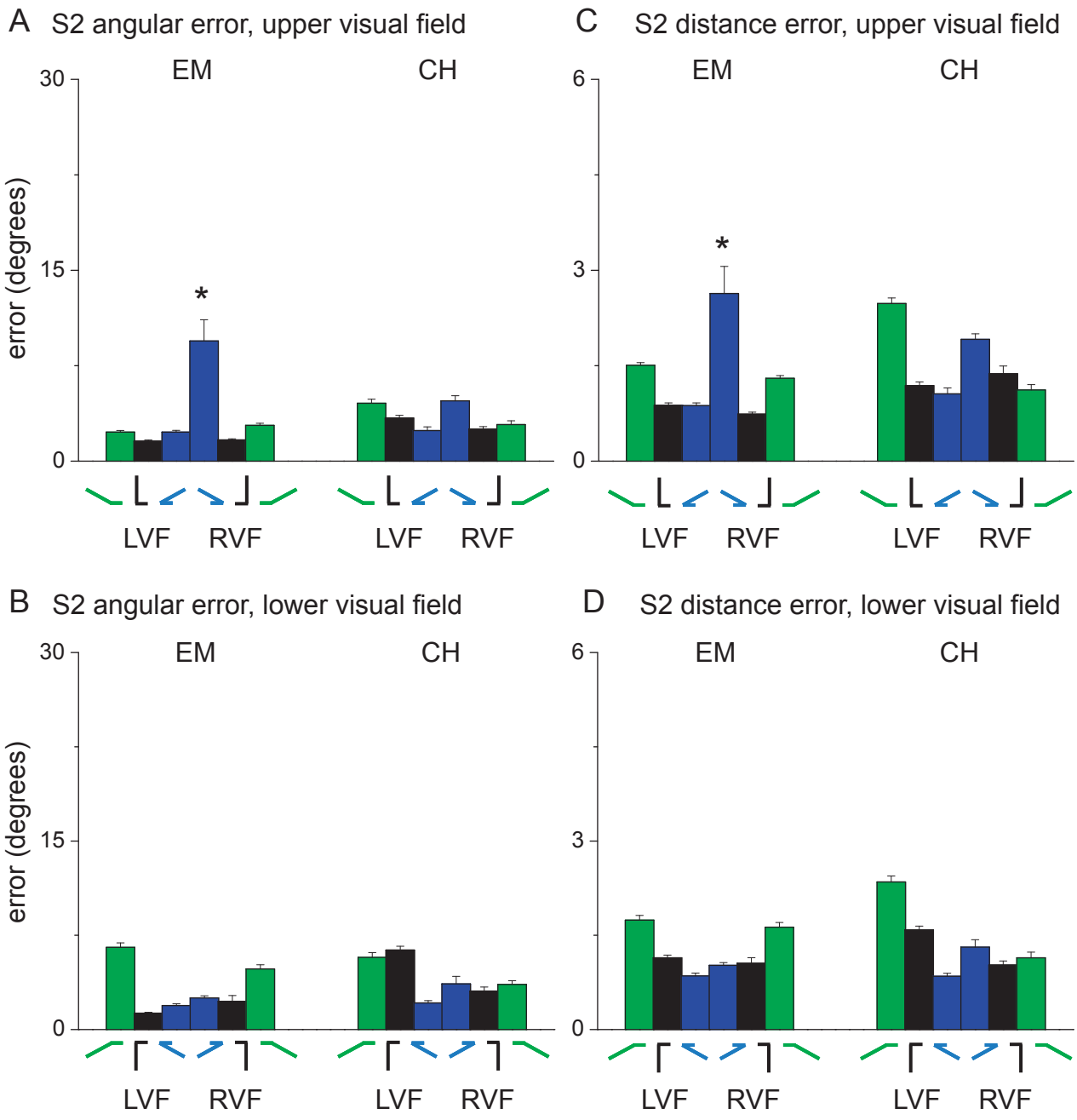


Figure 44. Measures of accuracy of double-step performance from the first session of testing the motor-across paradigm. A,B: Angular error (mean +/-SE) for each sequence in the upper field (A) and lower field (B). C, D. Distance error (mean+/-SE) for each sequence in the upper field (C) and lower field (D). Colors indicate the condition: black = central, green = within, blue = motor-across. All other conventions as in Figure 16. Axes are matched to those of Figure 16 for direct visual comparison. The asterisk indicates the only motor-across sequence that was significantly impaired relative to its corresponding central and within sequences (panels A,C, monkey EM, upper right sequence; $p<.05$, Tukey's HSD). For the remaining motor-across sequences, accuracy was unimpaired. These data indicate that the monkeys were capable of accurate performance in double-step sequences that presumably required an interhemispheric transfer of a corollary discharge signal.

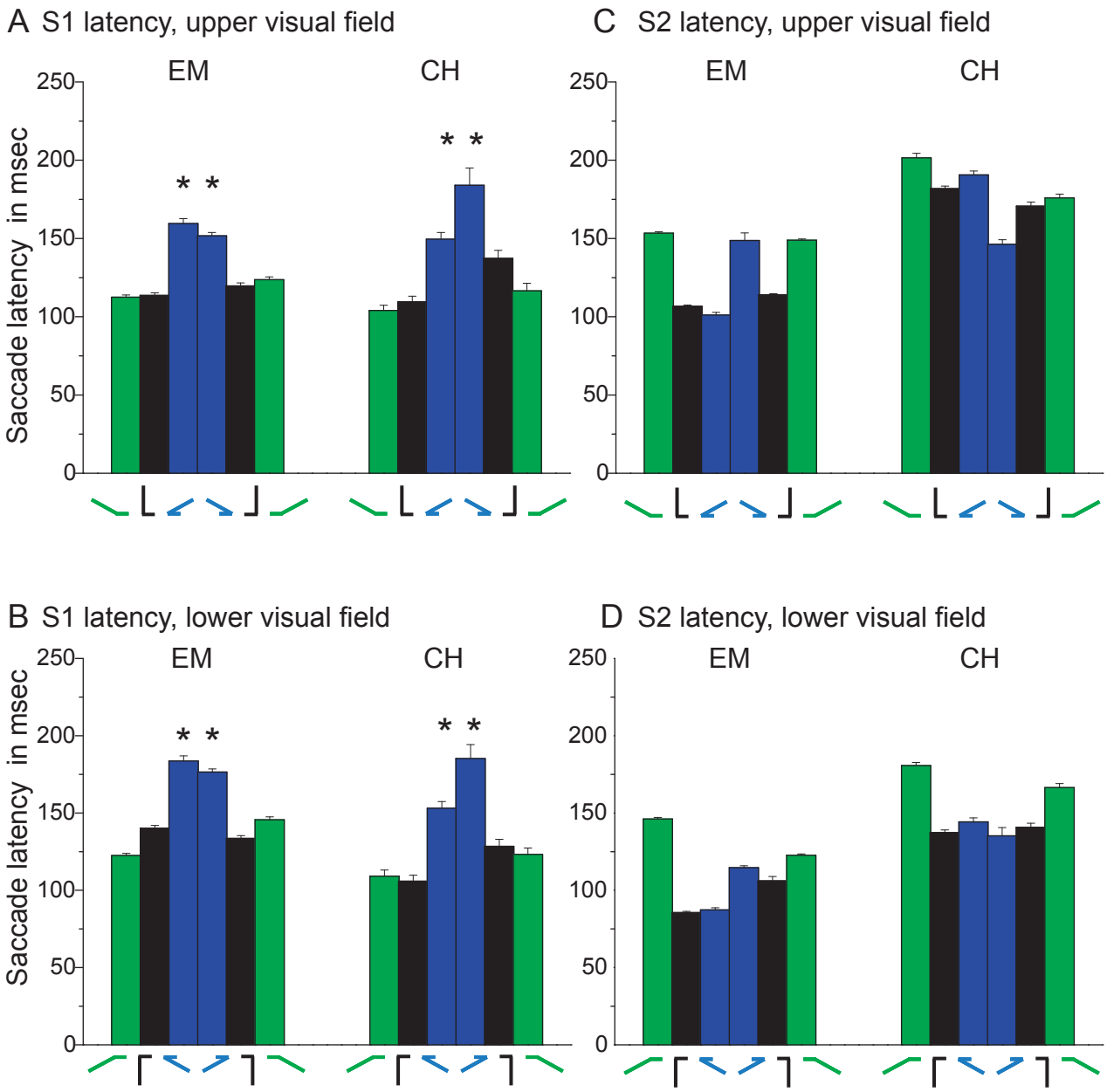


Figure 45. Measures of latency for individual double-step sequences, from the first session of testing the motor-across paradigm. A,B: Latency of the first saccade (mean +/-SE) for each sequence in the upper field (A) and lower field (B). C, D. Latency of the second saccade (mean+/-SE) for each sequence in the upper field (C) and lower field (D). All conventions as in Figure 44. Both monkeys showed prolonged reaction times for the first saccade of the motor-across sequence (panels A, B). For the second saccade (panels C,D), latency for the motor-across condition was equivalent to, or faster than, latency of the within condition. Asterisks indicate motor-across sequences with significantly prolonged latency relative to corresponding central and within sequences ($p<.05$, Tukey's HSD).

demonstrated significant impairment. This was the sequence in the upper left quadrant (Figure 44, panels A and C), which monkey EM had initially performed incorrectly. The remaining motor-across sequences were not significantly less accurate than their within-condition counterparts.

We considered the possibility that, despite the monkeys' accurate performance, the reaction times might still be slowed for the motor-across condition as compared to the within condition. We expected that prolonged latencies would be evident for the second saccade, but not for the first saccade, which was visually-guided. We found a significant main effect of updating condition for the latency of both the first and second saccades, in both monkeys ($p<.0001$). The saccade latencies for all sequences are shown in Figure 45. Both monkeys exhibited prolonged latencies for the first saccade of the motor-across sequence (blue bars, panels A and B). In contrast, latencies for the second saccade of the motor-across sequences were either equivalent to, or faster than, those of the within sequences. We next asked whether the reaction times for each visual-across sequence were significantly different from those of the matched central and within sequences. We found that latency of the first saccade was significantly prolonged for the visual-across condition in all four quadrants, in both monkeys. This increase in latency has no immediate explanation, considering that the first saccade is visually-guided. By contrast, reaction times of the second, memory-guided saccade were not significantly prolonged in any of the visual-across sequences. This finding, in concert with the accuracy data, indicates that performance of the motor-across double-step task is only minimally disrupted in the absence of the forebrain commissures.

Experiment 7: Direct comparison of motor-across and visual-across performance

Why was overall performance better for the motor-across sequences than the visual-across sequences? One explanation emerges from the use of different configurations for the motor-across and visual-across testing. The motor-across sequence may have been easier due to the spatial location of T2 or the metrics of the first saccade. We addressed this possibility by employing a new spatial configuration, in which the motor-across and visual-across sequences were directed to the identical T2 location. The sequences were also matched for the amplitude of the first saccade, and were interleaved randomly with the central sequences in the same session (Figure 46). We conducted this experiment in monkey EM, who showed visual-across impairment in all four quadrants at the time of testing.

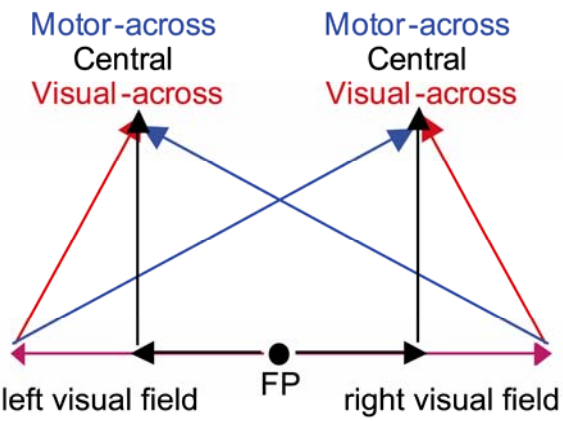


Figure 46. Configuration for comparison of double-step performance in the visual-across and motor-across conditions. Six sequences were randomly interleaved. Testing was conducted separately in the upper visual field (shown) and in the lower visual field. Horizontal lines represent the first saccade from central fixation (FP) to the first target, T1. In each quadrant, the second saccade (S2) was directed to the same target, regardless of condition. For the central condition, shown in black, amplitude of the first saccade was 6° and amplitude of the second saccade was 10.4°. The visual-across (red) and motor-across conditions (blue) were introduced simultaneously. The amplitude of the first saccade was 12° for the visual-across and motor-across conditions (pink line). The amplitude of the second saccade was 12° for the visual-across sequence, and 20.8° for the motor-across sequence.

The endpoints of the second saccade, shown in Figure 47, indicate that the monkey was able to perform the double-step task accurately for the motor-across but not the visual-across

sequences. Error measures for each sequence are shown in panels A-D of Figure 48. We assessed the conditional differences in both measures of accuracy by conducting an ANOVA, with updating condition (within, motor-across, and visual-across), S1 direction, and vertical field as factors. The ANOVA showed significant main effects of updating condition on angular as well as distance error ($p<.0001$). We compared the accuracy of individual sequences using our standard *post hoc* procedure, except that each visual-across sequence was now compared to its matched central and *motor-across* (rather than within) sequences. We found that both angular and distance error were significantly greater for the visual-across condition, in all four quadrants. This indicates that the split-brain monkey could accurately reach the location of the second target when updating was within-hemifield, even though the saccade that initiated updating was directed into the opposite hemifield. By contrast, the very same target location was not attained when updating was across-hemifield.

Finally, we compared the saccadic reaction times for the three conditions (Figure 48, panels E-H). The ANOVA showed that the latencies of both saccades were significantly dependent on updating condition (both $p<.001$), and on the interaction of condition, S1 direction, and vertical field. We found that the reaction time of the first saccade was significantly prolonged for the motor-across sequences in the lower visual field, whereas the motor-across and visual-across sequences did not differ significantly in the upper visual field ($p<.05$, Tukey's HSD). The increased latency for the first saccade in the motor-across condition was also observed in Experiment 6, suggesting that initiation of the first, visually-guided saccade is consistently slower in the motor-across condition.

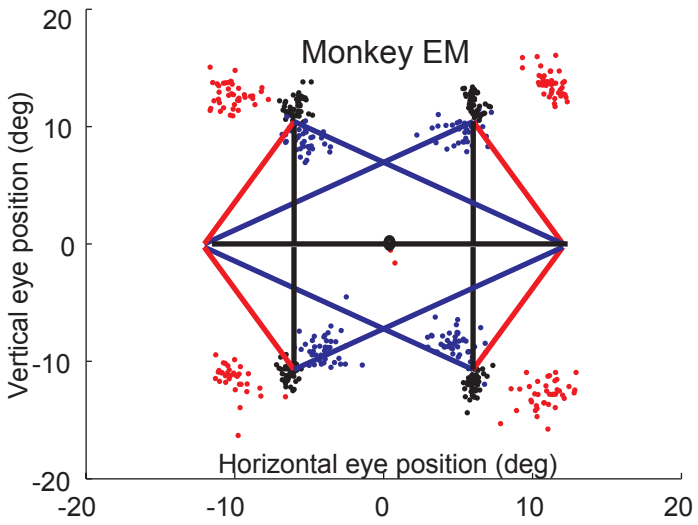


Figure 47. Endpoints of the second saccade when visual-across and motor-across sequences were directly compared. Black horizontal lines represent S1, which was either 6 degrees (central sequence) or 12 degrees (across sequences) . The target trajectories of S2 are colored by condition: black=central, blue=motor-across, red=visual-across. In a given quadrant, all three conditions had the same T2. Endpoints for central and motor-across sequences are clustered near T2. Endpoints for visual-across sequences (red) deviate from T2.

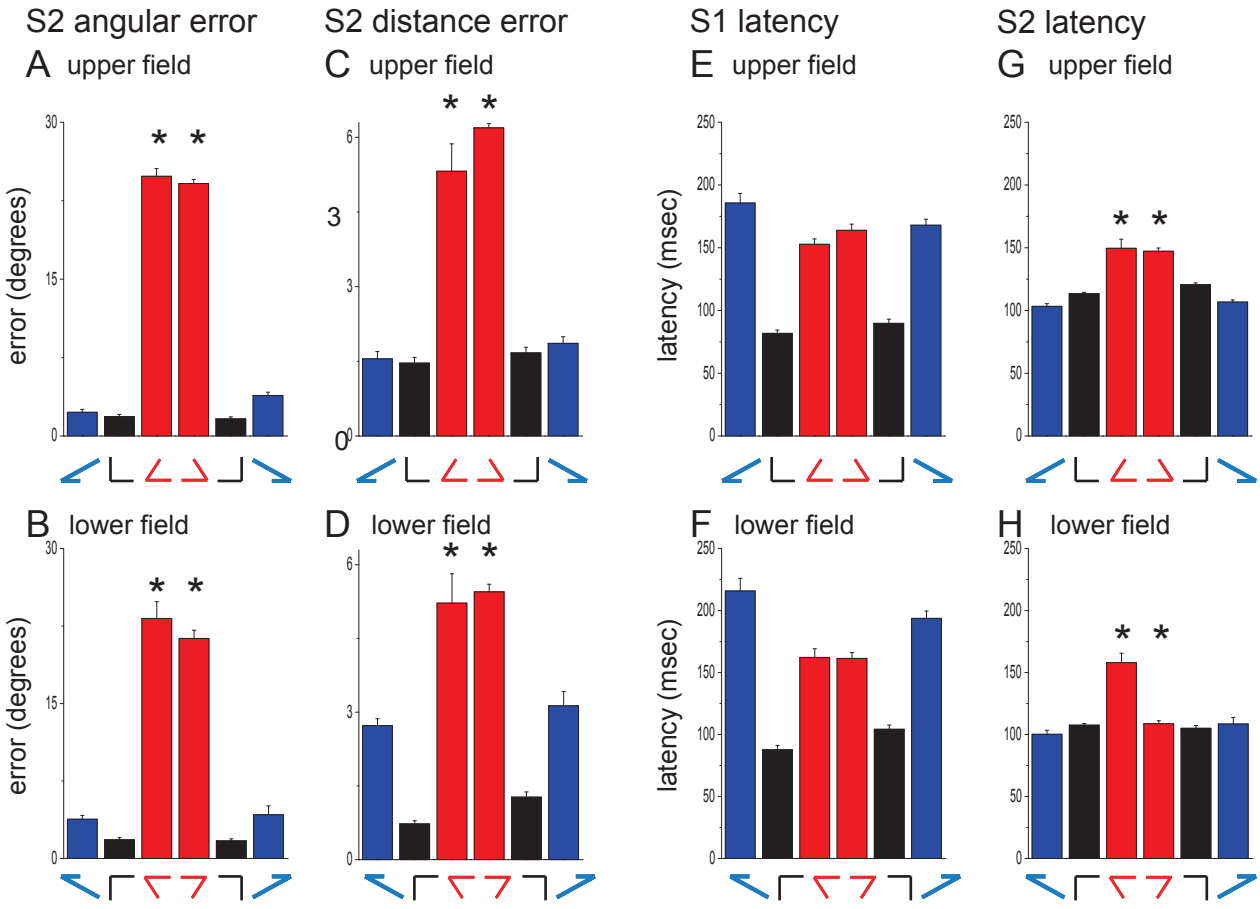


Figure 48. Measures of accuracy and latency for the matched comparison of visual-across and motor-across sequences. Both measures of error (A-D) were significantly greater for visual-across (red) as compared to motor-across (blue) in the upper (A,C) and lower field (B,D). Motor-across sequences had slightly more error in the lower as compared to the upper field, particularly for distance error (D). This increase reflects that the endpoints fell short of T2, but fell along the correct trajectory, keeping angular errors small. Initiation of the first saccade (E,F) was significantly prolonged for motor-across as compared to visual-across sequences, in all but the upper right quadrant. By contrast, initiation of the second saccade (G,H) was significantly prolonged for *visual-across* sequences, in all but the lower right quadrant.

The relative lack of impairment for motor-across sequences suggests that the forebrain commissures do not provide the primary path for relaying information about an upcoming saccade to the areas representing visual locations.

SUMMARY AND DISCUSSION

We measured the accuracy on a spatial task to assess the integrity of remapping in the absence of the forebrain commissures. We asked whether performance of the double-step task was impaired when updating required the interhemispheric transfer of either visual signals or corollary discharge signals. Three main findings emerge from these behavioral experiments.

The first is that split-brain monkeys demonstrated an initial impairment on double-step sequences that required updating of the second target from one visual hemifield to the other. We ruled out three alternatives for this initial impairment. It cannot be attributed to: 1) inaccuracy of the first saccade, 2) basic sensory, mnemonic, or oculomotor deficits, or 3) a general deficit in executing sequences that require a reversal in saccade direction. We found that the impairment persisted even when the target of the second saccade was placed very near to the midline, suggesting that ipsilateral representations were unavailable for updating. Finally, we found that the impairment was re-instated when we introduced new spatial arrangements of the targets. These findings indicate that across-hemifield updating is compromised in the absence of the forebrain commissures. This impaired performance stands in striking contrast to performance in the normal monkey. Several investigators have employed sequences that correspond to our visual-across and within-hemifield conditions. These studies report no impairment in either the accuracy or latency of sequences that require across-hemifield as compared to within-hemifield updating (Li and Andersen, 2001; Jeffries and Goldberg, 2003;

Zivotofsky, 2003). We conclude that the impairment in across-hemifield performance observed in the present study is due to the absence of a direct cortico-cortical pathway for interhemispheric transfer of visual information during spatial updating.

The second main finding is that this impairment of across-hemifield performance was not universal, nor was it permanent. One of the monkeys was effectively unimpaired on two of these sequences in initial testing. Both monkeys learned to perform the across-hemifield condition as they gained experience with the individual sequences. We found that learning of the individual across-hemifield sequences occurred over different timecourses, depending on the monkey and on the visual quadrant of the sequence. There are no obvious explanations for these differences. They may reflect complex differences in strategy or in the representation of visual space. The critical result is that both monkeys were ultimately successful in performing double-step sequences that required updating of the second target location from one hemifield to the other. Furthermore, we found that across-hemifield updating was under sensory control and was unaffected by increased working memory demands. These important and unexpected findings demonstrate that locations can be updated across visual hemifields in the absence of the forebrain commissures.

The third main finding is that split-brain monkeys demonstrated minimal, if any, impairment on double-step sequences that required the interhemispheric transfer of a corollary discharge signal. Both monkeys readily performed these sequences. The immediacy of successful performance suggests that corollary discharge signals are typically relayed to visual areas without reliance on the forebrain commissures.

Chapter 3: Neural correlates of spatial updating

OVERVIEW

In this chapter, we present physiological experiments that assess the neural correlates of spatial updating in the absence of the forebrain commissures. We used the single-step task to measure remapping activity in area LIP of the split-brain monkey, addressing two experimental aims. Our first aim was to determine whether LIP neurons are active when updating requires the interhemispheric transfer of visual signals. We report six findings on activity during the visual-across as compared to the within condition, characterizing the magnitude and neural latency of remapping activity. Our second aim was to determine whether LIP neurons are active when updating requires the interhemispheric transfer of corollary discharge signals. We report two findings on activity during the motor-across as compared to the within condition of the single-step task, focusing on the relative magnitude of activity.

BACKGROUND

Neurons in the lateral intraparietal cortex (area LIP) remap the locations of salient stimuli when the eyes move (Goldberg et al., 1990; Duhamel et al., 1992a; Gottlieb et al., 1998; Kusunoki et al., 2000). Area LIP is the putative site where oculomotor and visual signals converge to create updated spatial representations. Neurons in area LIP are modulated by sensory, oculomotor, and cognitive factors, including spatial working memory and attention (Gnadt and Andersen, 1988; Barash et al., 1991; Gottlieb et al., 1998; Colby et al., 1996; Kusunoki et al., 2000; Bisley and Goldberg, 2003). These functional properties, in conjunction with findings from neuropsychological and inactivation studies, are the basis for the proposal that remapping

activity is generated in area LIP. Neuropsychological studies in human have shown that parietal cortex is necessary for accurate performance of the double-step saccade task (Heide et al., 1995, Duhamel et al., 1992b). This observation is paralleled by inactivation studies in monkey, which demonstrate that inactivation of area LIP impairs double-step performance (Li and Andersen, 2001). These findings suggest that remapping activity in area LIP may be essential to spatial behavior. In the current experiment, we asked whether neurons in area LIP of the split-brain monkey exhibited remapping activity in conditions that required the interhemispheric transfer of the visual or corollary discharge signals.

At the outset of these studies, our expectation was that the interhemispheric transfer of visual and corollary discharge signals would be abolished in the absence of the forebrain commissures. Accordingly, our initial prediction was that neurons in area LIP would no longer exhibit activity in association with conditions that required the interhemispheric transfer of either signal. In our behavioral experiments, however, we found clear evidence that updating in these conditions was not abolished in the split-brain monkey. This led us to reconsider our original predictions regarding neural activity in area LIP. The monkeys' ultimate success in performing double-step sequences requiring interhemispheric transfer implies the existence of neurons that exhibit updating activity in these conditions, even in the absence of the forebrain commissures. Are such neurons found in area LIP? We considered two possibilities. The first is that the disconnected hemispheres accomplish this updating using circuitry entirely outside of parietal cortex. If this is the case, we would expect to observe no remapping activity in area LIP. Alternatively, activity in parietal cortex may be necessary for accurate spatial behavior in the double-step task (Duhamel et al., 1992b; Heide et al., 1995; Quaia et al., 1998). In this case, given that the monkeys eventually showed accurate behavior, we would expect LIP neurons to

exhibit remapping activity for conditions requiring the interhemispheric transfer of visual or corollary discharge signals.

EXPERIMENTAL AIMS

In Aim 1, we hypothesized that the forebrain commissures provide the pathway for the interhemispheric transfer of visual signals required for spatial updating. Our original experimental prediction was that, in the absence of these commissures, neural activity in area LIP would be absent when updating required the interhemispheric transfer of this visual information.

In Aim 2, we hypothesized that the forebrain commissures provide the pathway for the interhemispheric transfer of corollary discharge signals required for spatial updating. Our original experimental prediction was that, in the absence of these commissures, neural activity in area LIP would be absent when updating required the interhemispheric transfer of this motor information.

APPROACH

We addressed these aims by measuring the activity of single neurons in area LIP during two interhemispheric conditions ("visual-across" and "motor-across") and during the intrahemispheric condition ("within"). We addressed the first aim in both monkeys, recording from single neurons in area LIP during the visual-across and within conditions of the single-step task. We began Aim 2 later in the project, recording during the motor-across condition in monkey EM. For this monkey, the three conditions were fully interleaved.

The spatial configurations of the single-step task are determined by the receptive field location of each neuron. The stimulus and saccade must be arranged so that the saccade brings the neuron's receptive field onto the location where the stimulus was flashed. Prior to the saccade, however, the stimulus must be outside the neuron's receptive field. Receptive fields in area LIP, while sometimes restricted, can encompass a quadrant of the contralateral visual field. As a result, we were rarely able to use a horizontal saccade for the within-hemifield condition, because the corresponding location for the stimulus was still in the neuron's receptive field. The solution to this problem was to use a vertical saccade for the within-hemifield condition. We encountered the same problem when recording from neurons during the motor-across condition. For this condition, we typically used an oblique saccade, with a considerable vertical component but directed into the ipsilateral visual field (i.e., directed away from the hemifield in which the stimulus appeared). Saccade amplitude was the same for all conditions.

