How the brain constructs stable visual representations: Cortical and subcortical mechanisms

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Our eyes are constantly moving yet our perception remains stable. Neurons in lateral intraparietal cortex (LIP) update spatial representations by "remapping" visual information at the time of an eye movement. In order for remapping to occur over a wide range of eye movements, neurons must have access to visual information from the entire visual scene. The forebrain commissures appear to be the primary pathway for the transfer of visual information across hemispheres but they are not necessary. If the forebrain commissures are transected, behavior dependent on accurate spatial updating is impaired, but recovers. In three sets of experiments we examined different mechanisms of spatial updating in split brain monkeys.

First, we studied the relationship between neural activity in LIP and the behavior of the monkey. We found across the population a small but significant relationship between the activity in LIP and the performance of the split brain monkey on the double-step task. This result showed that information about the opposite visual field still reaches LIP, and this activity contributes to the overall behavior of the monkey.

Second, we determined if LIP neurons in the split brain monkeys have bilateral receptive fields. One explanation for the observed across-hemifield remapping is that information from both visual fields are represented in a single hemisphere. We found no neurons in the split brain monkeys with ipsilateral representations. We concluded that there must be a subcortical source for the across-hemifield remapping observed in the split brain monkeys.

Third, we examined the difference in spatial updating between intact and split brain monkeys in the superior colliculus (SC). In both the intermediate layers of the SC and LIP, neural activity is selectively reduced for the across-hemifield condition in split brain compared to intact animals. This suggest that remapping activity is passed from LIP to the intermediate layers of the SC. In contrast, remapping activity in the superfical layers did not differ between the intact and split brain monkeys. It may be that the superfical neurons contribute to recovered remapping activity observed in LIP.

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PREFACE

The second chapter of this document as already been published:

Berman RA, Heiser LM, Dunn CA, Saunders RC, Colby CL (2007) Dynamic circuitry for updating spatial representations. III. From neurons to behavior. J Neurophysiol 98:105-121.

This work was a collaborative effort. My contributions were data collection of a portion of the split brain monkey data, collection of all the intact monkey data and trial-by-trial analysis. The article was originally submitted without data from an intact monkey. Based on suggestions from the reviewers, we decided to collect data from an intact monkey to use as a control for the split brain data. I carried out a new experiment in the intact monkey. I trained the monkey on the task and collect all the data. After the original submission, we also added a new analysis. I designed and implemented a trial-by-trial analysis for the intact data I collected as well as the split brain data collected by me, R.A. Berman and L.M. Heiser. This new analysis become a significant portion of the final document.

1.0 GENERAL INTRODUCTION

Visual scenes are highly complex. In order to process the many details of an environment, we constantly move our eyes so that the part of the retina with the greatest acuity can be utilized. While these eye movements are necessary, they create a problem for perception. With each eye movement, the image of a stationary object changes position on the retina. Yet we perceive a stable scene. This phenomenon is known as spatial constancy.

1.1 BEHAVIORAL EVIDENCE FOR SPATIAL CONSTANCY

The need for spatial constancy was demonstrated experimentally in humans by Hallett and Lightstone using the double-step task (1976). In the double-step task, the subject began by fixating a visual target (Fig. 1A; FP). The fixation point was turned off, and two targets (T1 and T2) were flashed in succession. The subject made a first saccade to the remembered T1 location and then a second saccade to the remembered T2 location. It was critical to the task that there were no visual stimuli present during the execution of the saccades. The direction and amplitude of the first saccade could be computed based on the retinal position of the T1 target. This would not be the case for the second saccade to T2. If the second saccade were based on the initial retinal position of the target, the eye movement would be up and to the right (Fig. 1B). Correct