We describe the implementation of these conditions for a hypothetical neuron with its receptive field in the upper right quadrant (Figure 49). The within condition is shown in panel A. The stimulus appears in the lower right quadrant when the eyes are at the first fixation point (FP1). Its location is therefore encoded by neurons in the left hemisphere. After the disappearance of the central fixation point, the monkey makes a downward visually-guided saccade to the second fixation point (FP2). When the eyes are at FP2, the location where the stimulus appeared is still in the right hemifield. This location is now encompassed by the neuron’s receptive field. Updating in this condition therefore involves an intrahemispheric transfer of visual information to the neuron under study. Furthermore, this updating is initiated by a vertical saccade, which is represented bilaterally. Consequently, the transfer of the corollary discharge signal is also intrahemispheric. The visual-across condition is shown in

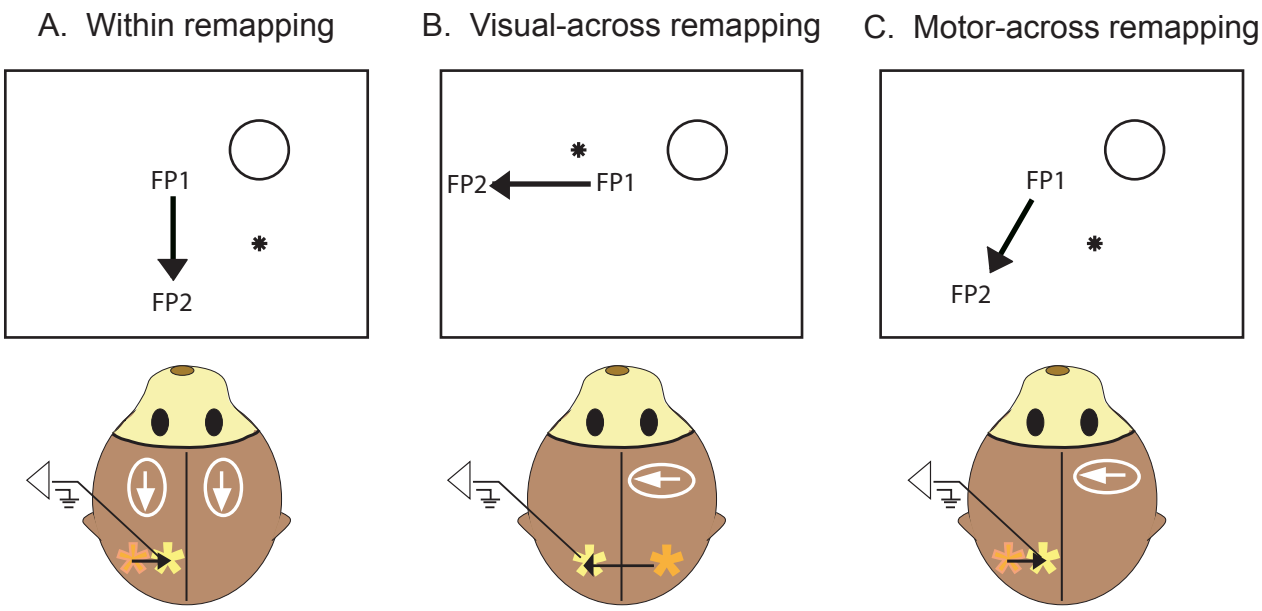


Figure 49. Experimental configurations for measuring remapping in the single-step task, in three conditions of interest. Spatial configurations are determined by the neuron's receptive field, located in the upper right quadrant; the hypothetical neuron under study is located in the left hemisphere. In the within condition (panel A), the stimulus appears in the right visual field when the eyes are at FP1. Its retinal location is represented by neurons in the left hemisphere (orange asterisk). After the monkey makes a downward saccade to FP2, the location where the stimulus previously appeared is still in the right visual field, and therefore represented by neurons still within the left hemisphere (yellow asterisk). The command to make the downward saccade is generated bilaterally (white arrow); therefore, both visual and corollary discharge signals are transferred within the same (left) hemisphere. In the visual-across condition (panel B), the stimulus is located in the left visual field when the eyes are at FP1, and therefore represented by neurons in the right hemisphere (orange asterisk). When the eyes reach FP2, the location where the stimulus appeared is now in the right visual field, represented by neurons in the left hemisphere (yellow asterisk). Updating in this condition involves a transfer of visual information between sets of neurons in opposite cortical hemispheres. The corollary discharge signal in this condition is transmitted within hemisphere. In the motor-across condition, the stimulus representation is always in the right visual field, and thus involves a transfer between neurons within the left hemisphere. However, the command to make the leftward eye movement is generated in the right hemisphere. Consequently, the corollary discharge signal must be transferred between hemispheres in order to initiate updating of the stimulus representation.

panel B. The stimulus appears in the left visual field when the eyes are at FP1. When the eyes reach FP2, however, the location where the stimulus had appeared is now in the right visual field. Its retinal location is now encompassed by the neuron's receptive field. Consequently, updating in the visual-across condition involves an interhemispheric transfer of visual information, from neurons in the left hemisphere to neurons in the right hemisphere, including the neuron under study. Note that in this condition, the corollary discharge signal for the leftward eye movement has intrahemispheric access to the memory trace of the stimulus, which appears in the left hemifield. This contrasts with the motor-across condition (panel C). In the motor-across condition, the location of the stimulus is updated within the same (right) visual field. The direction of the saccade, however, is into the left visual field. As a result, the corollary discharge command originates in the right hemisphere, whereas the visual updating occurs within the left hemisphere.

RESULTS

PART I. IS THERE EVIDENCE OF VISUAL-ACROSS REMAPPING IN THE SPLIT BRAIN?

The first aim of this experiment was to determine whether LIP neurons in the split-brain monkey can remap visual stimuli from one hemifield to another. We addressed this aim by monitoring LIP activity during the within and visual-across conditions of the single-step task in monkeys EM and CH. We expected that remapping activity would be intact for the within condition. At the outset of the experiment, we had expected that visual-across activity would be abolished in the absence of the forebrain commissures. The behavioral evidence of successful visual-across updating, however, suggested that visual-across activity might still be present in LIP.

Section 1: Are LIP neurons active for visual-across updating?

We found that neurons in area LIP demonstrated significant remapping activity, not only in the within condition, but also in the visual-across condition of the single-step task. A single neuron with remapping activity in both conditions is shown in Figure 50. This neuron had a receptive field located in the upper right quadrant of the visual field. In the within condition of the single-step task, the stimulus appeared briefly in the lower right quadrant and disappeared before the monkey initiated a downward saccade from FP1 to FP2 (panel A). This neuron exhibited a burst of activity beginning before the onset of the saccade, and fired strongly after the eye movement to FP2 (panel C). Remapping activity for the within condition thus resembled the activity observed in the normal monkey. In the visual-across condition of the single-step task, the stimulus appeared briefly in the left visual field, disappearing before the monkey initiated a leftward saccade from FP1 to FP2 (panel B). This condition required updating of the stimulus trace from the left to the right visual field, and presumably required a transfer of visual information between the right and left cortical hemispheres. We expected this transfer to be disrupted in the split-brain monkey. Nonetheless, the neuron fired briskly in the visual-across condition, with a strong burst of activity after the eye movement to FP2 (panel D). This activity demonstrates that memory traces can be updated across visual-hemifields in the absence of the forebrain commissures.

Can the neuron's activity in the single-step task be attributed simply to the appearance of the visual stimulus, or the generation of the eye movement? For each neuron, we addressed this possibility by measuring activity in two control tasks, a stimulus-alone control and a saccade-alone control. In the stimulus-alone control, the stimulus appeared while the monkey fixated centrally. In each condition, the stimulus was outside the neuron's response field and did not

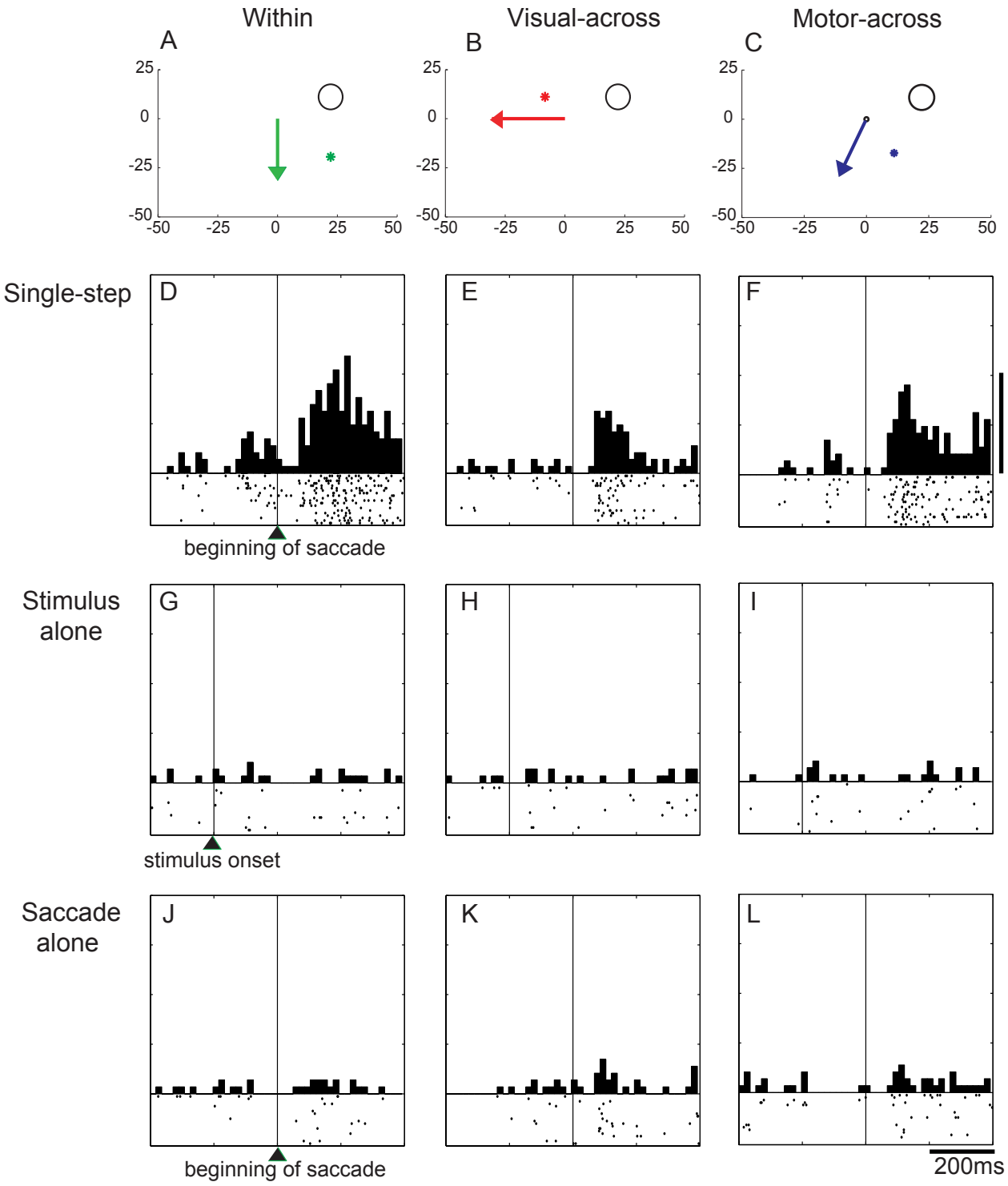


Figure 50. Activity of a single neuron in the single-step and corresponding control tasks. Top panels show the spatial configurations for the within (A), visual-across (B), and motor-across (C) conditions. The neuron fired briskly for all three conditions of the single-step task (panels D-F). The corresponding control conditions show that activity was minimal when the stimulus appeared alone (panels G-I) and when the saccade was generated in the absence of the stimulus (panels J-L). In each panel, the histogram shows summed activity in 18ms bins. Rasters represent individual trials; each tic mark is a single action potential. The vertical bar to the left of panel F indicates a firing rate of 40 spikes per second.

drive the neuron (panels E and F). In the saccade-alone control, the monkey made a saccade from FP1 to FP2, but no stimulus appeared. Each of these saccades was directed away from the response field, and the neuron did not fire in conjunction with either movement (panels G and H). The control tasks show that remapping activity did not reflect basic sensory or motor properties of the cell: it responded only when the stimulus and saccade co-occurred in the context of the single-step task. These data confirm that the neuron fired in response to the memory trace of the stimulus, even when the memory trace was updated from one visual hemifield to the other.

Is the neuron in Figure 50 an exceptional case? We recorded from a total of 223 visually-responsive neurons during the within and visual-across conditions of the single-step task (183 in monkey EM, 40 in monkey CH). For each neuron, we determined the significance of remapping activity, based on two criteria. First, we asked whether the firing rate during the remapping epoch was significantly greater than the firing rate during the stimulus-alone control (unpaired t-test, $\propto$=.05; remapping epoch = 0-200ms from the beginning of the saccade). This comparison was effectively a comparison to baseline activity, because we had excluded from analysis any neurons with significant responses in the stimulus-alone task. Second, we asked whether the firing rate during the remapping epoch was significantly greater than the firing rate during the corresponding epoch in the saccade-alone condition (unpaired t-test, $\propto$=.05). This second criterion was necessary because some neurons had significant firing in the saccade-control task, likely due to a remapping of the central fixation point; none was driven by the stimulus-alone task (see Appendix). Applying the two criteria described above, we found that 171/223 neurons demonstrated significant remapping activity in at least one condition of the single-step task.

We found that 84 neurons had significant visual-across activity (Figure 51). The majority of these neurons (74, yellow bar) also had significant activity in the within condition. Ten

neurons were significantly active *only* in the visual-across condition (red bar). Many more neurons in the population – 87 – had significant activity only in the within condition (green bar). These data indicate that LIP neurons in the split-brain monkey can remap stimuli from one visual hemifield to another. Neurons with visual-across activity are encountered less frequently, however, than those with within-hemifield activity.

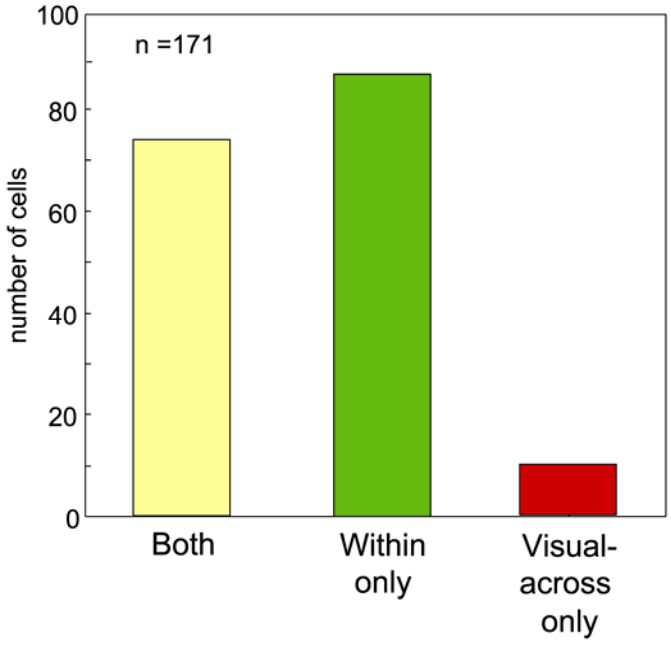


Figure 51. Number of neurons with significant remapping activity in the single-step task. Many neurons had significant activity in both within and visual-across conditions (n=74, yellow bar). An even larger number of cells responded only for the within condition (n=87, green bar). Few neurons had activity in the visual-across condition but not the within condition (n=10, red bar). Significance was determined by comparing average firing rate in the remapping epoch of the single step task (0-200 ms relative to saccade onset) to activity in the corresponding control conditions. These data indicate that many cells remapped the stimulus across visual hemifields.

Section 2: Firing rate for within vs. visual-across updating

Is the magnitude of updating activity equivalent for visual-across and within conditions? The cell in Figure 50 was active for both the within and the visual-across remapping configurations. The visual-across activity, however, appeared to be smaller than the within-hemifield activity. We asked whether the population of neurons demonstrated a bias toward weaker activity in the visual-across as compared to the within condition. For each neuron, we computed the average remapping activity for each condition (within and visual-across; see Appendix). We then plotted

the average activity of each neuron in the within condition against its activity in the visual-across condition (Figure 52). Points falling along the unity indicate that the neuron's response was equally strong for visual-across and within remapping. Most points fall above the line, attesting to increased firing rates for the within condition. This difference in magnitude of the remapped response was highly significant (paired t-test, $p<.00001$). This finding indicates that single neurons are likely to fire more strongly when stimuli are remapped within hemifield as compared to across hemifields.

Next, we expanded on this finding by asking whether the relative difference in response magnitude was evident when we normalized the firing rates. For this analysis, we computed an index value for each neuron. The within-across index was effectively the difference in mean firing rates (within-across), divided by their sum (within+across). We modified this computation to account for the fact that mean remapping activity was adjusted to control for any activity in the saccade-only control (see Appendix). This modified procedure yields smaller index values overall, but critically, it normalizes the data so that all values are between –1 and +1, and each neuron contributes equal weight, regardless of firing rate. Positive values indicate higher firing for the within condition, whereas negative values indicate higher firing for the visual-across condition. We found that index values were skewed significantly toward 1, confirming stronger responses for the within as compared to the visual-across condition (Figure 53; $p<.00001$, signtest).

Finally, we asked whether the relative strength of remapping was equivalent for the two monkeys. We computed the within:across index separately for each monkey; the separate

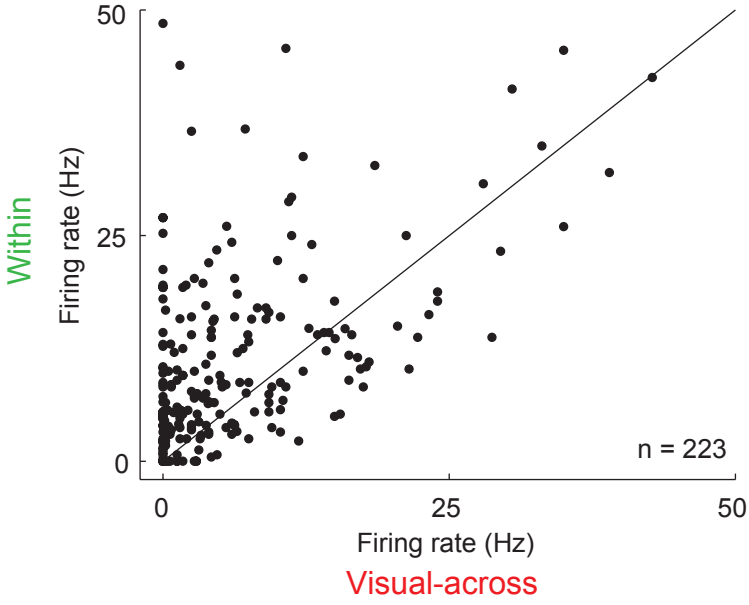


Figure 52. Firing rate in the single-step task. Each point represents a single cell. For each neuron, mean firing rate in the visual-across condition (x axis) is plotted against mean firing rate in the within condition (y axis). For this analysis, we included all visually-responsive neurons, regardless of the significance of remapping activity. Firing rate was computed for each neuron using a 200ms epoch, which began at saccade onset. Points falling along the unity line indicate that both single-step conditions elicited the same magnitude of remapping activity. Most points fall above the line, indicating that neurons fired more strongly for within-hemifield as compared to visual-across updating.

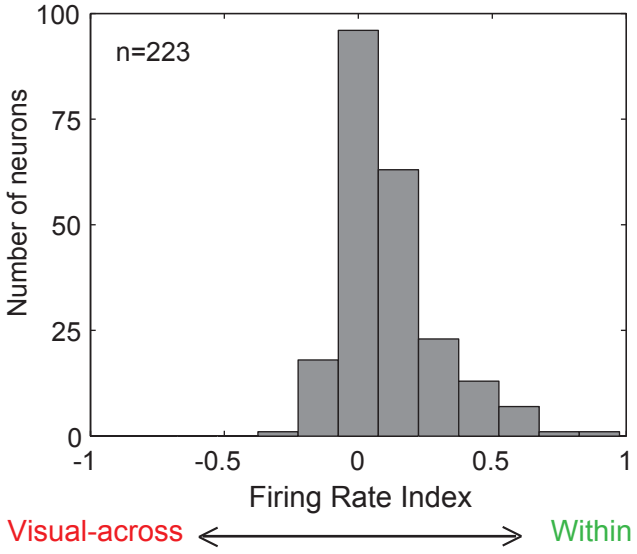


Figure 53. Histogram showing the distribution of index values for the population of neurons shown in Figure 52. The index is computed by comparing the adjusted mean firing rates for the within and visual-across conditions. Index values equal to zero indicate that the neuron fired equally strongly for the two conditions of the single-step task. A value of +1 indicates that the neuron responded only in the within condition; a value of -1 indicates that the neuron responded only in the visual-across condition. The distribution is skewed significantly toward 1 (signtest, $p<.01$). LIP neurons were more active for within-hemifield remapping as compared to visual-across remapping.

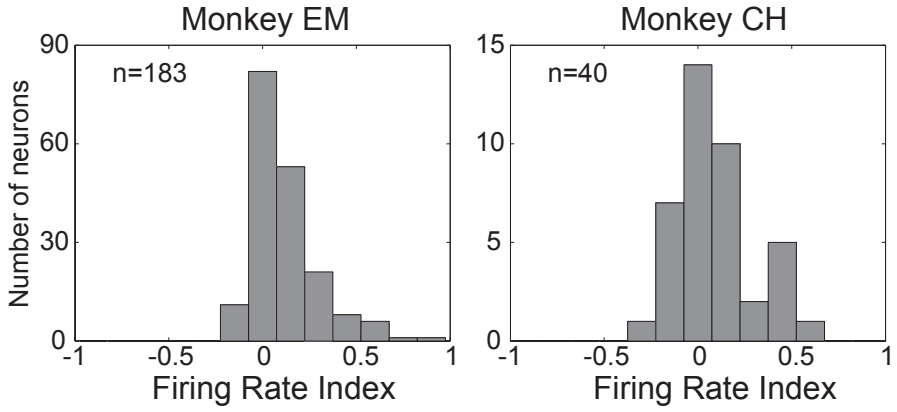


FIgure 54. The same neurons in Figure 53 are replotted separately for monkey EM (left) and monkey CH (right). The distributions of index values from the two monkeys were not

distributions are shown in Figure 54. We found that the distribution of index values was significantly skewed toward 1 in both monkeys (monkey CH $p < 0.01$, monkey EM, $p<.00001$, signtest). Furthermore, the distributions were statistically equivalent for the two monkeys ($p>.30$, K-S test). We conclude that, for both monkeys, the remapping signal of LIP neurons was diminished when stimuli were remapped from one visual hemifield to another, rather than within-hemifield.

Section 3: Latency of remapping activity

In the split-brain monkey, across-hemifield remapping cannot be accomplished by a direct transfer of visual information from one cortical hemisphere to another via the forebrain commissures. The absence of this direct pathway suggests that updating activity in area LIP may appear later for visual-across conditions as compared to within-hemifield conditions. This prompted us to ask whether the latency of updating activity was equivalent for visual-across and within conditions. We addressed this question by measuring the latency of remapping activity of each neuron. We conducted this analysis using neurons that met two selection criteria. First, the neurons had no significant activity in either control task. This selection criterion ensured that we were measuring the latency of remapping activity, rather than the latency of stimulus- or saccade-related activity. Second, the neurons had a detectable latency, as defined with a 20ms averaging window that moved in 2ms increments (Nakamura and Colby, 2000). For each neuron, we determined the neural latency of remapping in each condition (within and visual-across) of the single-step task.

We calculated the latency of remapping activity in 74 neurons that met the selection criteria described above. For each of these neurons, we plotted the latency of within-hemifield remapping activity against the latency of visual-across remapping activity (Figure 55). Points

that fall along the unity line represent neurons with remapping activity that began at the same time for the visual-across and within conditions. The vast majority of points fall below the line, representing neurons in which remapping activity began earlier for the within condition. This difference in neural latency was significant in the population ($p<.01$, paired t-test). These data indicate that single neurons in LIP were apt to exhibit an earlier latency of remapping activity when the stimulus was updated within the same hemifield; latency of remapping activity was delayed when the stimulus was updated across hemifields.

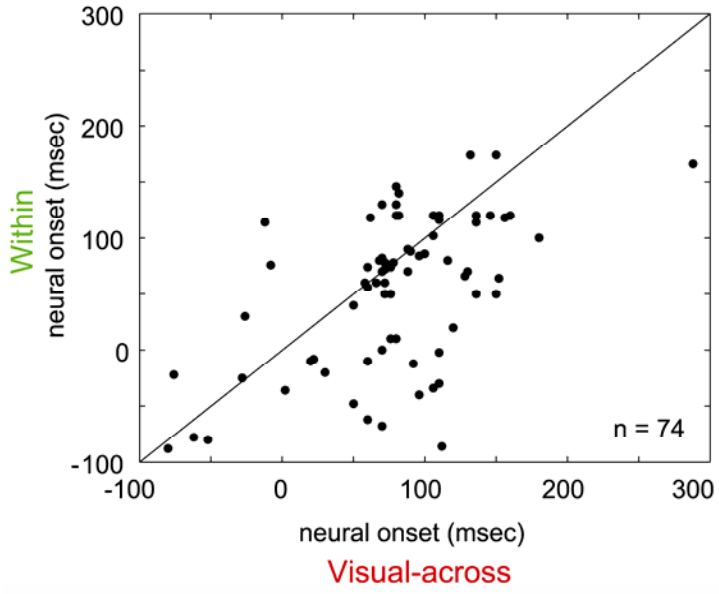


Figure 55. The latency of remapping activity in the single-step task. Each point represents a single cell. For each neuron, onset in the visual-across condition (x axis) is plotted against onset in the within condition (y axis). For this analysis, we included only those neurons that met the following two criteria: first, the latency was definable for both the within and visual-across conditions; and second, there was no significant activity in any control condition. Points falling along the unity line indicate that remapping activity began at the same time for the two conditions. Most points fall below the line, indicating that the onset of remapping activity occurred later for the visual-across condition.

We observed considerable variability in the latency of remapping activity, as seen in Figure 55. These data are in accord with findings in the normal monkey: previous physiological studies have shown a range of neural latencies for remapping in LIP (Quaia et al., 1998). One of the most intriguing observations is that remapping activity can begin surprisingly early. In LIP, FEF, and SC, a subset of neurons begin to respond in the single step task at a time that precedes the expected visual latency of the neuron (Duhamel et al., 1992a; Walker et al., 1995; Umeno

and Goldberg, 1997). These predictive neurons anticipate the new location of the eyes, providing an updated map that does not rely on reafferent visual signals. The neuron shown in Figure 50 exhibited predictive remapping. If this neuron responded according to its visual latency, it would have begun to fire roughly 70ms after the eyes had reached their new position. In other words, it would have shown a reafferent response to the memory trace, as if a stimulus had been presented during fixation. Instead, the neuron began to fire well before this time, indicating a predictive response; in fact, remapping began even before the beginning of the saccade. In the normal monkey, roughly one third of neurons in LIP exhibit predictive remapping activity. We asked whether a similar proportion of neurons in the split-brain monkey had predictive remapping. Further, we asked whether the proportion of predictive and presaccadic responses was similar for within and visual-across conditions. We conducted this analysis by measuring the neural latency for each condition separately, using all cases with a detectable latency in the single-step task and no activity in the corresponding control tasks. This selection method yielded 168 neurons for analyzing the onset of activity for the within condition, and 115 neurons for the visual-across condition.

We found that a majority of neurons – 61% – responded predictively in the single-step task. This proportion is larger than that reported in studies of remapping in LIP of the normal monkey (Duhamel et al., 1992a). Why did we observe predictive remapping more frequently in the split-brain monkey? This difference most likely reflects the timing of the single-step task. Critically, in our paradigm, the stimulus and saccade target appeared 50ms before fixation was extinguished. In previous studies, the stimulus and saccade target appeared exactly at the time when fixation was extinguished. The timing of our single-step task allowed for eye movement planning to begin earlier, and therefore may have hastened the onset of remapping activity. This task difference suggests that the increased percentage of predictive neurons in the split-brain

monkey is not attributable to the absence of the forebrain commissures. The question of greatest interest, however, was whether predictive activity occurred disproportionately for the within condition, as compared to the visual-across condition. We observed no difference: predictive remapping occurred in 63% of cells for the within condition (107/168), and in 59% of cells for the across condition (68/115). These data indicate that neurons in LIP were able to remap the memory trace and predictively, even when the stimulus representation was updated across visual hemifields. Furthermore, we found that remapping began even before the saccade, for both within and visual-across condition. More neurons had presaccadic responses in the within condition (38/169, 22%) than in the visual-across (13/117, 11%). Nevertheless, the observation of presaccadic remapping in the visual-across condition indicates that across-hemifield updating can occur very rapidly in the split-brain monkey.

Section 4: Does remapping activity vary as a function of receptive field location?

In our behavioral experiments, we asked whether performance of the visual-across double-step task improved when T2 was located near the vertical midline. The rationale for the behavioral experiment was that, in the normal monkey, the representation of space in area LIP can extend up to five degrees ipsilaterally. A similar rationale motivated the next analysis of updating activity. Specifically, we asked whether the location of the neuron's receptive field had an impact on the relative magnitude of within and visual-across updating activity. We reasoned that neurons with receptive fields nearer to the midline might show more equivalent remapping activity for the visual-across condition as compared to the within condition. We tested this possibility by plotting the firing rate index of each neuron as a function of the horizontal location of the receptive field (Figure 56). If the difference between visual-across and within activity were smaller when receptive fields were near the midline, we would observe a positive

relationship between the two variables. In other words, index values would be nearer to zero for receptive field locations near the midline (leftward on the x axis); the index values would increase toward +1 as the receptive field distance increased (rightward on the x axis). We did not observe a systematic change in relative firing rate as a function of receptive field location (Figure 56). Instead, there was a striking lack of a relationship between these two variables. This tells us that the strength of visual-across remapping, as compared to within-hemifield remapping, did not depend on the neuron's receptive field location. The implication is that neurons in LIP of the split-brain monkey have access to an updated representation of the visual-across stimulus, whether their receptive fields are proximal or peripheral.

Section 5: Does remapping activity vary as a function of hemisphere?

We next asked whether the strength of remapping activity depended on the recording hemisphere. This question was prompted by our observations in the behavioral experiments. In some cases, we found that performance of the visual-across double-step task varied, depending on whether the sequence was in the right or left visual field. This led us to ask whether neurons in LIP showed evidence of such an asymmetry. We addressed this possibility by analysing data recorded from both hemispheres in monkey CH. We asked whether the distribution of the Within:Across firing rate index was different for neurons recorded from the right hemisphere as compared to the left hemisphere (Figure 57). We found that the distributions of right-hemisphere and left-hemisphere index values were not significantly different from each other

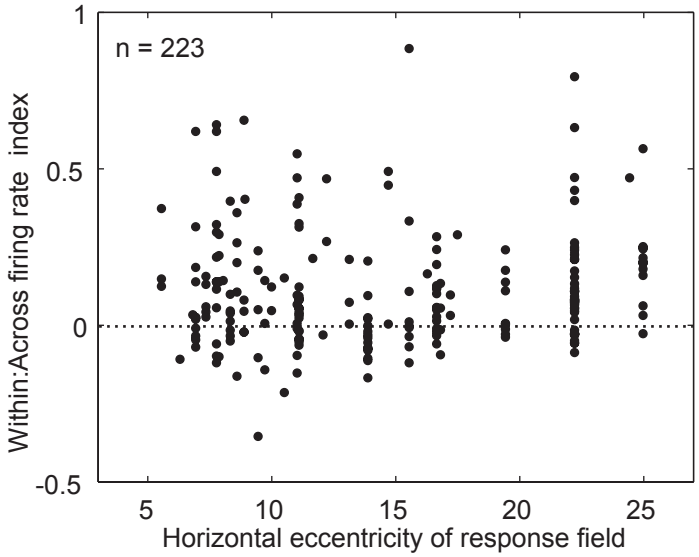


Figure 56. Relative magnitude of remapping activity for the within-hemifield as compared to the visual-across condition, as a function of receptive field location. For each neuron, the index value (y axis) is plotted against receptive field eccentricity (x axis). Positive index values (higher on the y axis) represent greater remapping activity for the within as compared to the visual-across condition of the single-step task. The distribution of index values does not change as receptive field eccentricity increases. These data indicate that neurons with receptive fields both near and far from the midline had similar patterns of remapping activity in the within and visual-across conditions.

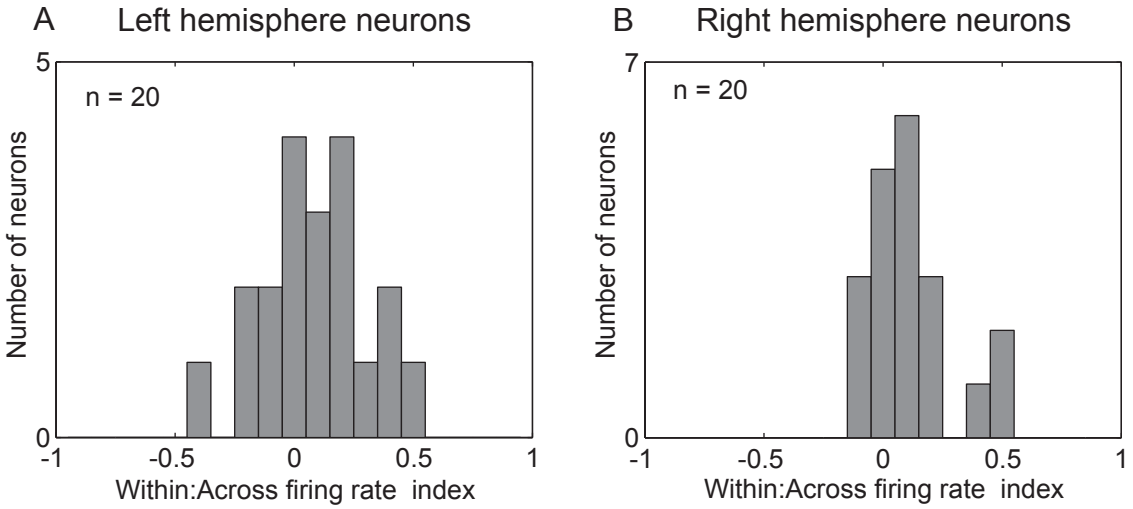


Figure 57. Distribution of the Within:Across index values for neurons recorded from the left (A) and right (B) hemispheres of monkey CH. Positive index values represent greater remapping activity for the within as compared to the visual-across condition of the single-step task The mean index value for left hemisphere neurons was 0.09, and the mean index value for right hemisphere neurons was 0.11. Each of these distributions is skewed toward +1 and did not differ significantly from each other. These data show that the relative magnitude of within-hemifield versus visual-across remapping activity did not vary depending on the recording hemisphere.

(p>.50, K-S test). These results indicate that neurons in both hemispheres had an equal propensity for remapping stimuli across visual hemifields.

Section 6: Magnitude and timecourse of population activity

In the above sections, we have focused on the signals carried by individual neurons. In this final section, we consider the remapping signals in the population activity of area LIP. We constructed population histograms of activity in the single-step task, for the within-hemifield and visual-across conditions. For these histograms, we included all neurons with no significant activity in either control task (N=91). Each neuron contributed to both the within-hemifield and visual-across population histograms. We found a robust population response for both conditions of the single-step task (Figure 58). The magnitude of the remapping signal is greater for the within-hemifield condition (green line) than the visual-across condition (red line). In the within-hemifield condition, remapping activity begins even before the onset of the eye movement, and peaks roughly 125ms after the beginning of the saccade. In the visual-across condition, remapping activity begins after saccade onset, with peak activity coinciding with that of the within condition.

The population activity illustrated in Figure 58A corroborates the key results described in the sections above. In area LIP of the split-brain monkey, remapping activity is diminished when a stimulus is updated across visual-hemifields as compared to within-hemifield. Visual-across remapping activity also has a later onset relative to within-hemifield remapping activity. The diminished strength of remapping activity in the across-hemifield condition is readily attributable to the absence of the direct commissural link between the cortical hemisphere. Previous studies of remapping in the normal monkey have employed across-hemifield

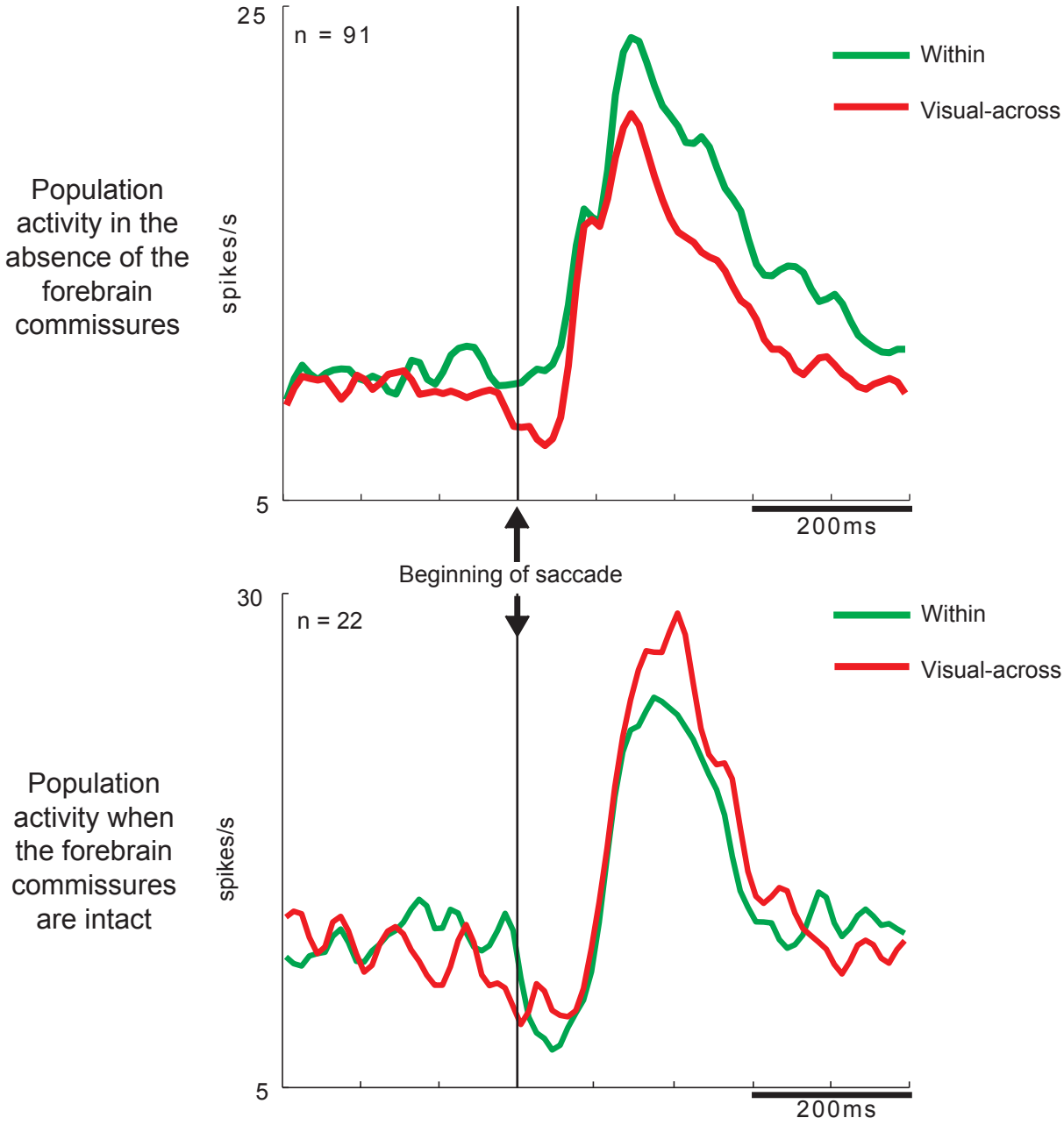


Figure 58. Average population activity in the single-step task, for within-hemifield (green) and visual-across (red) conditions. Activity is shown for the two split-brain monkeys (panel A) and for an intact monkey (panel B). Data are aligned at the onset of the saccade from FP1 to FP2 (vertical line). Each population is comprised of all neurons that did not exhibit significant activity in either control task. Panel A: In the split-brain monkeys, population activity in the within condition (green) increased roughly 100ms before saccade onset, indicating a predictive (as well as presaccadic) remapping of the memory trace. Activity was suppressed around the time of saccade execution, and resumed roughly 50ms after saccade onset. In the visual-across condition (red), remapping activity began roughly 50ms after saccade onset. Peak activity in the visual-across condition occurred simultaneously with the peak of within-hemifield remapping signal. Panel A shows that, in the split-brain monkey, 1) population activity in LIP is greater for within-hemifield than visual-across remapping; 2) population activity in LIP begins earlier when stimuli are remapped within the same hemifield; 3) there is nevertheless a substantial neural signal in relation to visual-across remapping. Panel B: In the normal monkey, across-hemifield remapping activity is not diminished or delayed relative to within-hemifield remapping.

configurations as the standard single-step paradigm, and show that area LIP neurons exhibit robust across-hemifield activity (Duhamel et al., 1992a; Kusunoki and Goldberg, 2003). We further verified that remapping in the normal monkey is not diminished for across-hemifield as compared to within-hemifield conditions, using the same paradigm employed in the present study. We recorded from neurons in area LIP of a rhesus macaque whose forebrain commissures were intact. As shown in the population histogram from this monkey (Figure 58B), remapping activity in the across-hemifield condition (red line) was neither diminished nor delayed relative to the within-hemifield condition (green line). These data provide an unambiguous demonstration, using the identical paradigm, that the compromised across-hemifield remapping in our split-brain experiments is indeed the result of the absence of the forebrain commissures. The most essential finding, however, is that the population of neurons in LIP of the split-brain monkey nevertheless encodes the updated location of the stimulus in the visual-across condition (Figure 58A). In conclusion, visual-across remapping activity persists in the absence of the forebrain commissures, suggesting the presence of alternative pathways for the interhemispheric transfer of visual information.

PART II. IS THERE EVIDENCE OF MOTOR-ACROSS REMAPPING IN THE SPLIT BRAIN?

The second aim of our physiological experiments was to characterize LIP activity when updating presumably required the interhemispheric transfer of a corollary discharge signal. In our behavioral experiments, we found that the monkeys were effectively unimpaired when performing the motor-across condition of the double-step task. This finding suggested that LIP neurons would exhibit robust updating activity in the motor-across condition of the single-step task. We embarked on this experiment later in the project, recording from 116 neurons in the

motor-across condition in monkey EM. For these neurons, the motor-across condition was interleaved randomly with the visual-across and within conditions. In the following sections, we compare remapping in the motor-across condition to both the within-hemifield and the visual-across conditions.

Section 1: Are LIP neurons active for motor-across updating?

We found that many LIP exhibited significant updating activity in the motor-across condition of the single-step task. One such neuron is shown in Figure 50. We previously described this neuron's activity in the within (panel D) and visual-across conditions (panel E), noting that it exhibited remapping in both conditions, though activity was reduced in the visual-across. This same neuron exhibited strong and significant activity in the motor-across condition (panel F). Of the 98 neurons with significant remapping in at least one condition, we found that more than half had significant neural activity in the motor-across condition (52/98). These same neurons also had significant activity in the visual-across condition. Nearly all neurons had activity in the within condition (93/98). The smaller number of neurons with significant activity in the motor-across condition suggests that the updating signal may be diminished when the spatial updating requires an interhemispheric transfer of the corollary discharge signal. We addressed this possibility in the next analysis.

Section 2: Magnitude of motor-across remapping activity

We next asked whether the magnitude of remapping activity in LIP differed for the motor-across condition, as compared to the within and visual-across conditions. The smaller number of neurons with significant remapping activity in the motor-across condition implies that activity was greatly diminished relative to the within condition. We found, however, a significant but

small reduction in the magnitude of remapping activity for the motor-across condition as compared to the within condition ($p<.05$, paired t-test). Remapping activity in these two conditions is plotted for each neuron, in Figure 59A. On average, the adjusted firing rate for remapping in the motor-across condition was 12.3 Hz, compared to 13.8 Hz in the within condition. The small difference in firing rate between these conditions (1.5Hz on average) seems to be at odds with the finding that nearly twice as many neurons had significant remapping activity in the within as compared to the motor-across condition. This suggests that remapping activity in the motor-across condition frequently approached, but did not meet, the significance criterion. We further evaluated the relative difference between the motor-across and within conditions by creating a distribution of index values, in which the contributions of individual neurons were equally weighted. We used the same procedure described for comparing the within and visual-across sequences in Part I. Positive values indicate stronger activity in the within condition, whereas negative values indicate stronger activity in the motor-across condition. The distribution of these values is skewed significantly toward +1 (mean=.036, $p<.05$, signtest; Figure 59B). This analysis confirms a slight yet systematic reduction in remapping activity for the motor-across as compared to the within condition.

We completed the analysis of remapping activity in the motor-across condition by asking whether it differed significantly from that in the visual-across condition. We found that neural activity was significantly stronger for the motor-across condition ($p<.001$, paired t-test). This is evident in Figure 59C, where firing rate in the motor-across condition (y axis) is plotted against firing rate in the visual-across condition (x axis), for each neuron. Average neural activity for

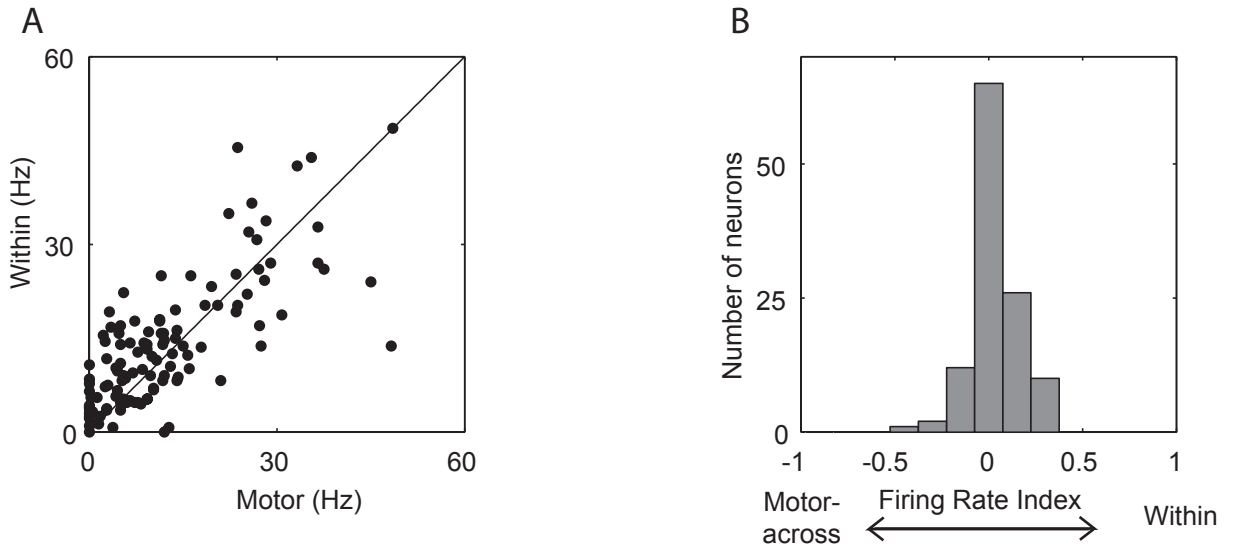


FIgure 59, panels A and B. Remapping activity in the single-step task, for the motor-across condition as compared to the within condition. In panel A, average remapping activity in the motor-across condition (x axis) is plotted against activity in the within condition (y axis). The distribution of points is primarily centered on the unity line, but more points fall above the line, indicating slightly higher firing rates for the within condition (mean = 13.8Hz for within, 12.3 for motor-across). This is evident in the distribution of index values shown in panel B. The distribution is skewed toward 1 (mean = .03), confirming slightly stronger activity in the within condition relative to the motor-across condition. These data show that, on average, the motor-across condition elicited remapping activity that was slightly diminished in magnitude compared to that of the within-hemifield condition.

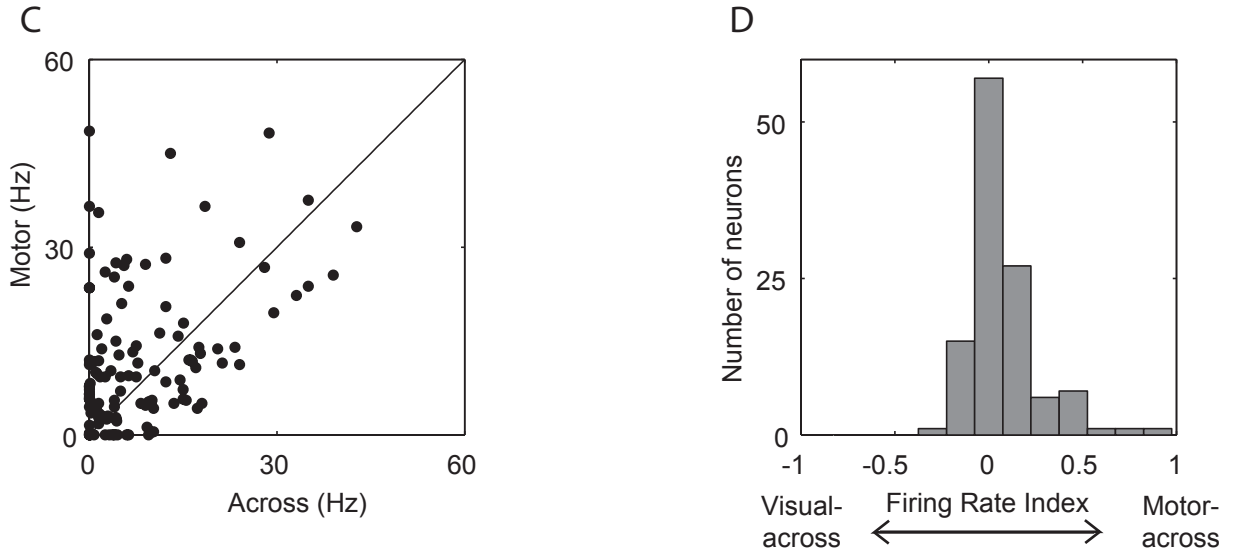


Figure 59, panels C and D. Remapping activity in the single-step task, for the motor-across condition as compared to the visual-across condition. In panel C, average remapping activity in the visual-across condition (x axis) is plotted against activity in the motor-across condition (y axis). Most points fall above the unity line, indicating higher firing rates for the motor-across condition. This is evident in the distribution of index values shown in panel B. The distribution is skewed toward 1 (mean = .07), indicating that remapping activity was stronger in the motor-across condition relative to the visual-across. These data show that, on average, the motor-across condition elicited more robust remapping activity than the visual-across condition.

the visual-across condition was 8.4 Hz, compared to 12.3 Hz in the motor-across condition. We again computed a firing rate index to characterize the relative difference between the two conditions. In this index, positive values indicate stronger activity in the *motor-across* condition, whereas negative values indicate stronger activity in the visual-across condition. The distribution of these index values, shown in panel D, was significantly skewed toward +1 (mean=.074; $p<.05$, signtest), confirming that LIP neurons were biased toward stronger remapping activity in the motor-across condition.

These observations indicate that neurons in LIP exhibit robust remapping in the motor-across condition; remapping activity in this condition was only slightly diminished relative to the within condition. Direct comparison of the two interhemispheric conditions – motor-across and visual-across – demonstrated that remapping signals in LIP were significantly stronger in the motor-across condition. This indicates that the interhemispheric transfer of corollary discharge signals is relatively unaffected by the absence of the forebrain commissures.

SUMMARY AND DISCUSSION

We assessed neural activity associated with spatial updating in the split-brain monkey, using the single-step task. We asked whether neurons in area LIP remap stimuli in two conditions that require the interhemispheric transfer of either visual or corollary discharge signals. We compared the neural activity in each of these conditions to activity in a condition in which both the visual and corollary discharge signals were transferred within the same hemisphere. Two main conclusions emerge from this experiment.

First, we demonstrated that LIP neurons in the split-brain monkey can still remap stimulus representations across visual hemifields. This important and unexpected finding indicates that visual representations can be updated from one cortical hemisphere to the other,

even when the most prominent route for interhemispheric transfer has been removed. Furthermore, we found that the relative difference in neural activity for the within and across-hemifield conditions did not vary as a function of receptive field eccentricity or recording hemisphere. This indicates that the capacity to remap stimulus representations across visual hemifields was not unique to neurons that represent only certain portions of the visual field. Rather, across-hemifield remapping was similarly robust for neurons with receptive fields both near to and far from the vertical meridian, in both visual hemifields. These observations highlight the functional capacities of the system for across-hemifield remapping in the split-brain. We also found evidence that across-hemifield remapping was compromised as compared to within-hemifield remapping. On average, neural activity in the across-hemifield condition was smaller in magnitude and occurred at a longer latency than in the within condition. These observations suggest that a more complex pathway supports the interhemispheric transfer of memory traces in the absence of the forebrain commissures.

Our second main finding is that LIP neurons exhibited robust remapping when the transfer of visual information in one hemisphere was initiated by corollary discharge signals arising from the opposite hemisphere. The magnitude of this remapping activity was only slightly smaller on average than in the comparable within condition, in which corollary discharge signals were communicated intrahemispherically. Furthermore, direct comparison of the two interhemispheric conditions demonstrated that neural activity was substantially greater when updating required the interhemispheric transfer of *motor* signals, as compared to the interhemispheric transfer of *visual* signals. We conclude that, in the absence of the forebrain commissures, corollary discharge signals from a single hemisphere can be communicated readily to update stimulus representations in both hemispheres.

Chapter 4: Behavior and physiology of the double-step task

OVERVIEW

In the double-step physiology experiment, we address three main questions that bring together the behavioral and physiological findings of the two previous chapters.

In Part I, we characterize the monkeys' performance on the double-step task during recording sessions. Specific double-step sequences were designed for each neuron, according to the location of the receptive field. We asked whether performance is impaired when updating requires the interhemispheric transfer of visual signals or corollary discharge signals. We found that the monkeys continued to perform the visual-across sequences less accurately than the within-hemifield sequences. In contrast, the monkeys showed little impairment for the motor-across sequences.

In Part II, we characterize the neural activity in parietal cortex associated with the double-step task. We asked whether neurons in LIP of the split-brain monkey exhibit remapping activity in the double-step task, for the within, visual-across, and motor-across conditions. In accord with the single-step findings, we observed significant remapping activity in LIP in all three conditions. Remapping activity was diminished, however, for the visual-across condition.

Finally, in Part III, we evaluate the relationship between the behavioral and physiological data. In particular, we asked: does remapping activity in area LIP correlate with performance of the double-step task? We found that the monkeys' performance of the double-step task corresponded to neural activity at the population level, though not at the level of single neurons.

APPROACH

In the sections that follow, we describe the behavioral performance and neural activity associated with double-step sequences during the recording of 216 single neurons in area LIP. We use the term 'session' to refer to the recording of a single neuron. In each session, we recorded a block of trials in the double-step task, after obtaining data in the control tasks and single-step task. In each block, we obtained a minimum of twelve trials for each condition (within, visual-across, and, where applicable, motor-across). The conditions were randomly interleaved. This design allowed for the comparison of neural activity performance of the double-step conditions within each session. In Parts I and II, we first describe comparisons of the visual-across and within condition, which we assessed in both monkeys (monkey EM, N=180; monkey CH, N=36), before characterizing performance of the motor-across condition, which we assessed in monkey EM (N=116). In Part III, we focus only on the comparison of within and visual-across updating.

PART I: PERFORMANCE OF THE DOUBLE-STEP TASK DURING PHYSIOLOGICAL RECORDING.

Predictions for accuracy and reaction time of double-step performance

In the behavioral studies described in Chapter 2, we discovered that both monkeys were eventually able to perform the visual-across condition of the double-step task. We nevertheless found that performance of the visual-across sequences remained less stable than performance of the within-hemifield sequences. This was evident in two observations. First, the monkeys continued to show decreased accuracy for the visual-across sequence in some quadrants, even after extensive experience (Figure 29). Second, when we introduced a novel spatial configuration, performance of the visual-across sequences deteriorated more than that of the within or central sequences (Figure 38). This second observation has particular implications for double-step performance during recording sessions. For each neuron, the spatial configuration of

the task was necessarily determined by the location of the response field. As a result, the monkeys encountered new spatial configurations of the double-step task with each session. We therefore predicted that the monkeys would continue to demonstrate an impairment for the visual-across sequences as compared to the within-hemifield sequences.

We further asked whether impairment of the visual-across sequences would be evident not only in reduced accuracy, but also in prolonged reaction times. In our initial behavioral testing, we had found that the monkeys were slower to initiate the visual-across sequences. Subsequently, however, we made two observations, which suggested that latencies for the visual-across sequences would not be prolonged during the recording sessions. First, by the end of behavioral testing, the monkeys were no longer delayed in saccade initiation in the standard visual-across sequences. On average, latencies for the first saccade were equivalent for the within and visual-across sequences, and latencies for the second saccade were faster for the visual-across as compared to the within sequence (Figure 32). Second, when we introduced a new spatial configuration, latencies for the visual-across sequences were not selectively prolonged (Figure 38). These observations raised the possibility that reaction times for the visual-across sequences would not be selectively slowed during physiological recording.

Performance of Within vs. Visual-Across conditions of the double-step task

We found that the monkeys exhibited impaired performance in the visual-across condition. An example of double-step performance during recording from a single neuron is shown in Figure 60. The eye traces from the first ten trials are plotted for the within and visual-across conditions. Black lines represent correctly executed trials, and pink lines represent incorrect trials. The

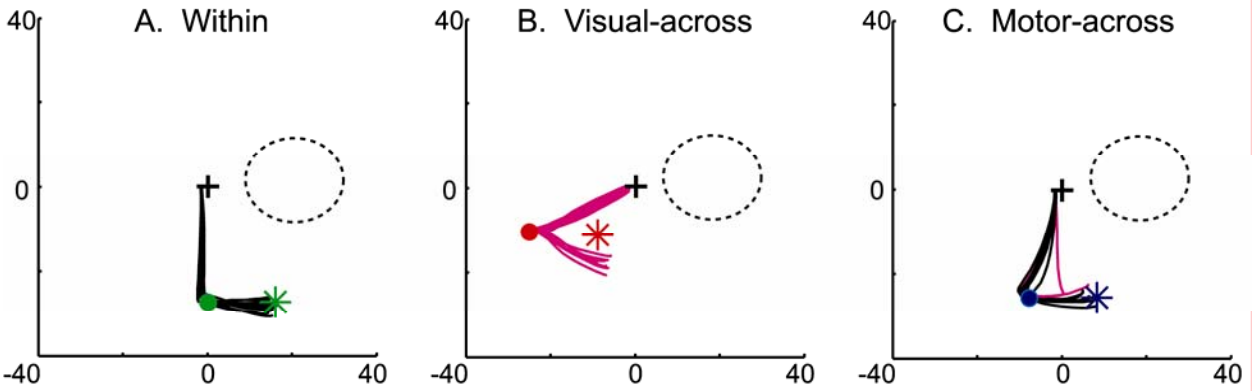


Figure 60. Eye traces from the first ten trials of a double-step configuration during recording of a single neuron. The neuron under study had a response field centered 18 degrees to the right of fixation. In each panel, the receptive field is represented by the dashed circle, the crosshair represents central fixation, the small circle represents the T1 location, and the asterisk represents the T2 location. Traces from correct trials are shown in black, from incorrect in pink. Eye traces in each panel correspond to one of the test conditions: panel A, within-hemifield; panel B, visual across; panel C, motor-across. The monkey performed all ten of the first trials correctly for the within condition (panel A) and incorrectly for the visual-across condition (panel B). The monkey performed nearly all the motor-across sequences correctly (panel C). These data show that double-step performance was accurate when the stimulus trace was updated within a single hemifield (panels A, C), but not when updating required the transfer of visual information across hemifields (panel B). Furthermore, performance was accurate when the stimulus location was updated in conjunction with a saccade into the opposite hemifield (panel C). These data are representative of those collected during physiological recording sessions: there was greater impairment in the performance of visual-across than in the within or motor-across double-step sequences.

monkey's performance in the within condition (panel A) was very accurate. In contrast, the monkey was unable to perform the visual-across sequence correctly (panel B). For this and every recording session, we quantified the accuracy and latency of the monkeys' double-step performance using the same methods described in Chapter 2. Specifically, we computed the angular and distance error of the second saccade, and reaction times for both saccades. For each condition, we calculated average error and latency using all double-step trials in which the monkey reached T1 successfully. For the double-step trials shown in Figure 60, average angular error for the visual-across condition was 20.5° greater than that of the within sequence, and average distance error was 4.0° greater. Saccade reaction times, however, were not selectively prolonged for the visual-across condition. The monkey initiated the first saccade at a latency of 160ms for both conditions (within: 160.2ms, visual-across: 159.9ms). Initiation of the second

saccade was nearly 30ms faster for the visual-across condition (within: 116.6ms, visual-across: 88.0ms). This surprisingly short latency suggests that the monkey generated the visual-across sequences in a stereotyped manner.

How representative is the double-step performance illustrated in Figure 60? We computed average accuracy and latency measures for double-step performance during the recording of 216 neurons in area LIP. For each session, we plotted the saccade measures for within-hemifield sequences against those for the visual-across sequences (Figure 61). Accuracy measures are shown in the top panels (A-D), and latency measures are shown in the bottom panels (E-H). We found that, on average, performance was less accurate for the visual-across sequences. For both angular error (panel A) and distance error (panel B), most points fall below the unity line. These points represent recording sessions in which the monkeys had increased error on the visual-across as compared to the within condition. This difference was highly significant for both accuracy measures ($p<.0001$, paired t-test).

We converted these raw accuracy measures into index values that reflected the relative accuracy for within and visual-across sequences. In this accuracy index, positive values indicate that performance was more accurate for the within sequence. Negative values indicate that performance was more accurate for the visual-across sequence. The distributions of index values were skewed toward 1 for both monkeys ($p<.001$, K-S test), and were not significantly different from each other ($p>.05$, K-S test). The combined data, shown in panels C and D of Figure 61, show that the monkeys performed the within-hemifield sequences more accurately than the visual-across sequences. These data provide compelling evidence that, during physiological

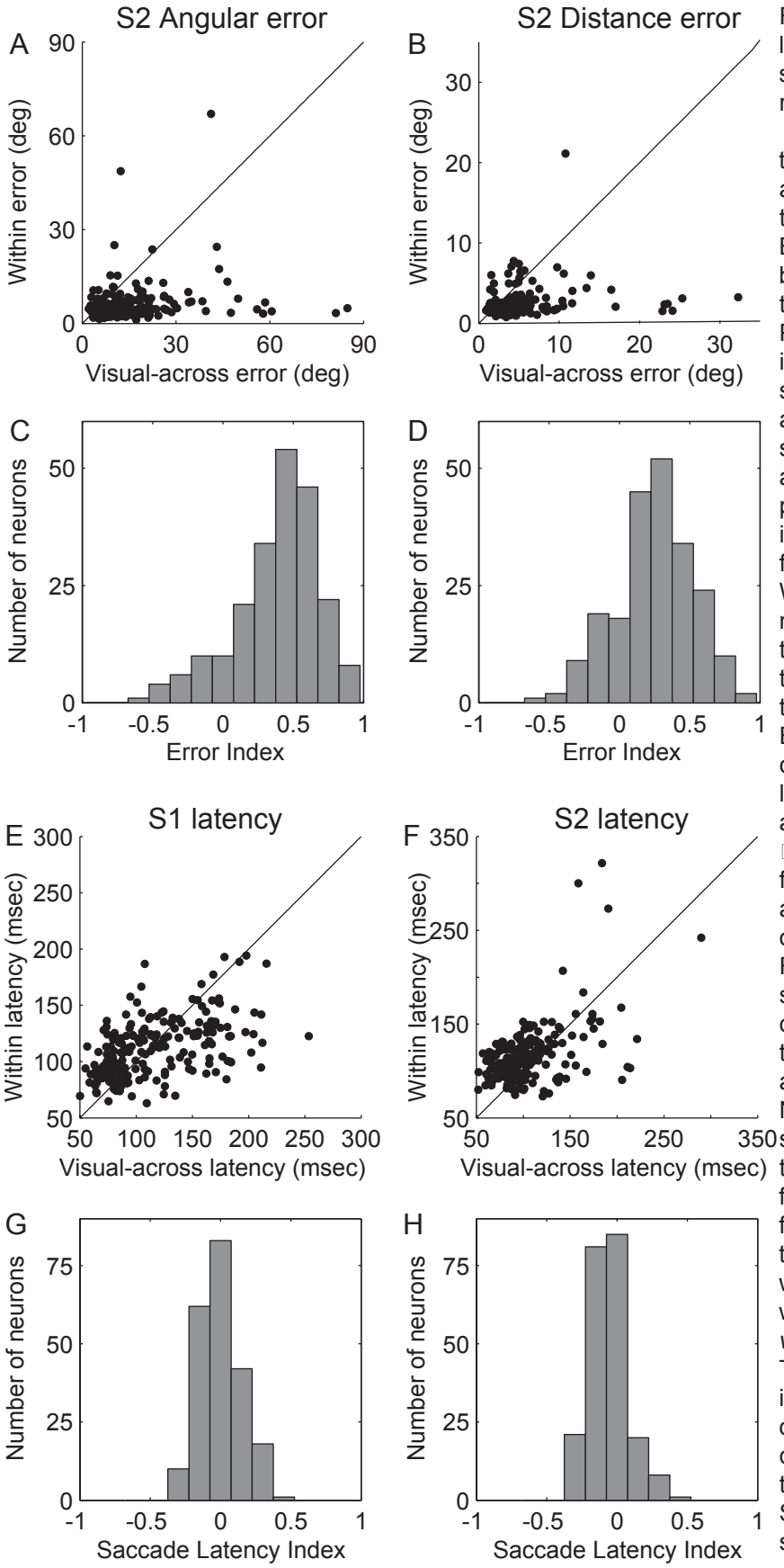


Figure 61. Accuracy and latency measures of double-step performance during recording sessions.

In panels A and B, error for the visual-across condition (x axis) is plotted against that of the within condition (y axis). Each point represents behavioral data acquired during the recording of a single neuron. Points falling along the unity line indicate that performance was similar for the within and visual-across conditions of the double-step task. For angular error (A) and distance error (B), most points fall below the line. This indicates that error was greater for the visual-across condition. We computed an index for each measure, which ranged from -1 to +1. Positive values indicate that performance was better for the within condition (less error). Error indices in panels C and D confirm that performance was less accurate for the visual-across than within condition.

In panels E and F, latencies for the visual-across condition (x axis) are plotted against those of the within condition (y axis). For both S1 and S2 latency scatterplots, points are distributed more equally around the unity line than were the accuracy measures. Nonetheless, there were significant differences between the condiitons. Reaction times for S1 were significantly faster for the within as compared to the visual-across condition, whereas reaction times for S2 were significantly faster for *visual-across* than for within. The distributions of latency index values (panels G, H) confirm these results. The S1 distribution was skewed slightly toward positive values, while the S2 distribution was skewed slightly toward negative values.

recording, the monkeys continued to demonstrate significant impairment in the visual-across condition of the double-step task.

Impairment of the visual-across condition was evident in the measures of accuracy of double-step performance, but was less apparent in measures of saccade latency. For each session, we plotted the latency measures for within-hemifield sequences against those for the visual-across sequences (Figure 61, panels E and F). Points below the line represent sessions in which latency was prolonged for the visual-across condition. Points above the line represent sessions where latency was prolonged for the within condition. The scatterplot of S1 latency suggests a slight delay in the reaction time of visual-across sequences, with more points falling below the line (panel E). Average S1 latency from all recording sessions was 113.5+-1.8ms for the within condition, and 118.8+-2.8ms for the visual-across condition. This difference was significant ($p<.05$, paired t-test). For S2 latency, more points appear above the unity line, suggesting slower S1 initiation in the within condition than in the visual-across condition (panel F). This slowing was significant; in other words, reaction times were significantly *faster* for the visual-across condition. Average S2 latency from all sessions was 116.3+-2.3ms for the within condition, and 105+-2.4ms for the visual-across ($p<.001$, paired t-test). This observation is in keeping with our findings at the end of behavioral testing: S2 latencies for the visual-across condition were no longer delayed, and were actually faster than those of the within condition. This suggests that the monkeys employed an automated strategy to perform the visual-across sequences. Such a strategy was likely easier to adopt during physiological recording than during initial behavioral testing, because the sequences were far more predictable. In most cases, the monkeys performed only two sequences interleaved (within and visual-across), and the location of the first target always predicted the location of the second target.

We next computed an index value for saccade latencies in each session. As with the indices described above, positive values indicate faster performance of the within condition. For the first saccade, the mean index value was slightly positive (0.0050; Figure 61, panel G). For the second saccade, the mean index value was slightly negative (-0.058; panel H). Both these distributions were significantly different from zero. These data tell us that, although the monkeys performed the visual-across sequences less accurately, reaction times for the first and second saccades were not systematically prolonged. On average, the monkeys initiated the first saccade more slowly for the visual-across than for the within condition, whereas they initiated the second saccade more quickly.

Performance of the motor-across condition of the double-step task

Our initial behavioral experiments revealed little evidence of impaired performance for motor-across sequences of the double-step task. Accordingly, we expected that the monkey would generate these sequences accurately during physiological recording sessions. Eye traces from a single recording session suggest that this was indeed the case (Figure 60). In this recording session, we obtained double-step data from all three conditions. Data from the within and visual-across condition, described above, illustrate accurate performance of the within (panel A) but not the visual-across condition (panel B). Eye traces from the motor-across condition show that the monkey performed all but one of these sequences correctly (panel C).

The single example shown in Figure 60 suggests that the monkey's performance of the motor-across condition was on par with performance of the within condition, and better than performance of the visual-across condition. We asked whether this same pattern held for all recording sessions. To do this, we computed the accuracy and latency measures for sessions in which we obtained data from all three conditions (monkey EM, N=116). We separately

compared performance of the motor-across condition to that of the within condition (Figure 62) and the visual-across condition (Figure 63).

The monkey's performance was quite accurate for the within and motor-across sequences, as shown in Figure 62 (panels A, B). For most sessions, the angular trajectory of the second saccade was within ten degrees of the ideal direction (panel A, points clustered near bottom left). The final endpoints of motor-across and within sequences were also very accurate overall, falling within three degrees of the final target (panel B, points clustered near bottom left). We nevertheless found significant conditional differences for both measures of accuracy. On average, directional accuracy was slightly worse for the motor-across as compared to the within condition (panel A, more points fall below the unity line). In contrast, the final endpoint accuracy was slightly worse for the within condition (panel B, more points fall above the unity line). Both of these differences were statistically significant ($p<.05$, paired t-test). These seemingly contradictory results can be understood in the following way. For the within sequences, the direction of the second saccade was computed very accurately, but the monkey was more likely to either undershoot or overshoot the target location than in the motor-across condition. For the motor-across sequences, the direction of the second saccade was computed less accurately, but the final endpoint came closer to the target location than in the within-hemifield condition. The conclusion of the data in Figure 62 is that, during most recording sessions, the monkey's performance on the motor-across condition was not strongly impaired relative to the within condition.

Given the accurate performance of the motor-across sequences described above, it is no surprise that performance of the visual-across condition was impaired by comparison. In Figure

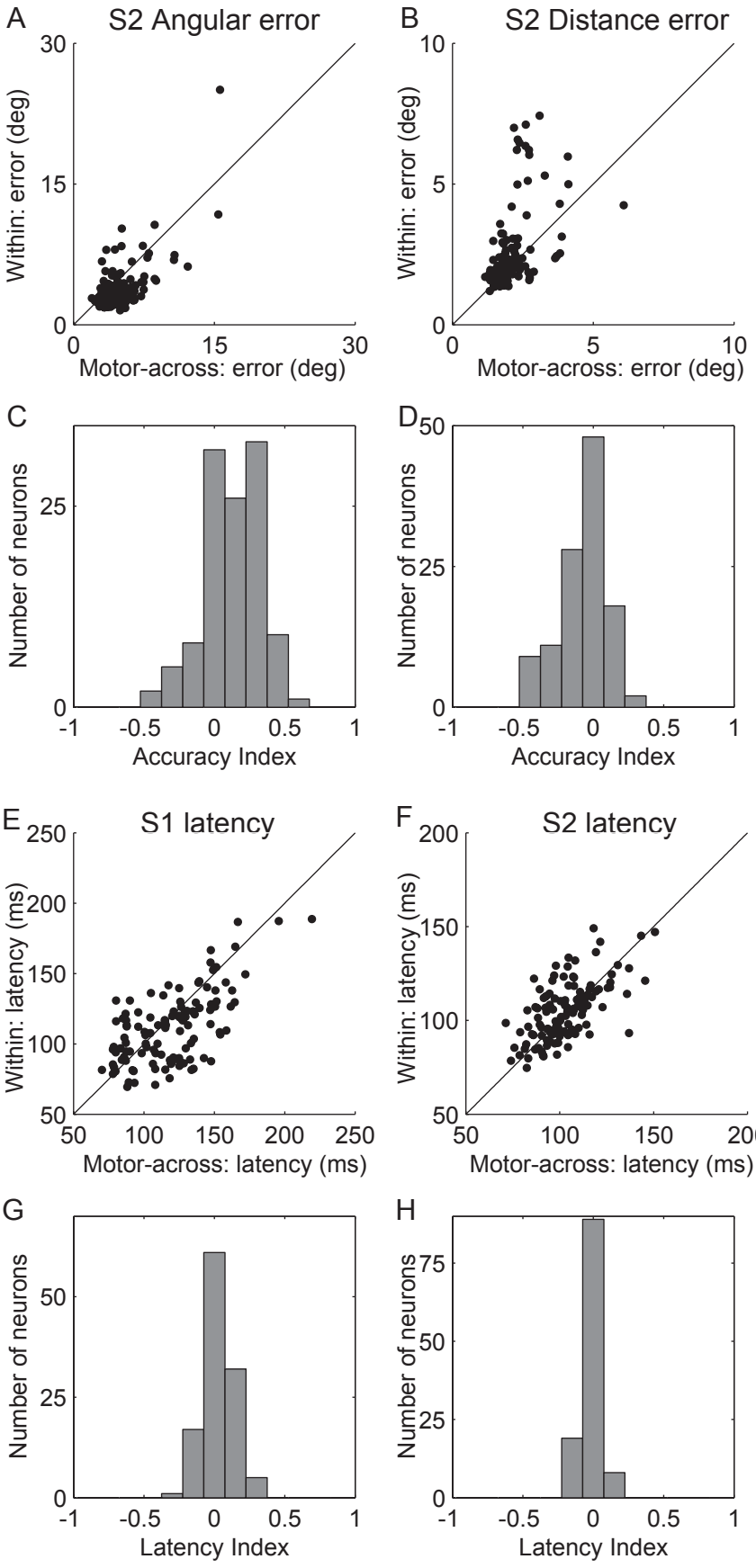


Figure 62. Accuracy and latency measures of double-step performance during recording sessions: comparison of within and motor conditions. Conventions as in Figure 61.

In panels A and B, error for the motor-across condition (x axis) is plotted against that of the within condition (y axis). For angular error, more points fall below the unity line, indicating that directional accuracy was worse for the motor-across condition. For distance error, however, more points fall above the line, indicating that the final saccade endpoint was less accurate for the within condition. These observations are borne out in the histograms of index values (panels C and D). Error indices were skewed toward +1 for angular error, (more accurate for within), and were skewed toward -1 for distance error (more accurate for motor-across). In general, these data indicate that for motor-across sequences, the angle of S2 was not accurately computed, yet the final endpoint was quite accurate.

In panels E and F, latencies for the motor-across condition (x axis) are plotted against those of the within condition (y axis). For S1 latency, more points fall below the unity line, indicating slower reaction times for the motor-across condition (panel E). This is confirmed by the positive skew of the index values for S1 latency (panel G). For S2 latency, most points fall near the unity line, indicating no difference in initiation time for the second saccade (panel F). This is confirmed by the fact that most index values are at 0 (panel H).

Taken together, these data indicate that the monkey's performance of the motor-across condition was largely unimpaired.

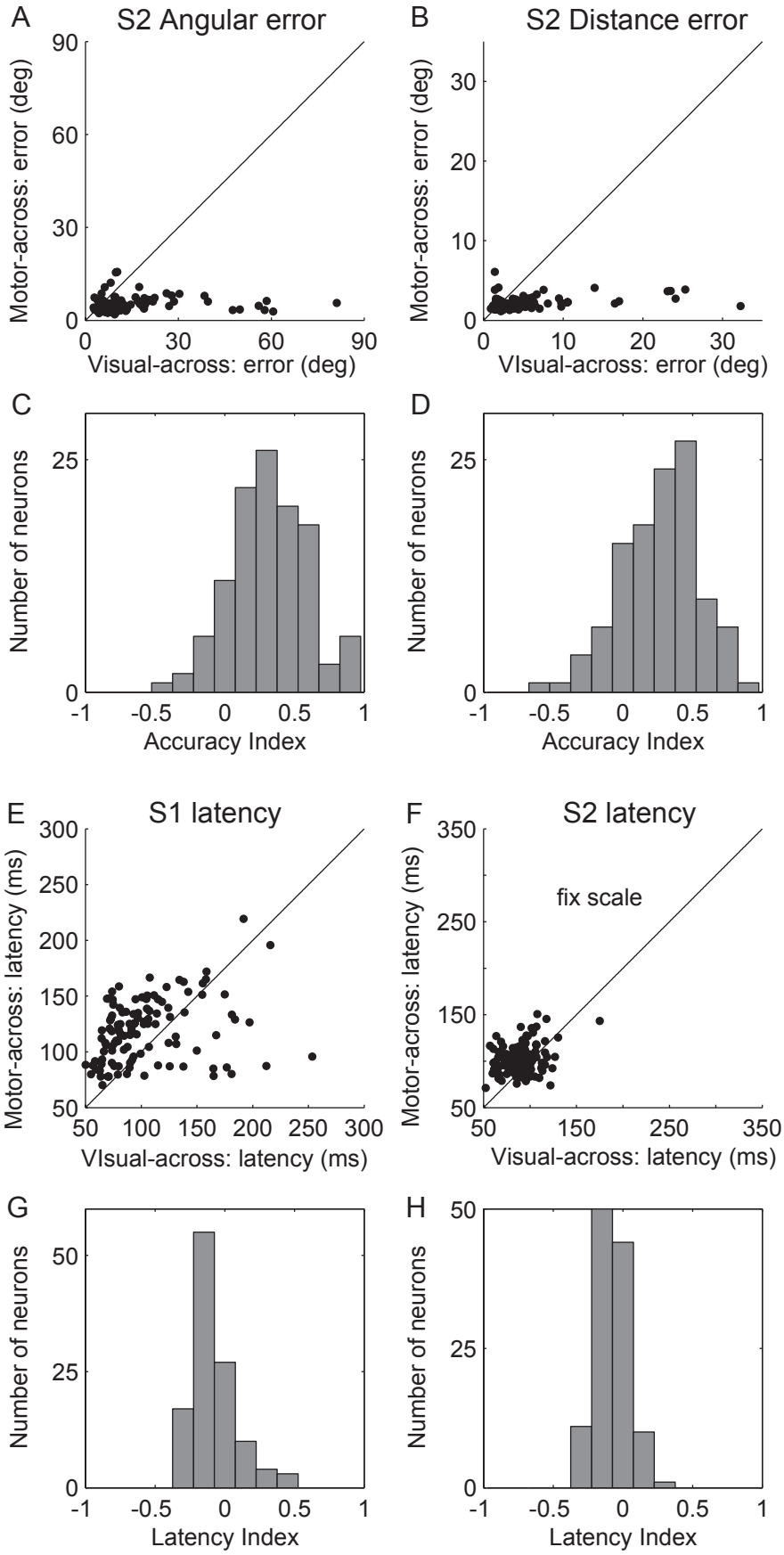


Figure 63. Accuracy and latency measures of double-step performance during recording sessions: comparison of motor-across and visual-across conditions. Conventions as in Figure 61.

In panels A and B, error for the motor-across condition (x axis) is plotted against that of the within condition (y axis). For both measures, error was greater for the visual-across as compared to the motor-across condition. Both error indices were skewed toward +1 In general. These data confirm that the monkey was better at performing the motor-across as compared to the visual-across sequences of the double-step task.

In panels E and F, latencies for the visual-across condition (x axis) are plotted against those of the motor-across condition (y axis). For both the first and second-saccade latencies, more points in the scatterplot fall above the line. This indicates that the monkey was slower to initiate eye movements in the motor-aross condition. The distributions of index values (panels G, H) confirm this, as they are centered toward -1. For these recording sessions, then, the monkey was actually faster to initiate the visual-across as compared to the motor-across sequences. Performance nevertheless was less accurate for the visual-across sequences.

63, error measures for the motor-across condition are plotted along the y axis, and error measures for the visual-across condition are plotted along the x axis. Most points are below the line, indicating increased angular error (panel A) and increased distance error (panel B) for the visual-across condition. Both differences were statistically significant ($p<.01$, paired t-test). By contrast, reaction times were not significantly slower for the visual-across condition. For the first saccade, latencies were faster on average for the visual-across as compared to the motor-across condition (panel E; 105ms for visual-across, 119ms for motor-across). This same conditional difference was evident for the second saccade (panel F; 89ms for visual-across, 103ms for motor-across). The faster reaction times for the visual-across sequence may again indicate that the monkey was performing this condition in a more stereotyped fashion.

In summary, the monkeys' performance of the double-step sequences during recording sessions was impaired for sequences that required across-hemifield updating of a memory trace. Performance was relatively unimpaired for sequences in which updating presumably required an interhemispheric transfer of an oculomotor command. These findings parallel our initial behavioral results in Chapter 2.

PART II: DO NEURONS IN LIP EXHIBIT REMAPPING ACTIVITY IN THE DOUBLE-STEP TASK?

We characterized the remapping activity of each neuron during the double-step task, using the approaches employed for the single-step task. Our expectation was that neurons would exhibit remapping activity in all three conditions of the double-step task, just as they had for the single-step task. We first describe remapping activity for the visual-across condition of the double-step task, as compared to the within condition. We then provide a brief description of activity for the motor-across condition.

Section 1: Remapping activity in the visual-across condition of the double-step task

We observed significant remapping activity for the visual-across condition of the double-step task. An example of this activity is shown for a single neuron in Figure 64. This is the same example neuron seen in Figure 50 for the single-step task. In the double-step task, the neuron fired a strong burst of spikes in the within-hemifield condition (panel C). It also responded vigorously in the visual-across condition (panel D). Overall, firing is stronger for the double-step task than for the single-step task (panels E and F). In fact, the enhancement of remapping activity is even more notable for the visual-across condition (panels D, F) than for the within condition (panels C, E). This neuron was not responsive for either the saccade-alone or stimulus-alone control tasks (panels G-J). We asked whether these observations were evident in the population of LIP neurons, focusing on four topics.

Proportion of neurons with visual-across remapping

First, we assessed the likelihood of observing significant remapping activity in the visual-across condition of the double-step task. We found that 181 of 216 neurons exhibited significant remapping activity in at least one condition. Of these neurons, the vast majority had significant remapping activity in both the visual-across and within conditions (n=137, yellow bar in Figure 65). Many neurons were active only for the within-hemifield condition (n=40, green bar), whereas only four neurons were active in the visual-across but not the within condition (red bar). These numbers indicate that the neuron shown in Figure 64 was by no means an exceptional case. Rather, it was part of the 78% of remapping neurons with significant activity in the visual-across condition.

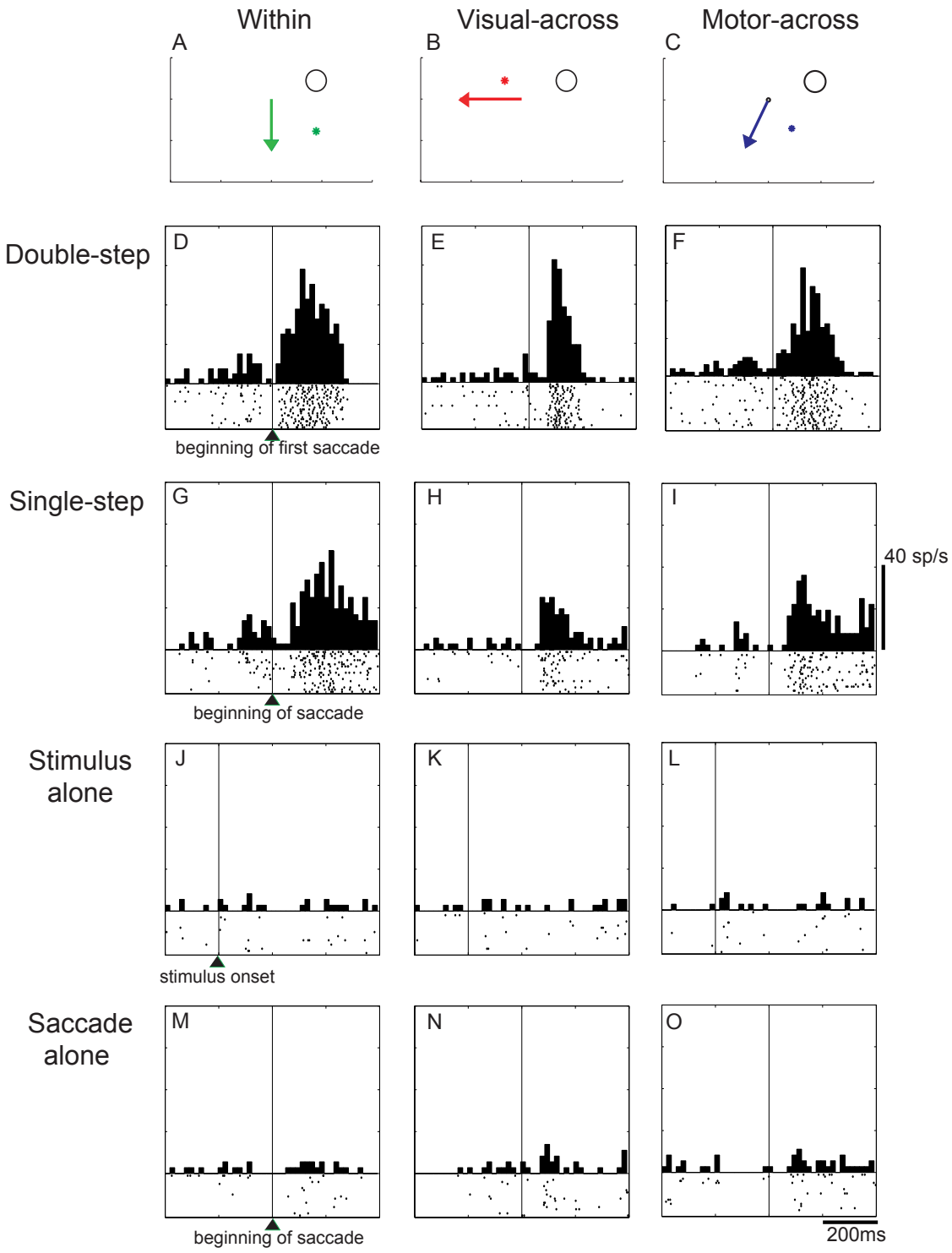


Figure 64. Activity of a single neuron tested in the double-step and single-step tasks, with corresponding control tasks. Top panels show the spatial configurations for the within (A), visual-across (B), and motor-across (C) conditions. The neuron fired briskly for all three conditions of the double-step task (panels D-F). Furthermore, activity in the double-step task was enhanced relative to remapping activity in the single-step task (panels G-I). The neuron's response was minimal when the stimulus appeared alone (panels J-L) and when the saccade was generated in the absence of the stimulus (panels M-O). Conventions as in Figure 51.

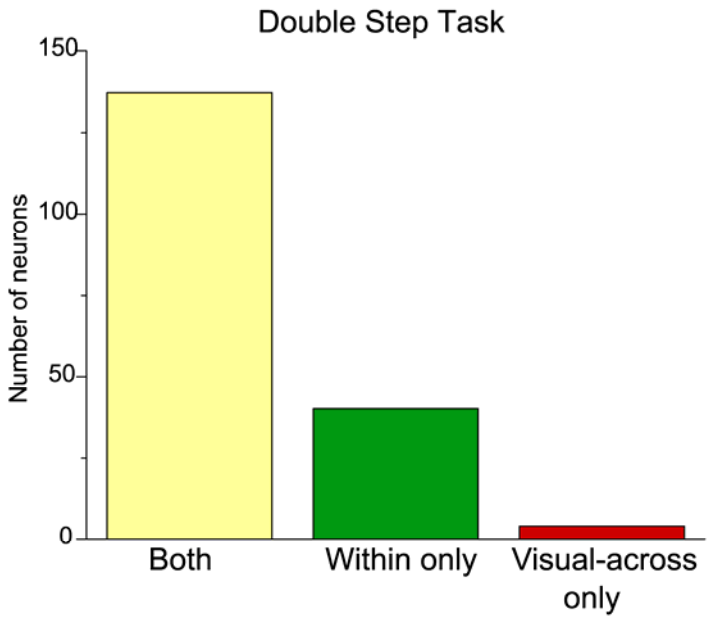


Figure 65. Number of neurons with significant remapping activity in the double-step task. The majority of neurons had significant activity in both within and visual-across conditions (n=137, yellow bar). A subset of cells responded only for the within condition (n=40, green bar). Only a few neurons responded in the visual-across condition but not the within condition (n=4, red bar). Significance was determined by comparing average firing rate in the remapping epoch of the single step task (0-200 ms relative to saccade onset) to activity in the corresponding control conditions. These data indicate that many cells remapped the stimulus across visual hemifields; however, visual-across remapping was observed less frequently than within-hemifield remapping.

Magnitude of visual-across remapping

Second, we asked whether the magnitude of remapping activity was equivalent for the visual-across and within-hemifield conditions. The neuron in Figure 64 fired very strongly in both conditions of the double-step task. On average, however, we found that neurons in area LIP fired more weakly for the visual-across condition as compared to the within-hemifield condition. In Figure 66, we plotted the average remapping activity of the visual-across condition (x axis), against that of the within condition (y axis). Each point represents data from a single neuron. Most points are above the unity line, indicating that firing rates during the remapping epoch were higher for the within condition. This observation is confirmed in the distribution of index values, shown in Figure 67. The index provides a normalized representation of relative firing rates in the two conditions, such that positive values indicate greater remapping activity in the within-hemifield condition. The distribution is skewed significantly toward 1 ($p<.01$, K-S test). Further, we computed the indices separately for each monkey. The resulting distributions for monkey EM and monkey CH were each skewed positively from zero, and were not different

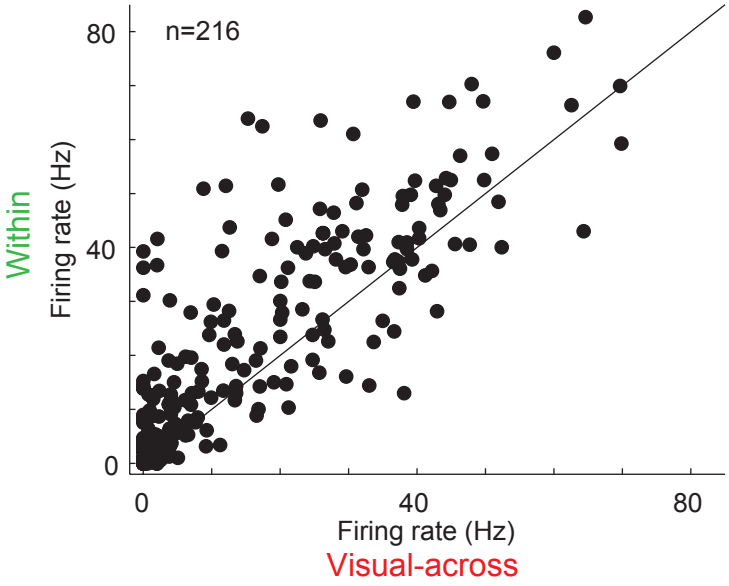


Figure 66. Firing rate in the double-step task. Each point represents a single cell. For each neuron, mean firing rate in the visual-across condition (x axis) is plotted against mean firing rate in the within condition (y axis). For this analysis, we included all visually-responsive neurons, regardless of the significance of remapping activity. Firing rate was computed for each neuron using a 200ms epoch, which began at saccade onset. Points falling along the unity line indicate that both double-step conditions elicited the same magnitude of remapping activity. Most points fall above the line, indicating that neurons fired more strongly for within-hemifield as compared to visual-across updating.

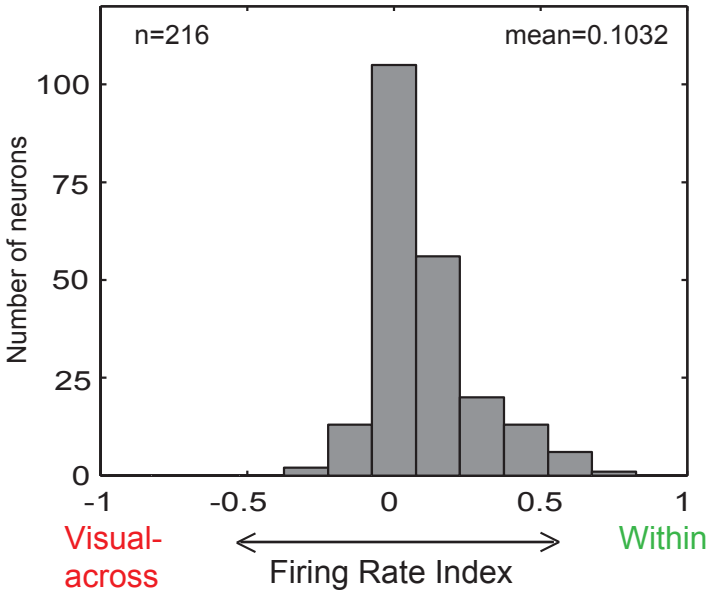


Figure 67. Histogram showing the distribution of index values for the population of neurons shown in Figure 66. The index is computed by comparing the saccade-adjusted mean firing rates for the within and visual-across conditions. Index values equal to zero indicate that the neuron fired equally strongly for the two conditions of the double-step task. A value of +1 indicates that the neuron responded only in the within condition; a value of -1 indicates that the neuron responded only in the visual-across condition. The distribution is skewed significantly toward +1 (signtest, $p<.01$). This suggests that the population of LIP neurons were more active for within-hemifield remapping as compared to visual-across remapping.

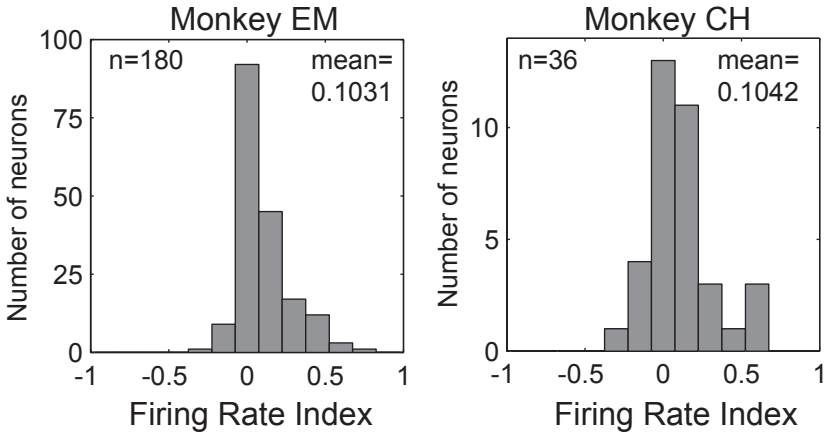


FIgure 68. The same neurons in Figure 67 are replotted separately for monkey EM (left) and monkey CH (right). The distributions of index values from the two monkeys did not differ significantly from each other. This indicates that the neural populations exhibited a similar pattern of differential firing for within as compared to visual-across remapping.

from each other (Figure 68). These data verify that remapping activity in the visual-across condition was diminished relative to activity in the within condition of the double-step task.

Increased neural activity in the double-step as compared to single-step task

Third, we investigated whether activity during the remapping epoch was increased in the double-step task as compared to the single-step task. The example neuron in Figure 64 illustrates this pattern, which has been observed previously in area LIP (Goldberg et al., 1990). The increase in activity is thought to reflect the added contributions of oculomotor and attentional factors. It is typically observed in neurons that carry visual as well as saccade-related signals. In the single-step task, these neurons exhibit remapping activity in conjunction with the first saccade, as they respond to the memory trace of the visual stimulus. In the double step task, these neurons are additionally active in relation to the second saccade, which is directed into the neuron's response field.

Attentional signals can also contribute to the intensified activity in the double-step task. Previous studies have demonstrated that remapping activity in LIP is modulated by the behavioral relevance of the stimulus to be updated, regardless of the intention to make an eye movement (Gottlieb et al., 1998). In the double-step task, the stimulus to-be-updated can elicit increased neural activity because, in addition to being salient by virtue of its brief appearance, it is relevant for the monkey's impending behavior. Thus, the heightened neural activity in the double-step task represents a concatenation of these visual, oculomotor, and attentional signals. We asked whether neurons in the split-brain monkey exhibited this increase, irrespective of condition. For each neuron, we plotted remapping activity measured during the single-step task against remapping activity during the double-step task (Figure 69). The vast majority of points fall above the unity line, indicating stronger activity in the double-step as compared to the single-

step task. This task-related increase in activity was statistically significant ($p<.0001$, paired t-test).

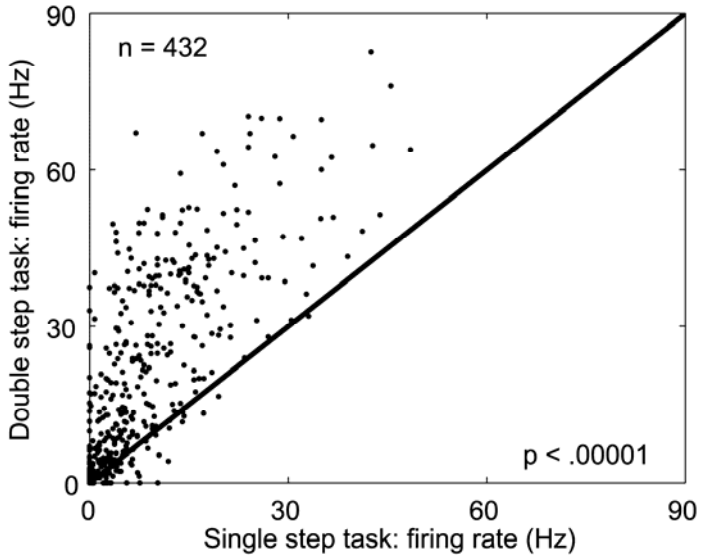


Figure 69. Comparison of remapping activity in the single-step and double-step tasks. Each point represents a single cell. Each neuron contributes two points, one for the within condition, and one for the visual-across condition. For each condition from each cell, average remapping activity in the single-step task (x axis) is plotted against average remapping activity in the double-step task (y axis). For both tasks, average remapping activity was computed using a 200ms epoch, beginning at the onset of the first saccade. Points falling along the unity line indicate that the magnitude of remapping activity was equivalent in the two tasks. Nearly all points fall above the line, indicating that neurons fired more strongly in the double-step task than in the single-step task.

Within vs. visual-across in the double-step as compared to the single-step task

Fourth, we asked whether the conditional differences observed in the single-step task were present to the same degree in the double-step task. In other words, did the increase in neural activity for the double-step task occur differentially for the within as compared to the visual-across condition? This question was motivated by the possibility that, in the absence of the forebrain commissure, the behavioral relevance of the to-be-updated stimulus might be conveyed more strongly when updating took place within the same hemifield (and thus, when information

was transferred within the same hemisphere). We addressed this question by comparing the relative difference between the within and visual-across conditions, for the single-step and double-step tasks. For each task, index values of zero indicate that a given neuron had the same magnitude of remapping activity in the visual-across and within conditions. If increased neural activity in the double-step task occurred preferentially for the within condition, index values would be *more* positive for the double-step as compared to the single-step task.

We found that performance of the double-step task did not differentially increase activity in the within as compared to the visual-across condition. The distribution of index values for each task are shown separately in Figure 70 (panels A and B). Both distributions are positively skewed, and are not significantly different from each other ($p>.05$, K-S test). The similarity of these two distributions indicate that conditional differences (within vs. visual-across) were unaffected by task (single-step vs. double-step). We next asked whether a difference in index values for the two tasks was detectable at the level of individual neurons. We plotted the Within:Across index values for each cell, for the double-step task (x axis) and single-step task (y axis). If the conditional difference were increased in the double-step task, we would observe more points above the unity line, indicating a stronger task-related increase for the within condition. Instead, the points are centered on the unity line, and do not differ significantly ($p>.05$, paired t-test). We conclude that, overall, individual neurons in LIP had the same relative activity for within as compared to visual-across remapping, in both the single- and double-step tasks. This finding suggests that the behavioral relevance of the stimulus can enhance remapping, even when the stimulus is updated across visual hemifields.

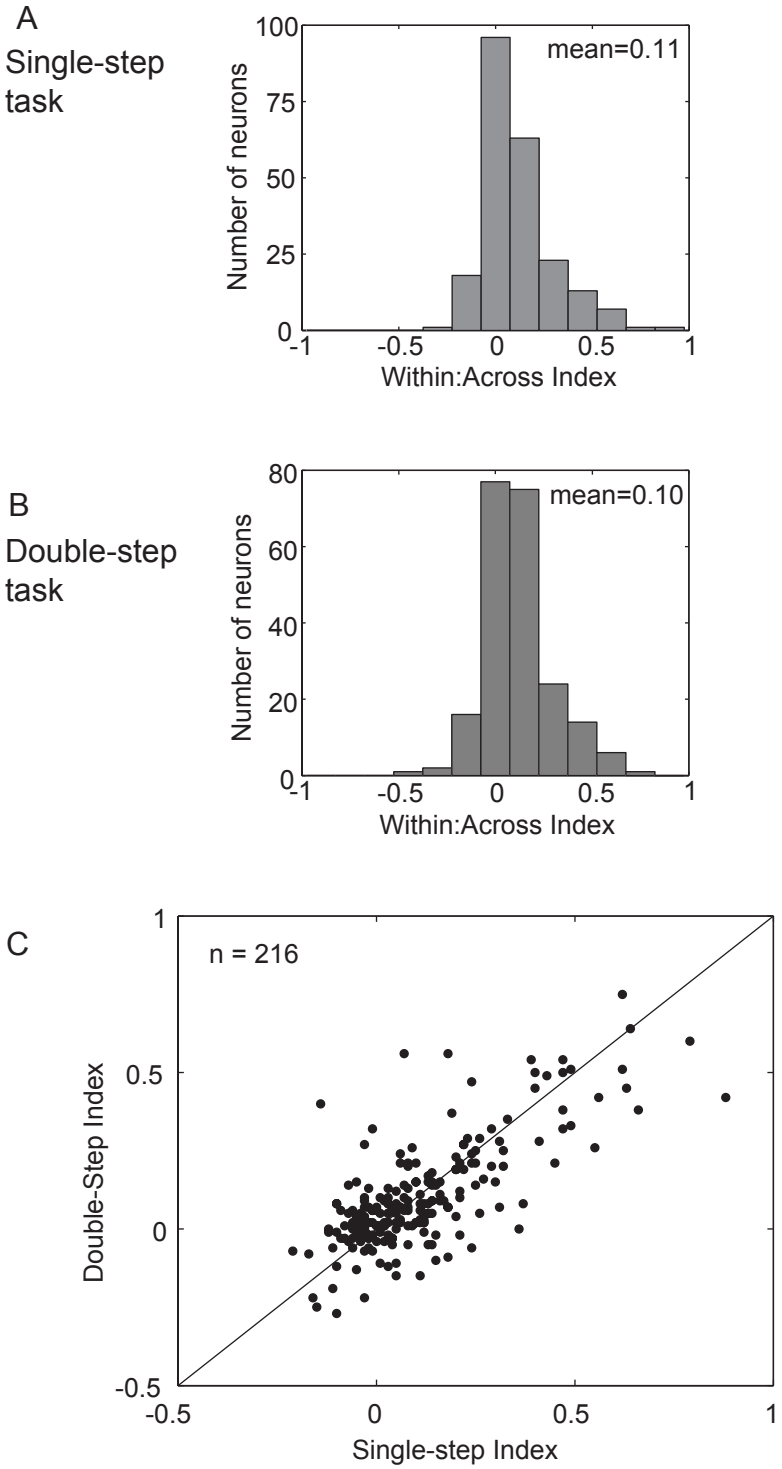


Figure 70. Comparison of the conditional differences in the single-step and double-step tasks. The distributions of within:across index values for each task are shown separately in panel A (single-step) and panel B (double-step). Both distributions were skewed toward +1, indicating stronger remapping activity in the within condition than the visual-across condition. Mean index values for the two tasks were nearly identical (.11 and .10). In the scatterplot in panel C, index values are plotted for each neuron, from the double-step task (x axis) and the single-step task (y axis). Most points fall along the unity line, indicating that the differences in firing rate for within and visual-across conditions were comparable for the two tasks. These observations indicate that heightened activity in the double-step task was equivalently present for both the visual-across and within conditions.

In summary, we made four key observations in regard to neural activity in area LIP during the within and visual-across conditions double-step task. First, the majority of LIP neurons in the split-brain monkey exhibit remapping activity in the double-step task, even when the second target must be updated from one visual hemifield to the other. Second, the magnitude of remapping activity is smaller for the visual-across as compared to the within condition. Third, remapping activity is increased for the double-step as compared to the single-step condition. Fourth, this increase is equivalent for the within and visual-across conditions, as indicated by the fact that the conditional difference in remapping activity (within vs. visual-across) is the same for the double-step and single-step tasks.

Timecourse of population activity in the within and visual-across conditions

We conclude our assessment of double-step activity for the within and visual-across conditions by evaluating the timecourse of population activity (Figure 71). The population histogram in panel A shows average activity from all neurons recorded during the double-step task, which did not exhibit significant activity in either of the control tasks (stimulus-alone or saccade-alone). Data are aligned on the beginning of the first saccade (vertical line). In the within-hemifield condition of the double-step task, population activity began to increase at the time of the onset of the first saccade. This activity peaked roughly 100ms later. In the visual-across condition, population activity began nearly 70ms after the onset of the first eye movement. The peak of remapping activity in the visual-across condition occurred simultaneously with the peak in the within condition; however, the magnitude of this peak was smaller for the visual-across condition.

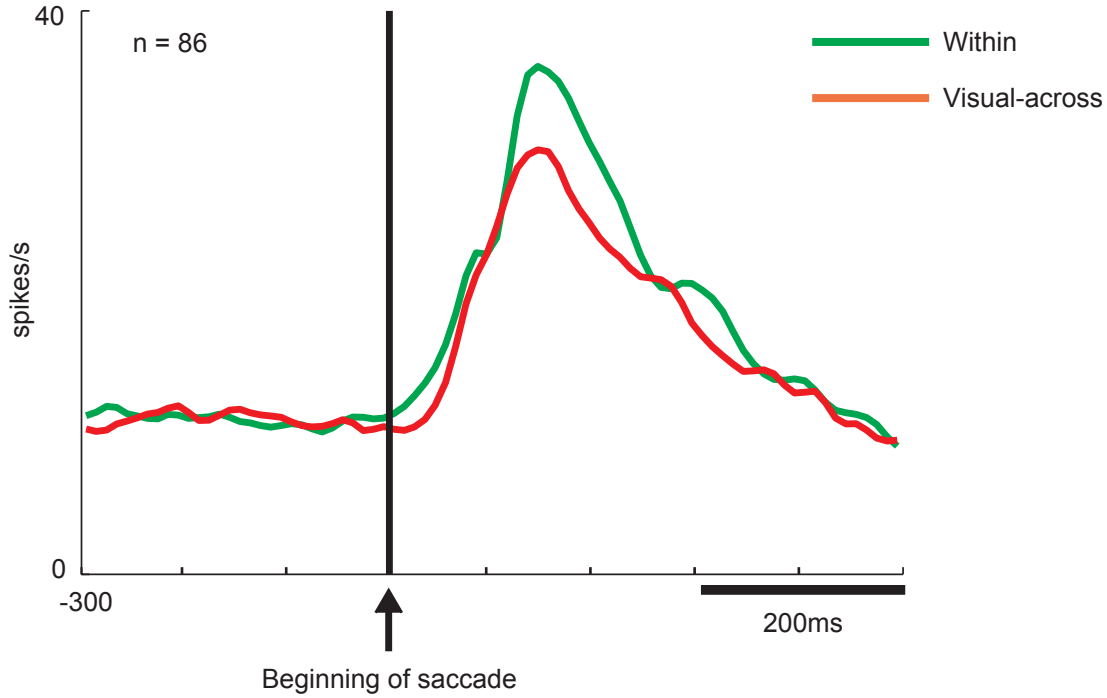


Figure 71. Average population activity in the double-step task, for within-hemifield (green) and visual-across (red) conditions. Data are aligned on the beginning of the saccade from FP to T1 (vertical line). The population is comprised of all neurons from both monkeys that did not exhibit significant activity in either control task. For the within-hemifield condition, population activity increased near the time of the first saccade; activity in the visual-across condition did not begin until nearly 70ms after saccade onset. The peak of remapping activity occurred simultaneously for the two conditions, roughly 100ms after the eyes reached T1. The magnitude of remapping activity was smaller, however, for the visual-across condition. These data show that 1) population activity in LIP is greater for within-hemifield than visual-across remapping; 2) population activity in LIP begins earlier when T2 locations are remapped within the same hemifield. There is nevertheless robust activity associated with updating a target location from one visual hemifield to the other.

Section 2: Remapping activity in the motor-across condition of the double-step task

In the final section of Part II, we briefly characterize remapping activity during the motor-across condition of the double-step task. We expected to observe significant activity in this condition, based on two of our previous findings: 1) neurons in LIP exhibited remapping activity for the motor-across condition in the single step task, and 2) the monkey's performance of the motor-across double-step condition was very accurate during physiological recording sessions. In this section, we describe the frequency and magnitude of remapping activity in the motor-across condition.

Proportion of neurons with motor-across remapping

We found that neurons in LIP exhibited strong remapping activity in the double-step task when spatial updating required an interhemispheric transfer of a corollary discharge signal. The familiar exemplar neuron is shown in Figure 64. This neuron fired strongly in the motor-across condition (panel F), just as it did for the within and visual-across conditions. In the population of 116 neurons, 113 had significant remapping activity in at least one condition of the double-step task. Nearly all neurons (n=94) had significant remapping activity in all three conditions. A subset of neurons (n=19) demonstrated activity only in the within-hemifield condition.

Magnitude of motor-across remapping

We next compared the magnitude of remapping activity in the motor-across condition to that of the within and visual-across conditions. Neurons responded similarly for the motor-across and within condition, as indicated by the scatterplot in Figure 72A. Activity for each neuron is plotted for the motor-across condition (x axis) compared to the within condition (y axis). The

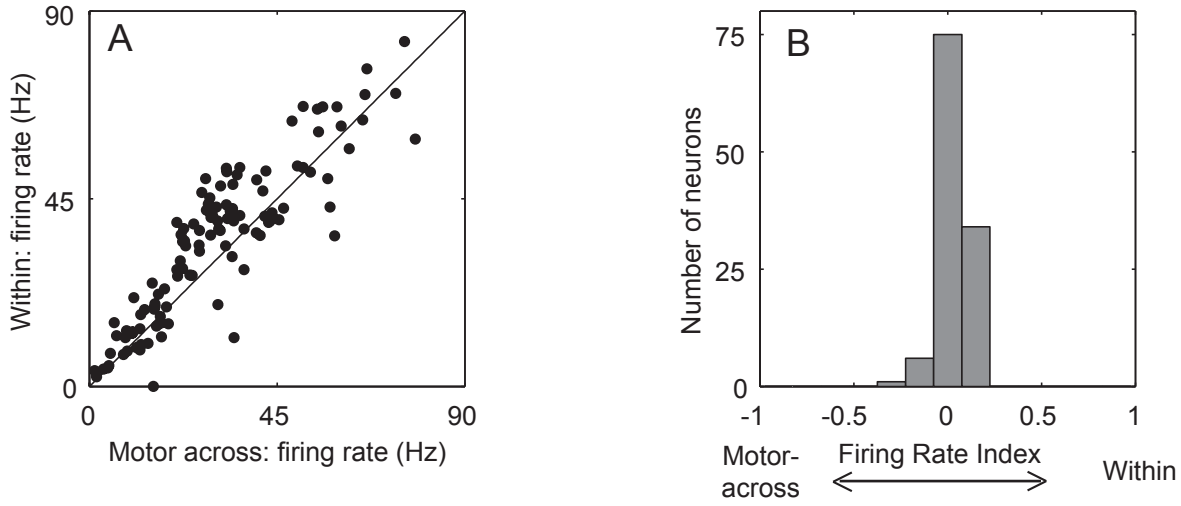


Figure 72. Comparison of remapping activity in the within and motor-across double step tasks (panels A, B). In panel A, average remapping activity in the motor-across condition (x axis) is plotted against activity in the within condition (y axis). The distribution of points is primarily centered on the unity line, but more points fall above the line, indicating slightly higher firing rates for the within condition. This is evident in the distribution of index values shown in panel B. The distribution is skewed slightly toward +1; positive values indicate that a neuron's remapping activity was stronger in the within condition relative to the motor-across. These data show that, on average, the motor-across condition elicited remapping activity that was slightly smaller in magnitude than that of the within-hemifield condition.

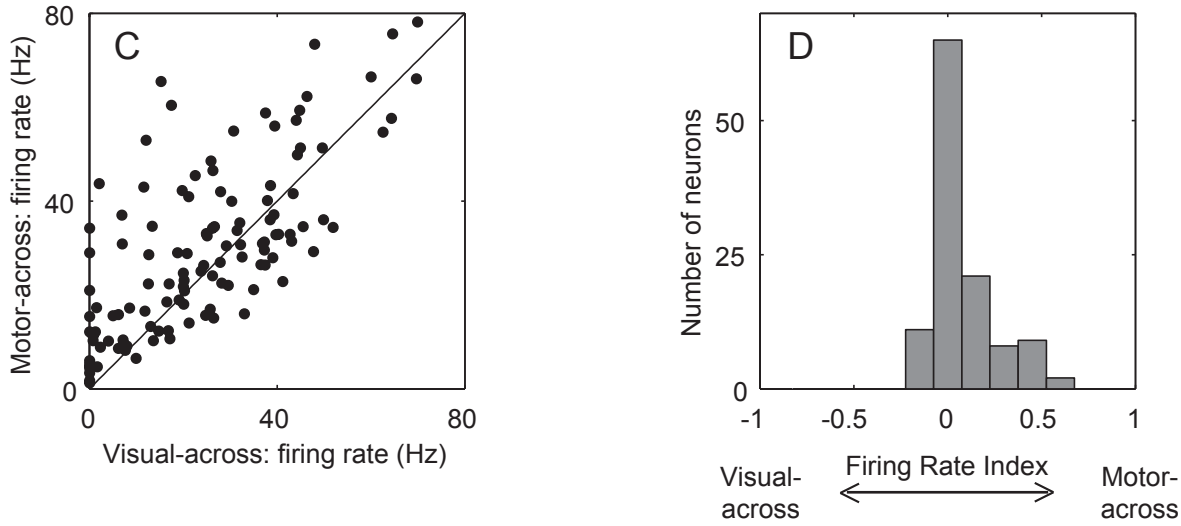


Figure 73. Comparison of remapping activity in the motor-across and visual-across double step tasks (panels C, D). In panel C, average remapping activity in the visual-across condition (x axis) is plotted against activity in the motor-across condition (y axis). Most points fall above the unity line, indicating higher firing rates for the motor-across condition. This is evident in the distribution of index values shown in panel B. The distribution is skewed toward 1; positive values indicate that a neuron's remapping activity was stronger in the motor-across condition relative to the visual-across. These data show that, on average, the motor-across condition elicited stronger remapping activity than the visual-across condition.

distribution of points is largely centered on the unity line, but more points appear above the line than below, indicating stronger remapping activity for the within condition. Indeed, average neural activity was slightly greater for the within condition: 34.3 +- 1.7sp/s, compared to 30.1+-1.6sp/s for the motor-across condition. Similarly, the distribution of index values, shown in panel B, is skewed slightly but significantly toward +1 (mean=0.0347, $p<.05$, K-S test). These data indicate that remapping activity in the motor-across condition, while still quite robust, was smaller than that of the within condition.

In our next comparison, that of motor-across and visual-across conditions, we observed more substantial differences in firing rate. In Figure 72C, we have plotted activity for each neuron in the visual-across condition (x axis) against activity in the motor-across condition (y axis). The majority of points are above the line, representing neurons with stronger remapping activity for the motor-across as compared to the visual-across condition. On average, neural activity in the motor-across condition was greater: 30.1+-1.6 sp/s, compared to 24.7+-1.6 sp/s in the visual-across condition. This difference is confirmed in the distribution of index values shown in panel D. Here, positive values indicate stronger activity in the motor-across condition. The distribution has a significant positive skew (mean=0.0814, $p<.01$, K-S test). These data reinforce the notion that, in the absence of the forebrain commissures, the interhemispheric transfer of visual updating signals is disrupted more severely than the interhemispheric transfer of corollary discharge signals.

Timecourse of population activity in the within, visual-across, and motor-across conditions

Finally, we evaluated the timecourse of activity for all three conditions of the double-step task (Figure 73). In the population histogram, remapping activity for the within and motor-across

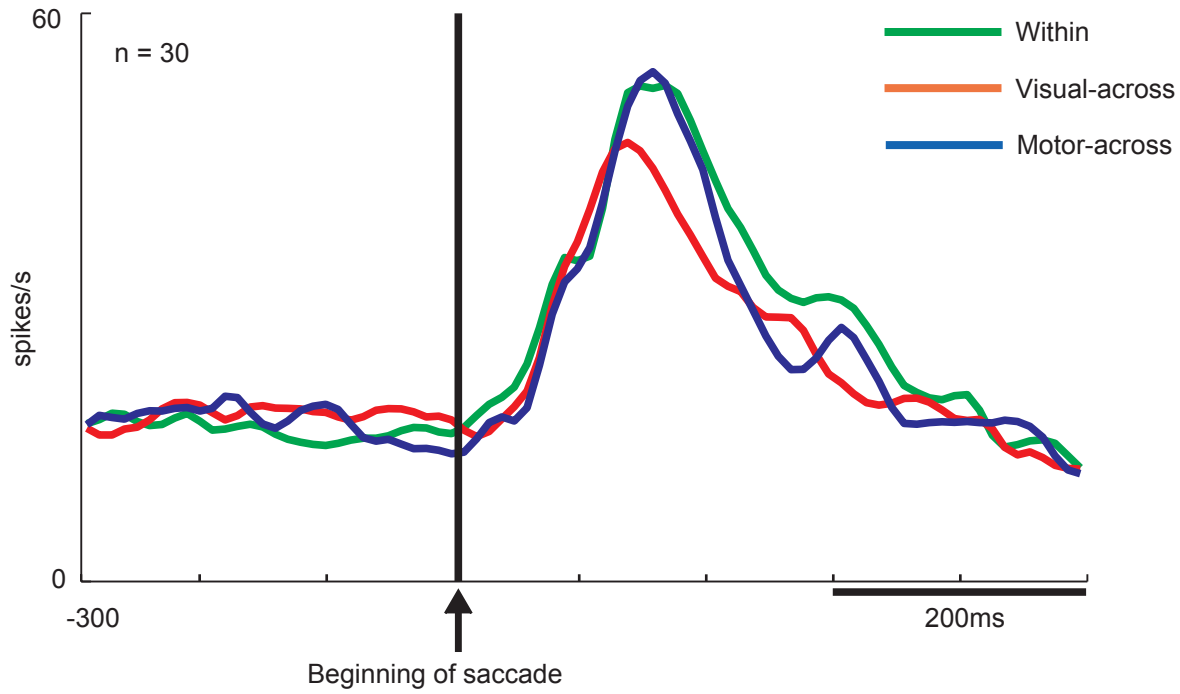


Figure 73. Average population activity in the double-step task, for within-hemifield (green) motor-across (blue) and visual-across (red) conditions. Data are aligned on the beginning of the saccade from FP to T1 (vertical line). The population is comprised of all neurons from monkey EM that did not exhibit significant activity in any control conditions. In this population of neurons (n=30), remapping activity begins at approximately the same time for all three conditions. The magnitude of remapping activity, however, is greater for the within and motor-across conditions than for the visual-across condition. These data confirm that neural activity in LIP of the split-brain monkey is robust when a stimulus representation is updated within the same hemifield (within and motor-across conditions), but less robust when the representation is updated across hemifields (visual-across).

sequences is nearly identical. In both conditions, activity peaked about 150ms after the onset of the first saccade, with a maximal firing rate of 55sp/s. Activity in the motor-across condition began slightly later, however, and dropped off more rapidly than activity in the within condition. These dynamics likely contributed to the small differences observed in average firing rates for the two conditions (Figure 73). In the visual-across condition, the rise in remapping activity coincided with that of the motor-across condition, beginning slightly after the onset of activity in the within condition. The maximal activity in the visual-across condition was reduced in relation to the other two conditions. The signals are nevertheless remarkably robust. This population activity implies that neurons in LIP of the split-brain monkey have access to updating signals – both visual and oculomotor – that are relayed both within and across hemispheres.

PART III: DOES REMAPPING ACTIVITY IN LIP PREDICT BEHAVIOR?

Is there a relationship between the monkeys' performance of the double-step task and activity in area LIP? Our findings in the previous chapters, and indeed, in the first two parts of the present chapter, suggest a parallel between the monkeys' performance of the double-step task, and the remapping activity observed in area LIP. We observed that the accuracy of double-step sequences was reduced for the visual-across condition as compared to the within condition of the double-step task, and we observed that remapping activity was reduced in the visual-across condition. In this final section, we have the opportunity to draw these two measures of spatial updating - behavior and neural activity – into direct comparison. We took two approaches. First, we asked whether there was a relationship between the firing rate of LIP neurons and double-step performance, regardless of condition. Second, we evaluated the relative difference between the within and visual-across condition, for remapping activity and for behavioral performance. In this analysis, we used the Within:Across index values to ask whether there was

a relationship between remapping activity and double-step performance, either at the population level or at the level of individual sessions. For these investigations, we analyzed data from the within and visual-across conditions only.

Section 1: General relationship between firing rate and saccade performance

Our first approach toward understanding the relationship between activity in LIP and double-step performance was simply to ask whether the activity preceding the second saccade predicts the performance of the second saccade, irrespective of condition. Presaccadic activity in several brain structures is known to be predictive of the monkey's impending oculomotor behavior. For example, the activity of a portion of neurons in the frontal eye field and superior colliculus is strongly correlated with the reaction time of the impending saccade (Dorris et al., 1997; Everling and Munoz, 2000). We asked whether there was evidence of a relationship between saccade performance and activity in area LIP of the split-brain monkey. Specifically, we asked whether activity was related to the execution of the second saccade of the double-step task. For each session, we computed the average remapping activity in a 200ms epoch preceding the onset of the second eye movement. We chose this epoch because we wanted to take into account not only the immediate presaccadic activity in LIP, but also the remapping activity exhibited in conjunction with the first saccade. As described previously, we used an adjusted measure of raw firing rate, which controlled for any activity in the saccade-alone task. We compared the average remapping activity to the average accuracy and latency of the second saccade, using angular and distance error to describe accuracy.

We observed a significant correlation between remapping activity and the accuracy and reaction time of the second eye movement. The strength of this relationship, however, was relatively weak (Table 2). We can visualize this relationship in Figure 74, where we have plotted average remapping activity (x axis) against the average accuracy and latency measures (y axis). In these plots, each recording session contributes two points, one for the within-hemifield condition, and one for the visual-across condition. The same data are shown in the left column (panels A-C) and in the right column (panels D-F), but are color-coded according to condition in the right column. For both angular error (panel A) and distance error (panel B), the datapoints representing the least accurate performance (large y axis values) are predominantly associated with low firing rates (small x axis values). A similar pattern is apparent for saccade latency: the longest reaction times in panel C are associated with low firing rates. The same low firing rates, however, are also associated with saccade performance that is accurate and rapid. It is not surprising, then, that we observed relatively small correlations between updating activity and accuracy measures. Regression analysis showed that firing rate was a significant predictor of all three behavioral measures. In each case, however, the variability in firing rate accounted for only a small proportion of the variability in saccade accuracy or latency (R^2 = .070 for angular

Table 2. Correlations between firing rate and measures of S2 accuracy and latency

		S2 Angular Error	S2 Distance Error	S2 Latency
Firing Rate	Pearson Correlation	-.264(**)	-.159(**)	-.166(**)
	Sig. (2-tailed)	.000	.001	.001
	N	432	432	432

** Correlation is significant at the 0.01 level (2-tailed).

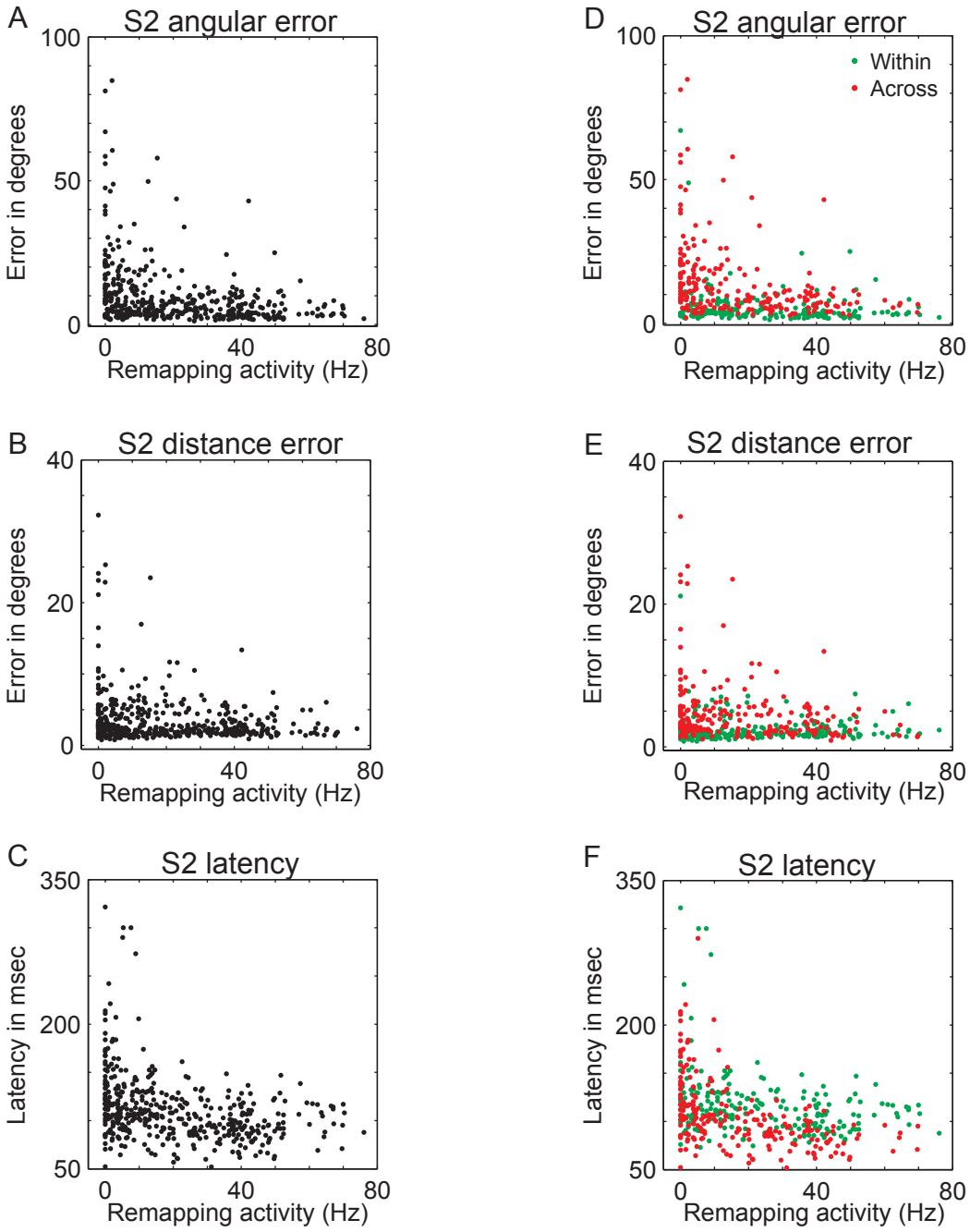


Figure 74. Relationship between average behavioral measures and average remapping activity for double-step recording sessions. Each point represents the remapping activity (x axis) and behavior (y axis) of a single neuron. Each neuron contributes two points: one for the within condition and one for the visual-across condition of the double-step saccade task. Remapping activity is plotted against three measures of performance for the second saccade: angular error (panels A,D), distance error (panels B,E) and latency (panels C,F). In panels A-C, all points are shown in black so as to visually collapse over the two conditions. In panels D-F, points are distinguished according to condition, with within shown in green, visual-across in red. These data demonstrate that sessions with the worst saccade performance (higher values on the y-axis) were associated with low remapping activity (leftward values on the x axis). On the whole, however, behavioral performance did not vary according to remapping activity: the majority of points in panels A-C form a horizontal line, indicating steady performance regardless of remapping activity. Panels D-F show that these general observations apply to both the within and visual-across conditions.

error, .025 for distance error, and .028 for latency, all $p<.01$). These data indicate that the activity of individual LIP neurons was not strongly predictive of the accuracy and latency of the second saccade in the double-step task.

Section 2: Within vs. visual-across in behavior and neural activity

Our second approach was to investigate the relative difference between within-hemifield and visual-across conditions of the double-step task. We asked whether this relative difference (within vs. visual across) was similar for remapping activity and for behavioral performance. At the population level, we compared the distribution of Within:Across indices for remapping activity to the distribution of Within:Across indices for the accuracy and latency of the second saccade (Figure 75, panels A-D). Values are smaller for the firing rate index, because these values were calculated using an additional step to adjust for activity in the saccade-alone control. The important point is that the distributions for remapping activity and saccade accuracy are all skewed positively ($p<.01$, K-S test). This confirms that, at the population level, activity in area LIP parallels behavioral performance.

Ultimately, we were interested in whether differences in the firing rate index could account for differences in the behavioral indices on a session-by-session basis. For example, if a single neuron fired more for the within than for the visual-across condition of the double-step task, did the monkey perform the second saccade more accurately or more rapidly for the within condition? An example of this relationship is shown in Figure 76. The neuron had strong remapping activity in the within condition and likewise, performed the double-step sequence accurately. Remapping activity was less robust in the visual-across as compared to the within condition. Likewise, double-step performance was less accurate in the visual-across condition as

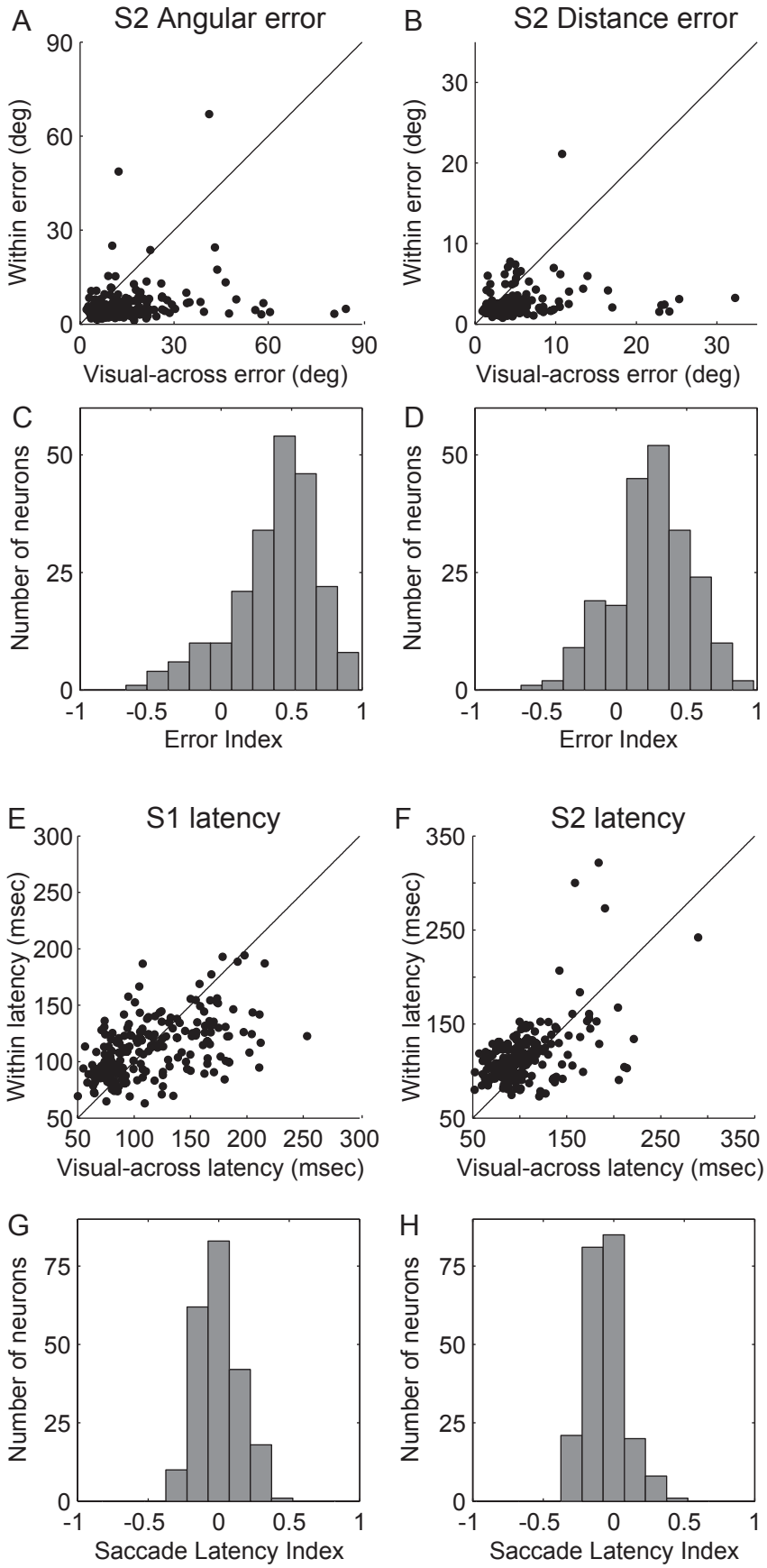


Figure 75. Accuracy and latency measures of double-step performance during recording sessions.

In panels A and B, error for the visual-across condition (x axis) is plotted against that of the within condition (y axis). Each point represents behavioral data acquired during the recording of a single neuron. Points falling along the unity line indicate that performance was similar for the within and visual-across conditions of the double-step task. For angular error (A) and distance error (B), most points fall below the line. This indicates that error was greater for the visual-across condition. We computed an index for each measure, which ranged from -1 to +1. Positive values indicate that performance was better for the within condition (less error). Error indices in panels C and D confirm that performance was less accurate for the visual-across than within condition.

In panels E and F, latencies for the visual-across condition (x axis) are plotted against those of the within condition (y axis). For both S1 and S2 latency scatterplots, points are distributed more equally around the unity line than were the accuracy measures. Nonetheless, there were significant differences between the condiitons. Reaction times for S1 were significantly faster for the within as compared to the visual-across condition, whereas reaction times for S2 were significantly faster for *visual-across* than for within. The distributions of latency index values (panels G, H) confirm these results. The S1 distribution was skewed slightly toward positive values, while the S2 distribution was skewed slightly toward negative values.

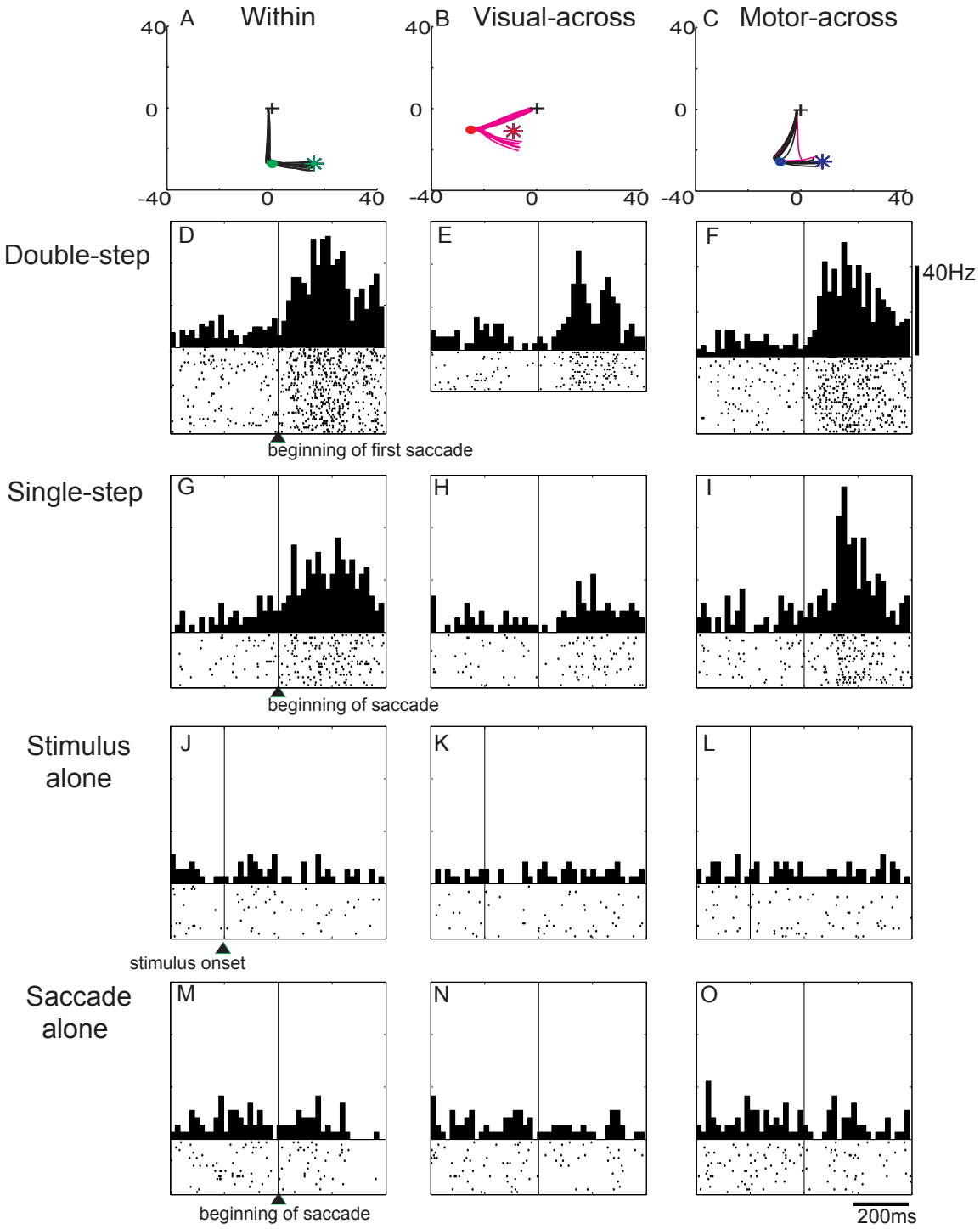


FIgure 76. Single neuron showing remapping activity that corresponds to behavioral performance. Panels A-C show the first ten trials of double-step performance for the within, visual-across, and motor-across conditions. Panels D-F show the firing of the neuron during all trials obtained during the double-step task. Fewer trials were available for the visual-across condition due to trials where the monkey did not reach the first target. The neuron fires most strongly in the within and motor-across conditions of the double-step task. It responds strongly in the visual-across condition, though less robustly than in the within or motor-across conditions. In parallel, the monkey came close to attaining the target for the visual-across double-step task (panel B) but nevertheless performed this sequence less accurately than the within and motor-across sequences. Activity in the single-step (panels G-I) and control tasks (J-O) below.

compared to the within condition. Consequently, this neuron (session) yielded positive index values for both remapping activity and for measures of S2 accuracy. We asked whether there was evidence of this relationship in the population of neurons recorded during the double-step task. If so, we would observe a positive correlation between index values associated with neural activity and the index values associated with saccade performance. We conducted this analysis only for the comparison of within and visual-across conditions, with data from both monkeys (n=216). The relationship between the observed index values is shown in Figure 77 (panels E-G). We conducted regression analyses to determine whether the Within:Across neural index predicted the Within:Across index for any of the behavioral measures.

We found a significant but small predictive relationship between the index for firing rate and that for angular error and latency (Figure 77, panels E and G). For angular error, the slope of the regression line was slightly positive. The positive slope indicates the expected relationship between neural activity and performance. Namely, when remapping activity is stronger for the within as compared to the visual-across condition, the directional accuracy of the second saccade is better for the within as compared to the visual-across condition. We did not observe a significant relationship between the indices for firing rate and distance error (panel F). We did observe a significant relationship between the firing rate index and the latency index (panel G). The slope of this regression line, however, is slightly negative. This represents a rather unexpected relationship between activity and reaction time: as neurons in LIP fire *less strongly* for the visual-across condition, reaction times in this condition become *faster.* This counterintuitive result can be understood if we consider the monkeys' strategy on the visual-across condition. Specifically, we observed very rapid saccade latencies for the visual-across condition, implying that the monkeys adopted an automated strategy to perform these sequences

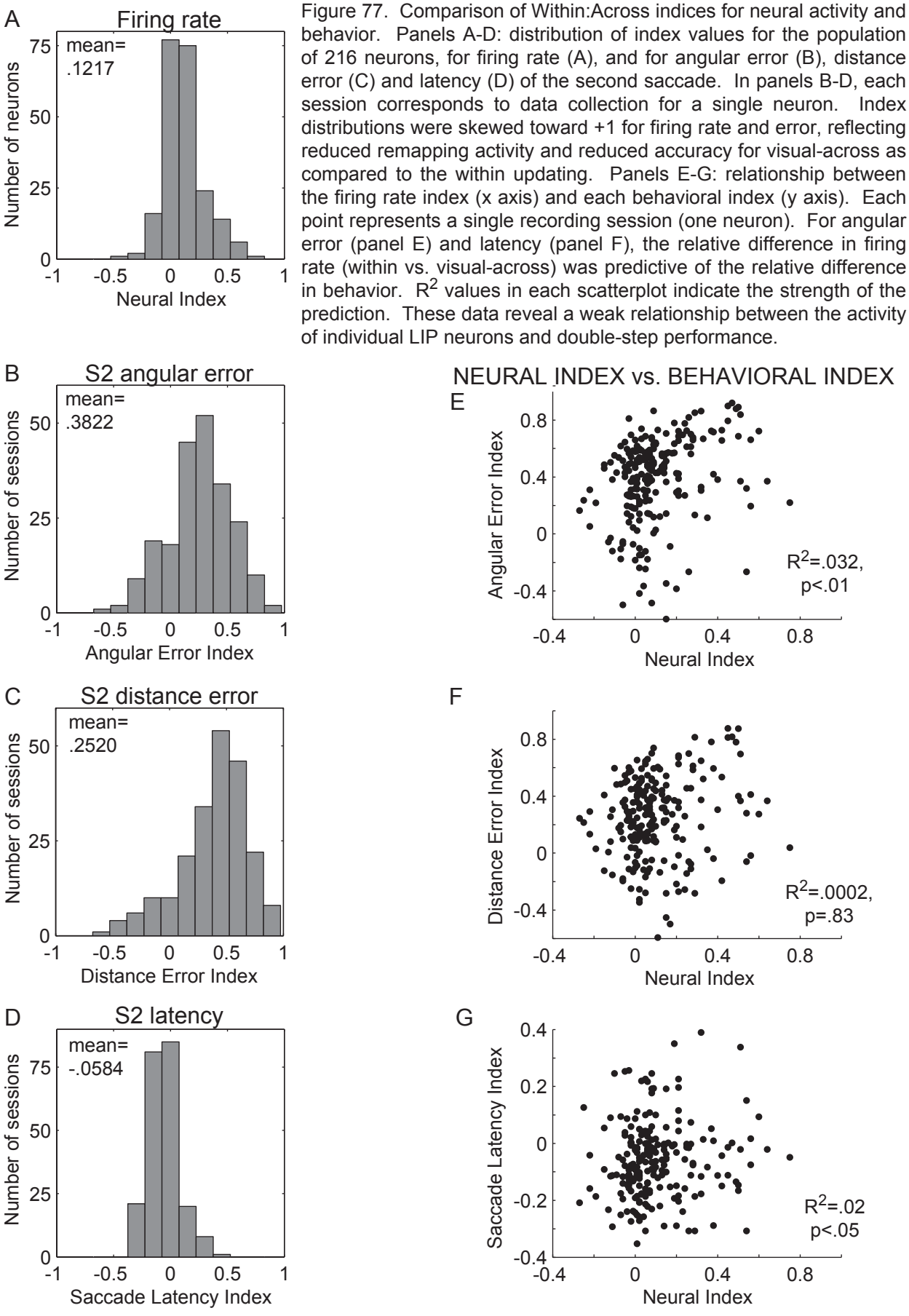


Figure 77. Comparison of Within:Across indices for neural activity and behavior. Panels A-D: distribution of index values for the population of 216 neurons, for firing rate (A), and for angular error (B), distance error (C) and latency (D) of the second saccade. In panels B-D, each session corresponds to data collection for a single neuron. Index distributions were skewed toward +1 for firing rate and error, reflecting reduced remapping activity and reduced accuracy for visual-across as compared to the within updating. Panels E-G: relationship between the firing rate index (x axis) and each behavioral index (y axis). Each point represents a single recording session (one neuron). For angular error (panel E) and latency (panel F), the relative difference in firing rate (within vs. visual-across) was predictive of the relative difference in behavior. R^2 values in each scatterplot indicate the strength of the prediction. These data reveal a weak relationship between the activity of individual LIP neurons and double-step performance.

(Figure 77). As a result, faster latencies were associated with worse performance. The negative relationship between the firing rate and latency indices suggests that the monkeys' performance became even more stereotyped on the visual-across condition as the associated neural activity was reduced.

These findings indicate that the neuron's relative activity for the within and visual-across conditions provides small but significant information about how well the monkey will perform the second saccade of the within-hemifield sequence as compared to the visual-across sequence. Two points are nevertheless critical to our interpretation of these findings. First, the relationship between the firing rate index and the behavioral indices, while significant for angular error and latency, is weak. This is visually appreciable in the scatterplots in panels E-G, and confirmed by statistics. Variability in the firing rate index accounts for a very small portion of the variability in behavior (R^2=.03 for angular error, .02 for latency). Second, insofar as there is a significant relationship between activity and behavior, we cannot address the possibility of a *causal* relationship between these variables. Inaccurate double-step performance of the visual-across condition may be the result of reduced remapping activity in area LIP. Alternatively, inaccurate performance may reflect activity in other structures. In turn, impaired performance itself could cause reduced activity in LIP. The present experiment was not designed to distinguish between these two possibilities. We can conclude, however, that there are parallels between remapping activity in area LIP and the monkeys' performance of the double-step task; these are weakly apparent at the level of single neurons, and clearly evident at the population level.

SUMMARY AND DISCUSSION

We investigated the spatial behavior and neural activity associated with updating in the absence of the forebrain commissures, using the double-step saccade task. This experiment provided the opportunity to evaluate simultaneously the monkeys' performance of the double-step task, and activity of neurons in area LIP. We made four primary observations.

First, our assessment of the monkeys' spatial behavior during recording sessions revealed significant impairment on sequences that required an interhemispheric transfer of visual signals. By contrast, performance was only slightly impaired for sequences that required the corollary discharge signal to cross between the hemispheres. Impairment of the visual-across sequences likely reflects the monkeys' difficulty in adapting to new spatial arrangement of the targets.

Second, we found that LIP neurons could remap the location of the second target in the double-step task, even when updating required the interhemispheric transfer of visual or corollary discharge signals. We nevertheless found that neural activity in the double-step task was substantially and significantly reduced in the visual-across condition relative to the within condition. For the motor-across condition, remapping activity was only slightly decreased relative to the within condition, and was significantly greater than activity in the visual-across condition.

Third, we observed an increase in neural activity for the double-step task as compared to the single-step task. This increase in activity suggests that activity in LIP neurons is modulated by the behavioral relevance of the updated stimulus location, even when it is updated across visual hemifields.

Finally, we observed an association between neural activity in the population and overall double-step performance. Specifically, if condition X elicits stronger population activity than condition Y, then average performance of the double-step task is more accurate for condition X

than for Y. We verified this relationship between population indices and behavioral indices for the three comparisons of interest: within vs. visual-across, within vs. motor-across, and motor-across vs. visual-across. At the level of individual neurons, however, activity in area LIP did not strongly predict performance of the double-step task. This finding is in contrast to the relationship between neural activity and behavior observed in some sensory areas, such as the motion-sensitive area MT. The activity of a single MT neuron can be used to predict the perceptual behavior of the animal (Newsome et al., 1990). The relationship between neural activity in LIP and double-step performance may to be more akin to what is observed in primary motor cortex and in other visuomotor structures. In M1, for example, one cannot account for behavior using information from only a single neuron. Behavior can be predicted, however, by activity at the level of the population (Georgeopoulos, 1982). Our findings indicate that information from a single LIP neuron is not sufficient to account for behavior, whereas neural activity in a population of LIP neurons is well-matched to performance in the double-step saccade task.

Chapter 5: General Discussion

OVERVIEW

The overarching goal of these investigations was to identify critical components of the neural circuitry that subserves spatial updating. We focused on the interhemispheric transfer of visual and oculomotor signals required for spatial updating. We addressed two specific aims. In the first aim, we asked whether the forebrain commissures are necessary for the interhemispheric transfer of visual signals involved in spatial updating. We demonstrated that the behavioral and neural correlates of spatial updating were not abolished in the absence of the forebrain commissures. We nevertheless found evidence that spatial behavior and neural activity were disrupted when visual information had to be transferred from one hemisphere to the other. In the second aim, we asked whether the forebrain commissures are necessary for the interhemispheric communication of the corollary discharge signals that initiate spatial updating. We obtained behavioral and physiological evidence that updating was essentially unaffected when motor information had to be transferred between the disconnected hemispheres.

Our experimental findings support two central claims regarding the interhemispheric circuitry of spatial updating. First, the forebrain commissures are not the sole route for the interhemispheric transfer of visual information in spatial updating, though they are likely the primary route. Second, the forebrain commissures are not the primary route for the interhemispheric transfer of oculomotor information in spatial updating. The purpose of this chapter is to evaluate the experimental evidence for these two claims in the framework of existing literature. We conclude by discussing the implications of the current findings for understanding the neural mechanisms of spatial constancy.

PART I. THE FOREBRAIN COMMISSURES ARE NOT THE SOLE ROUTE FOR INTERHEMISPHERIC TRANSFER OF VISUAL INFORMATION REQUIRED FOR SPATIAL UPDATING, THOUGH THEY ARE LIKELY THE PRIMARY ROUTE

At the outset of these studies, our hypothesis was that visual signals are transferred across the forebrain commissures when a memory trace is remapped from one visual hemifield to the other. Our experimental prediction was that across-hemifield remapping would be abolished in the absence of the forebrain commissures. Much to our surprise, we obtained both behavioral and physiological evidence that across-hemifield updating was still intact. Our behavioral experiments demonstrated that split-brain monkeys could learn to perform sequences of the double-step task that required an interhemispheric transfer of visual information. For a few of these sequences, in fact, accurate performance was immediate or rapidly acquired. Our physiological experiments demonstrated that the vast majority of neurons in area LIP of the split-brain monkey had significant remapping activity in the across-hemifield condition. We observed this remapping activity during both the single-step and double-step tasks. These findings indicate that interhemispheric updating of visual information can occur in the absence of the forebrain commissures.

What can we infer about the neural pathways that support interhemispheric updating of visuospatial locations in the split-brain monkey? In the following sections, we consider the functional capacities of this system in light of our current findings and existing literature. We first discuss experimental results suggesting ways in which updating is less effective in the absence of the forebrain commissures. We then consider the evidence that the system is nevertheless remarkably capable of transmitting the visual information necessary for spatial updating. Finally, we discuss the brain structures that may contribute to successful interhemispheric updating in the absence of the forebrain commissures.

1. Interhemispheric updating is less effective in the absence of the forebrain commissures

Our behavioral and physiological findings indicate that the interhemispheric updating of visual representations is compromised in the absence of the forebrain commissures. In behavioral experiments (Chapter 2), we found that split-brain monkeys exhibited an initial impairment in performance of double-step sequences that required updating across visual hemifields. This impairment was manifest in increased error and prolonged reaction times. Furthermore, the accuracy of learned sequences did not generalize readily to new spatial configurations when they required across-hemifield updating. In physiological experiments, we found that remapping activity in LIP was less robust when visual information had to be transferred across hemifields as compared to within. This was manifest in three ways. First, fewer neurons exhibited significant activity for across-hemifield remapping as compared to within-hemifield remapping. Second, the magnitude of activity was smaller for the across-hemifield condition. Third, neural activity began later in the across-hemifield condition than in the within-hemifield condition. These deficits suggest that the forebrain commissures provide the principle, direct route for visual information to be updated from one hemisphere to the other.

Despite these clear deficits, remapping was not abolished, as we had expected. Instead, we observed substantial preservation of function in some conditions, and significant recovery of function in others. These preserved abilities suggest that additional pathways are used to transmit information from one hemisphere to the other. Our experimental findings suggest two potential limitations of the compensatory pathway. First, the delayed neural onset of remapping activity in area LIP suggests that the alternate pathway may involve additional synapses to transfer the memory trace activity from one hemisphere to the other. The use of such an indirect route might also lead to the observed reduction in the strength of remapping activity in the

across-hemifield condition, and to the prolonged reaction times during initial performance of the double-step task. Second, our behavioral findings indicate that learning in the across-hemifield condition is not readily generalized to new spatial targets. This suggests that the alternate interhemispheric route may be established on an as-needed basis between restricted portions of the visual field. This intriguing possibility would be consistent with reports of experience-dependent plasticity in other systems, both perceptual and motor (Karni and Sagi, 1991; Recanzone et al., 1993; Padoa-Schioppo et al., 2004)

2. Remaining capacities of the system

The limitations discussed above are consistent with studies demonstrating that interhemispheric transfer of visual information is disrupted in the absence of the forebrain commissures (Seacord et al, 1979; Eacott and Gaffan, 1989; Gazzaniga 1987, 1995). The importance of these fibers for interhemispheric integration is implied by their sheer number. Together, the corpus callosum and anterior commissure are comprised of more than half a billion axons that travel from one hemisphere to the other (Lamantia and Rakic, 1990). It is not surprising, then, that their absence has significant behavioral consequences. The greater surprise is that their absence has relatively *few* outstanding consequences. Multiple studies in human, monkey, and cat have demonstrated that a remarkable number of faculties remain intact in the absence of the forebrain commissures, particularly in the visuospatial domain (Trevarthen, 1990; Corballis, 1995). This suggests that other pathways, particularly those that recruit subcortical structures, provide for communication between the disconnected cortical hemispheres. Studies of human split-brain patients have suggested that subcortical-cortical interactions can support the interhemispheric transfer of coarse spatial information, for use by perceptual as well as oculomotor systems (Holtzmann, 1984). Consistent with these observations, we obtained behavioral and physiological evidence

that the system for interhemispheric spatial updating is remarkably sound in the absence of the forebrain commissures. We now discuss three aspects of spatial updating that remain intact in the absence of the forebrain commissures.

First, the system is capable of updating locations across hemifields with considerable spatial precision. This conclusion emerges from an observation in our behavioral experiments. We found that the monkeys accurately adjusted their double-step performance to account for small shifts in the location of the second target. This indicates that subcortical pathways are capable of transferring fine spatial information. At first glance, our result stands in contrast to the claim of Holtzmann (1984) that the corpus callosum is required for the transfer of fine spatial information. In the experiments by Holtzmann, however, the conditions that required fine spatial information also required an analysis of form. Thus it appears that the subcortical pathways may provide spatial precision sufficient for localization and action – at least the action of generating eye movements – but not for the perception of form (Corballis, 1995).

Second, the system is able to update spatial locations in a predictive fashion. We found that the neural latency of remapping activity is delayed on average when an interhemispheric transfer of visual information was required. Nevertheless, equivalent *proportions* of neurons exhibited predictive updating activity for the interhemispheric and intrahemispheric conditions of the single-step. This suggests that the alternate pathway has access to eye movement command signals that can rapidly modify visual representations. Predictive updating is typically observed in roughly a third of neurons in LIP, FEF, and SC (Duhamel et al., 1992a; Walker et al., 1995; Umeno, et al. 1997, 2001). The fact that predictive updating still occurs for the across-hemifield condition suggests that the system has the capacity to achieve a rapid convergence of corollary discharge and visual signals, even with the use of pathways that are less direct.

Third, the system has the capacity to convey the behavioral relevance of the stimulus to be updated. This is indicated by the observed increase in neural activity when the monkey performs that double-step task as compared to the single-step task. In the normal animal, this increase is thought to reflect the fact that the second stimulus location is the target of an upcoming saccade. The observation suggests that, in the normal monkey, spatial updating is influenced by attentional mechanisms, and makes use of salience maps of visual space (Gottlieb et al., 1998; Kusunoki et al., 2000; Goldberg et al., 2002). We observed the same increase in activity in the split-brain monkey, suggesting that remapping is still modulated by attention in the absence of the forebrain commissures. This notion is compatible with data from human split-brain subjects demonstrating interhemispheric transfer of spatial attention (Holtzmann et al., 1981; Gazzaniga, 1987; Corballis, 1995).

Summary of capacities in the absence of the forebrain commissures

We have discussed the functional capacities of the system for interhemipheric spatial updating in the absence of the forebrain commissures. This system is limited in two ways: it is less direct, and does not immediately adapt when new spatial targets must be updated from one hemisphere to the other. The system is nonetheless effective in providing precise and relevant spatial information, and has the capacity to do so rapidly.

3. Potential neural substrates for interhemispheric updating in the absence of the forebrain commissures

What brain structures participate in interhemispheric updating in the absence of the forebrain commissures? The superior colliculus likely plays an important role. Neurons in the intermediate layer of the SC demonstrate remapping activity (Walker et al., 1995). In the normal

monkey, this activity is thought to be a reflection of signals generated in area LIP, which is considered to be critical for spatial updating (Quaia et al., 1998; Li and Andersen, 2001). In the split-brain monkey, remapping may still be generated in LIP, by use of a more circuitous route, and imposed on the SC. Alternatively, remapping activity in LIP may reflect processes that originate in the SC.

The functional and anatomical properties of the SC suggest that it could independently support interhemispheric remapping in the absence of the forebrain commissures. Neurons in the intermediate layers of the SC exhibit visuo-movement activity in conjunction with saccadic eye movements (Wurtz and Albano, 1980; Sparks and Mays, 1980; Mays and Sparks, 1980; Munoz and Wurtz, 1995). Recent physiological findings indicate that the functions of the SC extend beyond its role in oculomotor function. In addition to remapping, neurons in the intermediate layer are active in relation to higher cognitive functions such as target selection, response suppression, and covert attention (Walker et al., 1995; Basso and Wurtz, 1997, 1998; Horwitz and Newsome, 1999; Pare and Hanes, 2003; Munoz and Everling, 2004; Ignashchenkova et al., 2004; Krauzlis et al., 2004). These observations indicate that SC neurons have access to a range of sensorimotor and cognitive signals that are integral to the computations of spatial updating. These functional properties are conferred by the cortical inputs to the SC. The intermediate layers of the SC receive strong input from both FEF and area LIP (Fries, 1984; Lynch et al., 1985). The cortico-tectal projections from FEF convey a spectrum of visual, mnemonic, and saccade-related activity (Segraves and Goldberg 1987; Sommer and Wurtz 2001). Projections from area LIP to SC also transmit a range of signals, with an emphasis on visual information (Pare and Wurtz, 1997, 2001). Furthermore, all dorsal stream extrastriate visual areas project to the SC (Fries, 1984), and neurons in all these areas have remapping activity (Nakamura and

Colby, 2000). These multiple projections presumably provide oculomotor, visual, and mnemonic signals to the SC.

How might these signals be transferred interhemispherically in the absence of the forebrain commissures? Neurons in the intermediate and superficial layers of the SC are linked via the intertectal commissures. Recent anatomical studies have demonstrated that these commissures connect the entire rostrocaudal extent of the SC (Munoz and Istvan, 1998; Olivier et al., 1998). In principle, then, communication could take place between neurons representing all portions of space, including locations near the fovea (rostral neurons) and location in the periphery (caudal neurons). These anatomical findings suggest that the intertectal commissures have the potential to transmit the information necessary for across-hemifield updating of salient locations.

The SC, via the intertectal commissures, is an obvious candidate for supporting interhemispheric visual transfer in the absence of the forebrain commissures. Yet it is one among many structures that may participate in interhemispheric updating. Visual and oculomotor signals converge in multiple subcortical and cortical areas. Two other subcortical structures may be particularly well-suited to contribute to interhemispheric remapping: the pulvinar and the cerebellum. Remapping has not yet been investigated in these structures, but both are interconnected with areas that exhibit remapping (Hardy and Lynch, 1992; Lynch et al., 1994). Furthermore, both structures have been implicated as pathways for interhemispheric transfer in the absence of the forebrain commissures (Glickstein, 1990; Corballis, 1995). These findings underscore the likelihood that a broad network of regions may work together to carry out interhemispheric remapping of visual locations when the predominant pathways – the forebrain commissures – are absent.

PART II. THE FOREBRAIN COMMISSURES ARE NOT THE PRIMARY ROUTE FOR THE INTERHEMISPHERIC TRANSFER OF COROLLARY DISCHARGE SIGNALS DURING UPDATING

In contrast to our observations on transfer of visual signals, our behavioral and physiological findings indicate that transection of the forebrain commissures has only a minimal effect on the transfer of the corollary discharge signals that initiate spatial updating. Both monkeys readily performed the condition of the double-step task that required an interhemispheric transfer of this oculomotor information. Likewise, neurons in area LIP had strong remapping activity in this condition.

Evidence for intact communication of corollary discharge signals

Studies in split-brain humans have suggested that the disconnected hemispheres are capable of generating eye movements in both directions (Holtzmann, 1984; Hughes et al., 1992). This claim is further supported by the observation that hemispherectomy patients are capable generating bidirectional saccades (Sharpe et al. 1979). Hughes et al. postulated that, in split-brain subjects, there is either an ipsilateral representation of oculomotor commands at the cortical level, or there is a subcortical transfer of information.

If ipsilateral saccade representations are present in the cortex of the split-brain monkey, they provide a ready explanation for the relative ease of updating observed in our experiments. In effect, updating in this condition would be accomplished easily, because the transfer of corollary discharge signals is intrahemispheric. Physiological studies provide scant evidence, however, that the cortical eye fields represent ipsiversive saccades. Stimulation in the frontal and supplementary eye fields can elicit ipsiversive eye movements, but occurrences are rare and the saccades are small (Schlag and Schlag-Rey, 1987; M. Goldberg, personal communication).

Furthermore, it is not known whether these ipsiversive movements can be elicited in the absence of the forebrain commissures.

A growing body of evidence favors a role for subcortical pathways in relaying the corollary discharge signal required for spatial updating. One of the most promising pathways for the communication of corollary discharge signals is the ascending path from the superior colliculus to the frontal eye field. Anatomical and microstimulation studies have shown that neurons in the intermediate layer of the SC project to the FEF via the mediodorsal thalamus (Lynch et al., 1994; Sommer and Wurtz, 1998). These projections are predominantly ipsilateral. In other words, information about a rightward saccade is represented in the left hemisphere, at the level of SC and at the level of cortex.

Of direct relevance to our results, stimulation studies have recently identified a *crossed* pathway from the SC to the FEF. In a population of FEF neurons receiving input from the SC, roughly 20% of the cells received projections from the contralateral SC (M. Sommer, personal communication). This crossed ascending path could serve to transmit a corollary discharge signal interhemispherically, in both the normal and the split-brain monkey. In other words, a copy of a the command to make a rightward saccade - generated in the left SC - could be sent to the right FEF. This corollary discharge command could then act upon visual representations in the right cortical hemisphere, potentially in area LIP. An alternate possibility is that the corollary discharge signal generated in one SC could cross at the level of the intertectal commissures, then travel via the uncrossed ascending tecto-cortical pathway. Either route could support the accurate updating observed in the present study. The anatomical basis of corollary discharge signals is just beginning to be explored (Guillery, 2003; Sommer and Wurtz, 2002, 2004a,b). They may arise from many brain structures, both cortical and subcortical. Our

findings indicate that corollary discharge signals are readily available to modify visual representations in both hemispheres.

PART III. GENERAL IMPLICATIONS FOR THE MECHANISMS OF SPATIAL CONSTANCY

How do the current findings provide insight to the larger problem of spatial constancy?

In this final section, we discuss two broad implications of our research.

Flexible circuits for spatial updating

In the present experiments, we found that interhemispheric remapping was not abolished in the absence of the most prominent and direct route for communication between the two cerebral hemispheres. The system, although less effective in the absence of the forebrain commissures, supports a remarkably accurate updating of visual representations from one visual hemifield to the other. These findings indicate that spatial updating is subserved by a redundant circuit/by a network of regions, capable of rapid reorganization. That the brain reorganizes on behalf of remapping suggests that spatial updating is an integral and important function. is an integral and important component of visuomotor function.

The resilience of across-hemifield updating in the split-brain monkey is reminiscent of previous demonstrations of recovery of function in the oculomotor system. Lesions to the colliculus or frontal eye field induce deficits in saccadic eye movements, but these deficits are quite transient unless both structures are removed (Schiller et al., 1979, 1980). If either the SC or FEF remains intact, voluntary saccade generation recovers within several weeks. These findings have been interpreted as evidence of parallel pathways (Schiller et al., 1980; Schiller et al., 1987), and more recently as evidence of reorganization in the oculomotor system (Hanes and

Wurtz, 2000). The plasticity of cortico-subcortical interactions likely contributes to the success of across-hemifield updating observed in the present study.

Experimental validation of the model of spatial updating

A recent model of spatial updating proposes that remapping activity reflects a transfer of retinotopic visual information brought about by the eye movement (Quaia et al., 1998). Specifically, the model postulates that one set of neurons ("pre" neurons) maintains a memory trace of a salient stimulus location before the eyes move. When the eye movement command is issued, these neurons transfer their activity to another set of neuron ("post" neurons). The "post" neurons encode the salient location after the eyes reach their new position. In the across-hemifield condition employed in the present study, these "pre" and "post" neurons were located in opposite hemispheres, providing a unique opportunity to investigate the transfer of information. Our findings of impaired across-hemifield updating in the split-brain provide experimental validation of the model. We can infer that, in the normal monkey, information about stimulus location is transferred from "pre" to "post" neurons via the forebrain commissures. This finding is consistent with the notion that the brain maintains a dynamic representation of the visual world in retinal coordinates, a coordinate system compatible with the generation of eye movements – and thus with the active perception of the visual world.

Appendix

OVERVIEW

In the following sections, we describe the procedures for the experiments described in Chapter 2-4. This appendix has three main sections: 1) General procedures 2) Methods for behavioral experiments 3) Methods for physiological recording.

I. GENERAL PROCEDURES

SUBJECTS

Subjects were two adult rhesus macaques, one male and one female, weighing 6.6-7.3 kg. All experimental protocols were approved by the University of Pittsburgh Institutional Animal Care and Use Committee, and were certified to be in compliance with guidelines set forth in the Public Health Service Guide for the Care and Use of Laboratory Animals.

SURGICAL PROCEDURES

The commissurotomy was performed at the outset of the experiment. Details of the surgical procedure can be found in Vogels et al., 1984. The monkeys were prepared for this surgery with dexamethasone, and anesthesia was induced with ketamine and maintained with isoflurane. Mannitol was administered throughout the surgery to minimize tissue swelling. During the following two weeks, analgesics were given to control postsurgical pain, and antibiotics were administered daily to prevent infection. Additionally, the monkey's health and behavior were closely monitored for signs of epileptiform activity or subdural swelling, and additional drugs were administered as needed to counteract these effects.

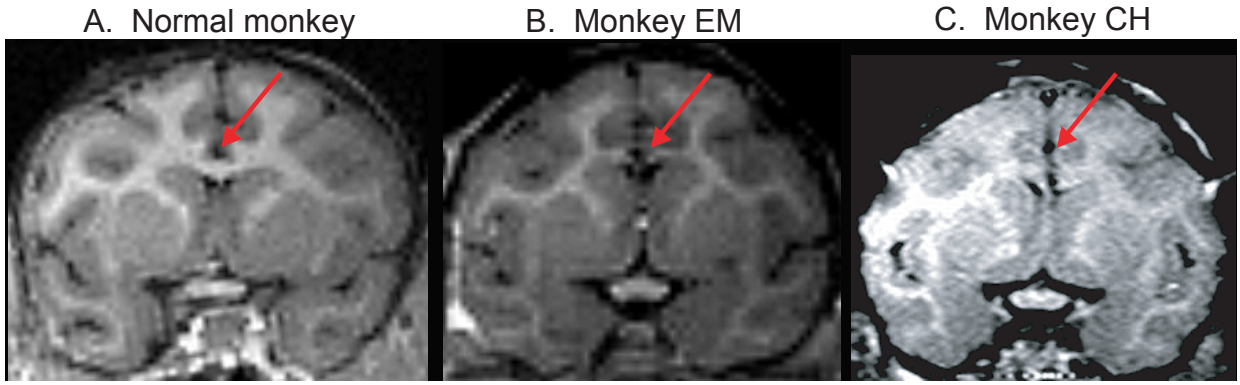
We verified the absence of the corpus callosum using magnetic resonance (MR) imaging. Structural MR images were acquired for each monkey, using the 4.7 T magnet at the Pittsburgh NMR Center. Coronal MR images, from a normal monkey and from each of the split-brain monkeys used in the present study, are shown in Figure A1 (panels A-C).

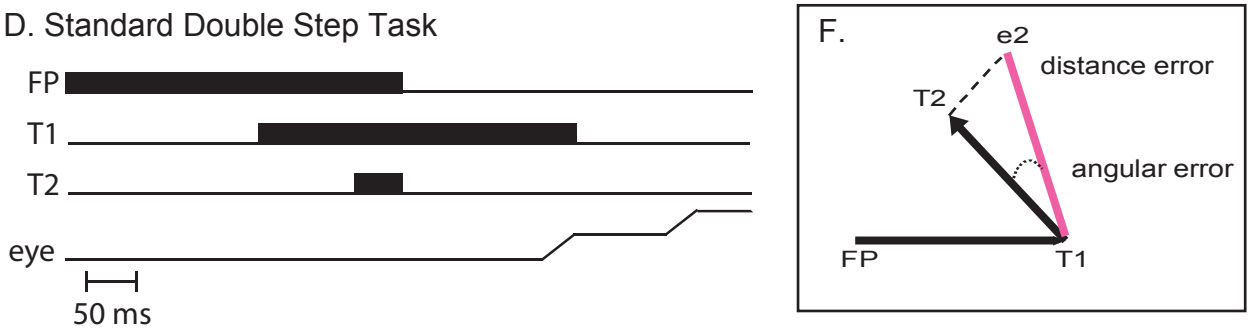
Following several months of recovery, a second surgery was performed to prepare the animal for behavioral training. In this surgery, scleral search coils were implanted for monitoring eye position, and head restraint bars were affixed for the purpose of holding the monkey's head stable during testing sessions. Following completion of the behavioral experiments described in Chapter 2, monkeys underwent a third surgery to install a chamber for recording from area LIP. The placement of the recording chamber was determined using 1) the standard stereotaxic locations for area LIP (5mm posterior and 12mm lateral in Horsley Clarke coordinates) and 2) anatomical information from structural magnetic resonance images. Surgical procedures are described in Nakamura and Colby, 2002.

STIMULUS PRESENTATION

Stimuli

During behavioral and recording sessions, the monkey sat with its head fixed in a primate chair, in a darkened room. The monkey faced a tangent screen, which subtended approximately 100° horizontally and 75° vertically. Visual stimuli were back-projected onto the screen using an LCD projecter. Background luminance was 5.215 cd/m^2, and stimulus luminance was 205.9 cd/m^2. Stimulus presentation was under the control of two computers running a C-based program, CORTEX, made available by Robert Desimone at the National Institutes of Mental Health.





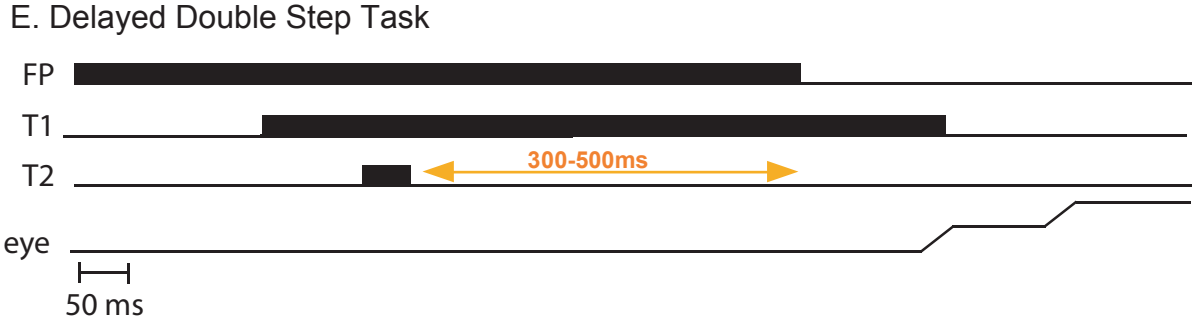


Figure A1. Verification of commissurotomy (panels A-C) and timing of the double-step saccade tasks used in behavioral experiments (panels D,E). **Panel A-C**: Coronal MR images from a normal monkey (panel A) and from the two split-brain monkeys studied in the present experiment: monkey EM (panel B) and monkey CH (panel C). Arrows point to the location of the corpus callosum (A) or its absence (B,C). **Panel D:** Timing of the standard double-step task, employed in all experiments except for Experiment 5 (Chapter 2). In the standard task, the monkey maintains gaze on the central fixation point FP for 300-500 ms. The first target (T1) is illuminated for 100 ms, afterwhich the second target (T2) is illuminated for 50 ms. Then FP and T2 are turned off simultaneously, cueing the monkey to make a visually guided saccade to T1. T1 is turned off once the monkey acquires this target. The monkey makes a second memory guided saccade to the location of T2. If the monkey's saccade is accurate, the target is re-illuminated after 100 ms, and the monkey maintains its gaze on T2 for an additional 300-500 ms. **Panel E**: Timing of the delayed double-step task used in Experiment 5. This task is identical to the standard, except that a delay period is imposed between the appearance of T2 and the monkey's cue to initiate the first saccade (disappearance of FP). The length of the imposed delay varied randomly between 300 and 500ms. The monkey had to maintain fixation during this time. Upon disappearance of FP, the monkey initiated the double-step sequence. **Panel F:** Accuracy was quantified using two complementary measures, angular error and distance error. The target sequence is shown in black, the monkey's second saccade in pink. Distance error refers to the absolute vector distance between the target (T2) and the saccade endpoint (e2). Angular error refers to the angle between the target trajectory and the trajectory of the monkey's eye movement.

Measurement of stimulus decay

In behavioral and physiological experiments, it was critical that the to-be-updated stimulus had disappeared before the monkey initiated the saccade away from central fixation. We measured the phospho-persistence of the stimulus and determined the psychophysical threshold for each monkey, in order to ensure that the stimulus was perceptible only when the eyes were at central fixation. The stimulus did not vanish instantaneously when it was turned off, but decayed with a time constant of 8ms. We calculated the luminance threshold for each monkey in the memory-guided saccade task, using a staircased design. We determined that the stimulus used in the remapping tasks was below perceptual threshold within 8ms after its offset for monkey EM, and 16ms for monkey CH. The monkeys typically initiated the saccade with a latency of 150ms (minimum acceptable latency was 50ms). Taken together, these observations show that the monkeys had access only to retinal information about the stimulus when the eyes were fixated centrally.

DATA COLLECTION

Eye position was monitored using scleral search coils (Judge, 1980). Eye position was sampled at 250 Hz (initial behavioral testing of monkey EM; physiological testing of both monkeys) or 100 Hz (initial behavioral testing of monkey CH). Eye data were stored for offline analysis, along with CORTEX event markers, which indicated when stimuli appeared and were extinguished.

DATA ANALYSIS

Data processing and statistical analyses were carried using custom-written MATLAB programs and SPSS. For all experiments, saccades were identified on the basis of velocity criteria, using a custom-written MATLAB program. The beginning of the saccade was defined as the timepoint when velocity exceeded 50°/sec. The end of the saccade was defined as the timepoint when velocity fell below 20°/sec. The program used additional spatial and temporal criteria to ensure that each saccade was identified correctly. The accuracy of saccade identification was verified by the experimenter.

Saccade latency was defined as the difference between the time of the beginning of the saccade, relative to the time when central fixation was extinguished. We excluded from analysis any trials in which the latency was less than 50ms.

II. METHODS FOR BEHAVIORAL EXPERIMENTS IN CHAPTER 2

TASKS

We used the double-step saccade task to assess the monkeys' ability to localize briefly presented targets following an intervening eye movement (Hallett & Lightstone, 1976).

Timing of the double-step task

The timing of the standard double step task is shown in Figure A1 (panel D). Each trial began with the appearance of a central fixation point (FP). Once the monkey attained fixation, an initial fixation period of 300-500ms ensued. The first target (T1) then appeared. The second target (T2) appeared 100ms after the onset of T1. T2 was extinguished 50ms later, simultaneously with the offset of FP. Up to this point of the trial, the monkey was required to maintain central fixation within an electronic eye window of ± 2º. When FP was extinguished,

the monkey initiated the double step sequence, with the first saccade to T1 and the second saccade to T2. T1 was extinguished once the monkey attained it, within an eye window of ± 2º. If the monkey successfully reached the location of T2 within an eye window of ±2.5º, this target reappeared after 100ms. The monkey was required to refixate this target for an additional 300-500ms to receive juice reward. The eye windows described here applied to the standard paradigm, in which target amplitudes were 12º. In other paradigms, eye windows were adjusted for target amplitude, such that the T1 eye window was equal to ~15% of target amplitude, and the T2 eye window was equal to ~20% of target amplitude. In Experiment 5, we measured performance on the delayed version of the double-step task, which was identical to the standard task in all respects, except that the monkey had to maintain fixation during a 300-500ms delay period before generating the sequence (Figure A1, panel E).

Spatial configurations of the double step task

Training on the double-step task took place in two stages, in which the monkey was trained first to perform multiple sequences in the vertical version of the task, and then to perform the central sequences in the horizontal version of the task. These training sequences are described in Chapter 2. For each experimental testing session, we measured double-step performance in three conditions. 1) A well-trained *central* condition, in which the second saccade was strictly vertical. This sequence did not require interhemispheric transfer of either visual or corollary discharge information. 2) A novel *within* condition, in which both the visual and corollary discharge signals were transferred within the same hemisphere. 3) A novel interhemispheric condition, either *"visual-across"* (Experiments 1-5) or *"motor-across"* (Experiments 6,7). In the visual-across condition, updating of the second target required an interhemispheric transfer of visual signals. In the motor-across condition, updating of the second target required an

interhemispheric transfer of motor signals, namely, the corollary discharge signal. We tested these conditions separately in the upper and lower visual fields. In each vertical visual field, there were two sequences for each condition, one in each quadrant (Chapter 2, Figure 11). This yielded six sequences, which were randomly interleaved without replacement. Trials did not repeat on error.

ANALYSIS OF BEHAVIORAL DATA

Classification of trials

We excluded from analysis any double-step trials in which the latency of the first saccade was less than 50ms or greater than 500ms. In addition, we excluded trials in which the monkey attained T1 but directed the second saccade into the wrong vertical visual field. These highly erratic trials were observed primarily in monkey EM in the visual-across condition, during later sessions of testing the standard sequences. Having removed anticipatory or otherwise erratic trials from analysis, we classified the trials according to error type, defined in the following way. Correct trials were those in which the first saccade reached T1 and the second saccade reached T2. S2 error trials were those in which the first saccade reached T1 but the second saccade failed to reach T2. Reversal trials were those in which the first saccade was directed to T2, rather than to T1. S1 error trials, in which the first saccade went to neither T1 nor T2, were excluded from further analysis. We determined the percentage of the three remaining error types – correct, S2 error, and reversals (Chapter 2, Figure 14). For quantification of accuracy and latency, we used only those trials where the monkey accurately reached T1, i.e. correct trials and S2 error trials. The criteria for saccade to "reach" a target location were as follows. For the first saccade to reach T1, the distance error between the saccade endpoint and the target had to be less than 15% of the target's amplitude (i.e., a gain of .85), and angular error had to be less than 10°. For the

second saccade to reach T2, the distance error had to be less than 20%, and angular error had to be less than 12°. These offline criteria approximated the size of the online electronic eye windows. The criteria were less stringent for the second saccade because it was memory-guided.

Measures of saccade accuracy

We report the results obtained using two complementary measures of accuracy (Figure A1, panel F). Angular error measures the directional discrepancy between the monkey's trajectory and the ideal trajectory. Distance error measures the difference between the endpoint of the monkey's saccade and the target. We report unsigned, rather than signed error, for each of these measures. We chose this approach because the use of a signed measure leads to an exaggeration of differences between the within and visual-across conditions. This exaggeration is illustrated in Figure A2, which shows the results of the first experiment using the unsigned measure of angular error. For both the within and visual-across conditions, the second saccade tended to be directed more toward the target of the well-trained central condition. For this analysis, we designated the sign of the error relative to the vertical meridian; in other words, positive errors meant that the saccade were displaced from the target, in the direction away from central fixation. This led to a positive angular error for the visual-across condition (red bars in all panels), but a negative angular error for the within condition (green bars in all panels). Alternatively, if we designated the sign of the error relative to the central T2 location, we under-estimated systematic errors

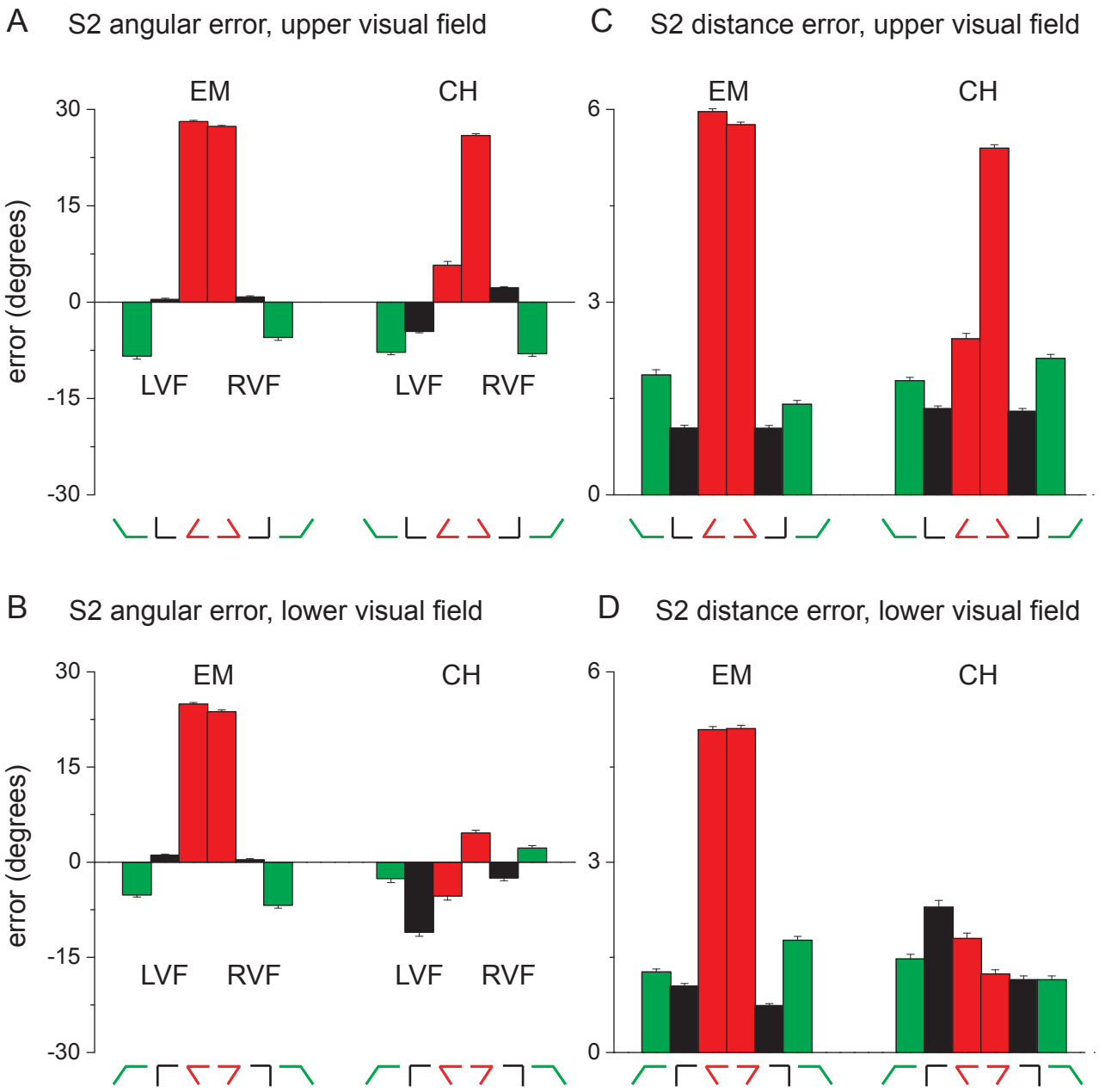


Figure A2. Accuracy measures for double-step performance from the first session of testing, using signed measures of angular error (panels A,B). Measures of distance error, shown in panels C and D, are identical to those in presented in Chapter 2. For angular error, negative values indicate that the monkey's saccade was hypometric, relative to central fixation. In other words, hypometric saccades were those in which the endpoints landed between the target and central fixation, whereas hypermetric saccades were those with endpoints that landed beyond the target location, relative to central fixation. Using this designation, differences between the within (green) and visual-across sequences (red) was exaggerated. This exaggeration occurs primarily because, in both conditions, the monkey's errors tended to be directed toward the well-trained central target, resulting in more negative error values for the within condition, but more positive error values for the across condition. This similarity in error - that saccades in both sequences tend toward the central T2 - is not captured by the signed measure.

relative to the vertical meridian. We employed the unsigned measure of angular error to avoid this complication introduced by multiple reference frames.

III. METHODS FOR PHYSIOLOGICAL EXPERIMENTS IN CHAPTERS 2 AND 3

We recorded from 306 visually responsive LIP neurons in three hemispheres of two monkeys. We examined the activity of 223 of these neurons, which met criteria for inclusion in analysis, as described below.

PHYSIOLOGICAL RECORDING

Neural activity was recorded using tungsten microelectrodes (FHC) introduced into the cortex through stainless steel guide tubes placed flush with the dura. The guide tubes were stabilized by a nylon grid (Crist Instruments) held rigidly in the recording chamber. Action potentials were amplified and filtered with a band-pass of 500 Hz to 5 kHz, and digitally sampled using template matching at 20 kHz. The template matching system was SPS-8701 (Signal Processing Systems).

Identifying area LIP

We identified recording sites within the lateral bank of the intraparietal sulcus on the basis of anatomical landmarks and functional criteria. In initial recording sessions, we mapped the location of the intraparietal sulcus within the chamber. We systematically recorded from the anterior-most to the posterior-most part of the chamber. Using this procedure, we were able to localize the sulcus as the transition from somatosensory responses on the medial bank, to visual responses on the lateral bank. Within the lateral bank, the response properties of neighboring areas 7a and VIP provided additional landmarks for the identification of area LIP. Area 7a is located superficially, and neurons here exhibit broad visual responsiveness and post-saccadic

firing (Barash et al., 1991). Area VIP is located in the fundus of the sulcus, and neurons here exhibit striking selectivity for directional motion (Colby et al., 1993). Area LIP is located between these two functionally distinctive areas. We identified LIP neurons according to the conjunction of two criteria. First, the depth of the recorded neuron had to be at least 2mm below the cortical surface. Second, the neuron had to respond selectively to contralateral visual stimuli.

TASKS DURING PHYSIOLOGICAL RECORDING

After isolating an individual neuron in area LIP, we recorded its activity during three kinds of tasks, which 1) characterized the response properties of the neuron, 2) measured neural activity associated with remapping, and 3) measured neural activity during critical controls. In each task, we obtained 12-20 trials per condition. Conditions were randomly interleaved for the remapping and control tasks.

Characterizing receptive field properties

Memory-guided saccade task

We used the memory-guided saccade (MGS) task to determine the response field of each neuron. This task allows the separation of sensory, mnemonic, and saccade activities (Hikosaka and Wurtz, 1983). Each MGS trial began with a period of initial fixation (300-500ms). A stimulus was flashed briefly (50ms) while the monkey continued to fixate. The monkey had to maintain fixation for a variable delay (300-500ms). At the end of the delay period, the fixation point disappeared. This cued the monkey to make a saccade to the remembered location of the flashed target. If the monkey made a saccade to the target that fell within an electronically-defined eye window, the target reappeared after 100ms and the monkey was required to hold fixation at this

location for an additional 300-500 before receiving juice reward. The size of the electronic eye window was equivalent to 20% of the target amplitude.

For initial mapping of the receptive field, MGS targets were presented in eight canonical directions, in three concentric rings of increasing amplitude. For example, if the 'base amplitude' was set to 10º, targets appeared in each direction at distances of 10º, 20º, and 30º, yielding 24 targets total. We adjusted the base amplitude as needed in order to identify the location of best responsiveness. When recording from a familiar track, we focused the initial mapping in the contralateral hemifield, typically using a base amplitude of 8 º.

Stimulus in receptive field

This task was used to measure the neural response to a passively-viewed stimulus in the response field. After an initial fixation period (300-500ms), a stimulus appeared in the response field, for 50ms. The monkey maintained central fixation throughout the trial, including another 300-500ms after stimulus appearance. This task was distinguished from the memory-guided saccade task in two ways. First, the color of the fixation spot was pink instead of white as in the memory-guided saccade task. Second, the intertrial interval was very short (10ms). This discouraged the monkey from attempting to make a saccade to the RF when the fixation point disappeared between trials.

Remapping tasks

Single-step task

This task was used to measure remapping activity of the cell. Timing of the task is shown in Figure A3. Each trial began with an initial fixation period of 300-500ms. Then a stimulus appeared for 50ms. Then three events occurred simultaneously: the stimulus disappeared, the fixation point disappeared, and a new fixation point (FP2) appeared. The monkey made a saccade to the new fixation point. The spatial arrangement of targets and stimulus was such that the saccade to FP2 brought the neuron's RF onto the location where the stimulus had appeared. For all remapping and control tasks, the conditions of interest (within, visual-across, and motor-across) were randomly interleaved. We included in analysis only those trials on which the saccade met three criteria: 1) latency was between 50 and 350 ms; 2) angular error was less than 10°; and 3) distance error was less than 15% of the target's amplitude (i.e., a gain of .85).

Double-step task

This task was used to measure simultaneously remapping activity of the cell and the monkey's spatial behavior. The timing of the double-step task during physiological recording was identical to that employed in the behavioral experiments described above. The spatial configuration was identical to that of the single-step task; the critical difference was that the monkey now made two eye movements. Thus, we refer to the FP1 location as T1. The location of the flashed stimulus is no longer irrelevant to the monkeys' behavior, but instead serves as the target of the second eye movement (T2). The spatial configuration used in each session was determined by the receptive field of the neuron. The conditions were matched for amplitude of the first and second saccades. The direction of the first saccade differed, depending on the condition. The direction

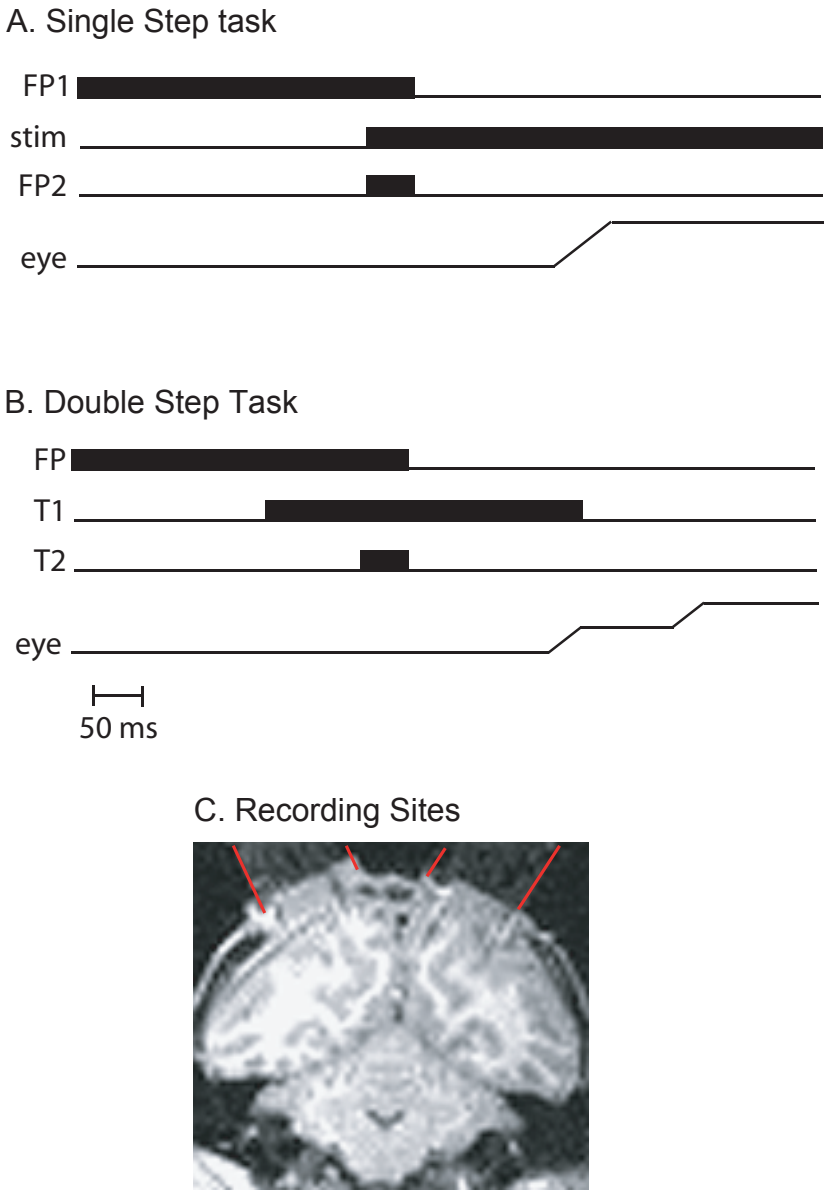


Figure A3. Behavioral paradigms and recording locations for physiological experiments. A. Timing used in the single step task. The monkey holds its gaze on fixation point FP1 300-500 ms. Two events then occur simultaneously: a peripheral stimulus flashes for 50 ms and a new fixation point (FP2) is illuminated. The offset of the stimulus is concident with the offset of FP1. This was the monkey's cue to make a visually guided saccade to FP2. The monkey maintains its gaze on FP2 for an additional 500-700 ms. B. Timing used in the double step task. Timing is similar to the single step task, but the monkey is required to make two sequential eye movements. Temporal features of the trial are identical to those described for behavioral experiments in Chapter 2 (Figure A1). C. Coronal magnetic resonance image shows recording locations in monkey CH. The red lines mark the locations of the recording chambers. Neurons were recorded on the lateral bank of the intraparietal sulcus in both hemispheres.

and amplitude of the second saccade was the same for the updating conditions (within, visual-across, and when possible, motor-across), as it corresponded to the location of the neuron's response field. For all conditions, the second target was placed at least five degrees away from the midline, as receptive fields in area LIP of the normal monkey can extend five degrees ipsilaterally (Ben Hamed et al., 2001). For the analysis of double-step performance described in Chapter 4, we quantified accuracy and latency according to the same methods applied in the behavioral experiments in Chapter 2. We used only those trials in which the monkey accurately reached T1, defined as a distance error less than 25% of the target's amplitude (i.e., a gain of .75), and angular error less than 10°.

Control tasks

Stimulus-only control

This task was used to determine the neuron's responsiveness to stimuli used in the single-step task (T2 in the double-step task), when they were presented alone with no accompanying eye movement. The task was identical to the Stimulus-in-RF task, except that the stimulus was placed at the location that would be encompassed by the neuron's receptive field after completion of the saccade (main saccade in the single-step task, S1 in the double-step task).

Saccade-only control

This task was used to determine the neuron's responsiveness in conjunction with the saccade to FP2. The timing and spatial configurations are identical to the single-step task, except that no peripheral stimulus is presented.

Order of presentation

The tasks were presented in the following order: 1) memory-guided saccade, 2) Stimulus in RF, 3) Stimulus-alone control, 4) Saccade-alone control, 5) Single-step task, 6) Double-step task. The neuron was then retested in the stimulus-in-RF task, to verify that its responsiveness was maintained. We recorded during the control tasks before the remapping tasks in order to prevent contamination of neural activity in the control tasks by lingering memory traces (Umeno and Goldberg, 2001).

ANALYSIS METHODS FOR NEURAL DATA

Defining significant neural activity

In experiments measuring updating activity in the normal monkey, single step conditions are rejected for analysis if either the stimulus or saccade control conditions elicit any activity above baseline. Using this stringent criterion, one can be assured that any activity observed in the single step task is attributable to spatial updating. Our experiments required two sets of control conditions in which no activity was elicited in either control task. Due to the nature and extent of LIP receptive fields, it was often the case that we observed activity in at least one of the control conditions. The average width of LIP receptive fields is 12 degrees (Ben Hamed et al, 2001), but can extend to encompass an entire quadrant. It was thus sometimes the case that the stimulus appeared in the receptive field when the eyes were at the initial fixation position. Additionally, neurons sometimes exhibited activity in the saccade-alone task. This activity was predominantly post-saccadic and likely reflected a remapping of the central fixation point.

In order to include as many neurons as possible in our analyses, we devised a method to isolate updating activity in each of the single step conditions. First, a neuron was rejected for analysis if there was a visual response in either stimulus control condition. We assessed this with a t-test ($p < 0.05$) comparing activity in the visual epoch 50 to 250 ms after stimulus onset to

baseline activity (the final 100 ms before stimulus onset). Second, we used a standard epoch to analyze activity in the single step tasks. Activity was measured in a 200ms epoch beginning at saccade onset. We chose this epoch based on inspection of the population histograms (Figure A4, panel A), and because previous experiments have demonstrated that the onset of the remapped response occurs with a latency of -52 to 272 ms relative to saccade onset (Umeno and Goldberg, 1997). Furthermore, by analyzing activity in a standard epoch, we have an unbiased way to compare activity between the test conditions. Third, to be certain that the activity observed in the single step task was not elicited by the saccade alone, we measured activity in the same 200ms epoch of the saccade controls. Any activity that could not be attributed to the generation of the saccade was considered remapping activity. In other words, Remapping activity = Single step activity – Saccade control activity.

To assess the significance of remapping, we used a t-test ($p < 0.05$) to compare activity in each of the single step tasks to that of the corresponding stimulus and saccade control conditions. To compare the single step and saccade control tasks, we measured activity in the epoch described above (0 to 200 ms relative to saccade onset). To compare activity in the single step and stimulus control tasks, we measured activity in the epoch from 200 ms to 400 ms relative to stimulus onset. We chose this epoch because when the population histograms are aligned on stimulus onset, the remapping response begins at 200 ms relative to stimulus onset (Figure A4, panel B). If the activity in the single step task was significantly greater than the activity measured in each of the control conditions, remapping was considered statistically significant.

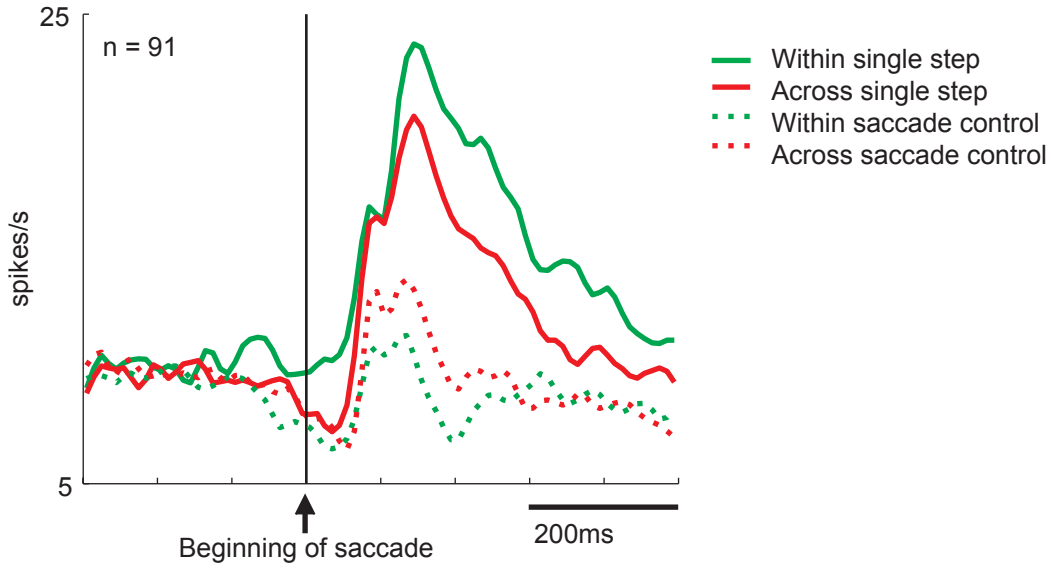


Figure A4, panel A. Average population activity in the single-step task, for within-hemifield (green) and visual-across (red) conditions. Solid lines represent activity in the single-step task. Dotted lines represent activity in the saccade-alone control task. Data are aligned on the onset of the saccade from FP1 to FP2. The population is comprised of all neurons that did not exhibit significant activity in either control task. Activity for the within condition of the single-step (solid green) diverged significantly from its saccade-control (dotted green) even before initiation of the eye movement. Activity in the visual-across condition of the single-step (solid red) diverged significantly from its saccade-control nearly 100ms after saccade onset. These data indicate that population activity in LIP 1) is greater for within-hemifield than visual-across remapping, and 2) begins earlier when stimuli are remapped within a single hemifield.

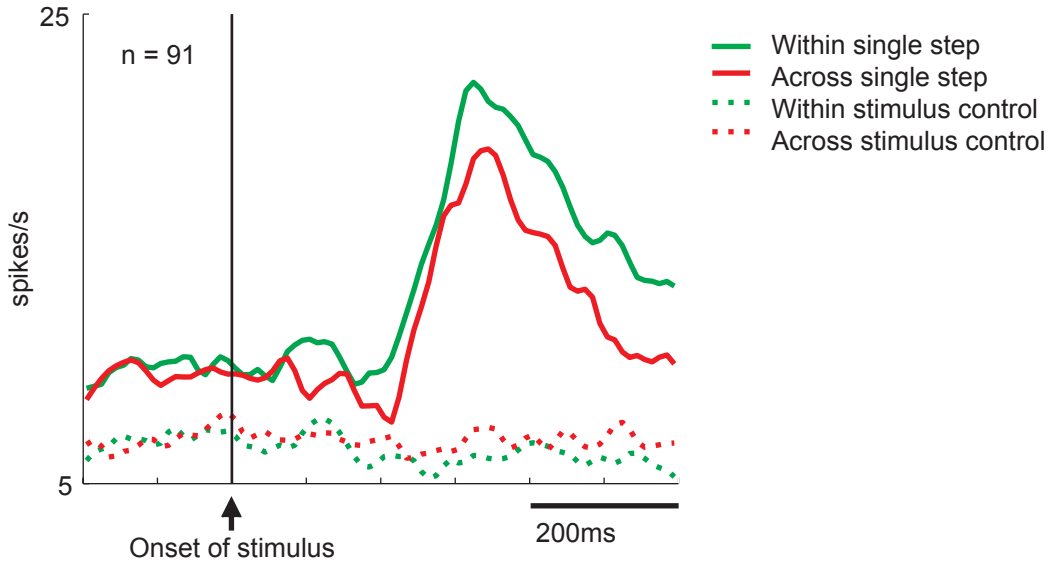


Figure A4, panel B. Average population activity in the single-step task, aligned on stimulus onset. Conventions as in SS_WApophist_sac. Solid lines represent activity in the single-step task. Dotted lines represent activity in the stimulus-alone control task. Activity for the within condition of the single-step (solid green) diverged significantly from the visual-across activity (solid red) about 100ms after stimulus onset. For both conditions, the baseline of single-step activity is shifted relative to the baseline of the stimulus control. This reflects an increase in baseline activity that occurred when the monkeys were engaged in the saccade tasks.

Calculation of neural index values

We computed a Within:Visual-across Remapping Index for each neuron in order to assess how robustly neurons remap stimulus traces across hemifields as compared to within hemifields. This index normalizes remapping activity observed in the single step tasks to the total activity observed in the single step and saccade control tasks. With such an index, each neuron in the population contributes equally, regardless of the magnitude of the response.

$$\text{Within:Visual-across Index} = \frac{(SSw - SACw) - (SSa - SACa)}{(SSw + SACw) + (SSa + SACa)}$$

Where *SSw* and *SSa* are the firing rates measured in the within and visual-across versions of the single step task, and *SACw* and *SACa* are the firing rates measured in the corresponding saccade control tasks. Positive values indicate that updating was more robust for within hemifield than for across hemifield updating. We used a similar method to compute a Within:Motor-across Index and a Motor-across:Visual-across Index.

Defining neural latency

We used the method of Nakamura and Colby (2000) to measure the latency of the remapped response in individual neurons. For the single step task, we were interested in neural latency relative to saccade onset, so we constructed histograms of neural activity aligned on saccade onset. To detect when the firing rate first began to differ significantly from baseline firing rate (200-300 ms after attainment of fixation), we measured activity in a 20ms response window beginning 100 ms before saccade onset. A t-test ($p < 0.05$) was used to asses whether activity in the response window differed significantly from baseline activity. If there was no significant difference, the window was shifted up by 2 ms, and the procedure was repeated until the activity in the response window was significantly greater than baseline activity. In order to avoid

spurious results, we defined latency based on the time of occurrence of the first of two consecutive bins that achieved significance. The midpoint of the first bin was considered the onset of the neural response. If this criterion was not met by any bins up to 300 ms after saccade onset, we concluded there was no response associated with remapping the stimulus trace. In all cases, the calculated latency was verified by inspection. Neural latency can only be reliably defined with this method if we are certain that all of the activity present in the single step task is attributable to remapping the stimulus. Therefore, if there was any significant activity in the saccade control associated with a particular single step condition, we excluded that single step condition in analyses of latency.

We used an analogous method to determine the visual response latency in the memory guided saccade task. We used a t-test ($p < 0.05$) to compare activity in the 100 ms epoch beginning at the onset of the visual response to baseline activity (100 to 300 ms after achievement of fixation). Only neurons with a significant visual response in the memory guided saccade task were included for analysis. We also used this task to assess memory and saccade responses. The memory epoch was 250 to 350 ms after stimulus offset. The saccade epoch was -100 to +100 ms relative to saccade onset.

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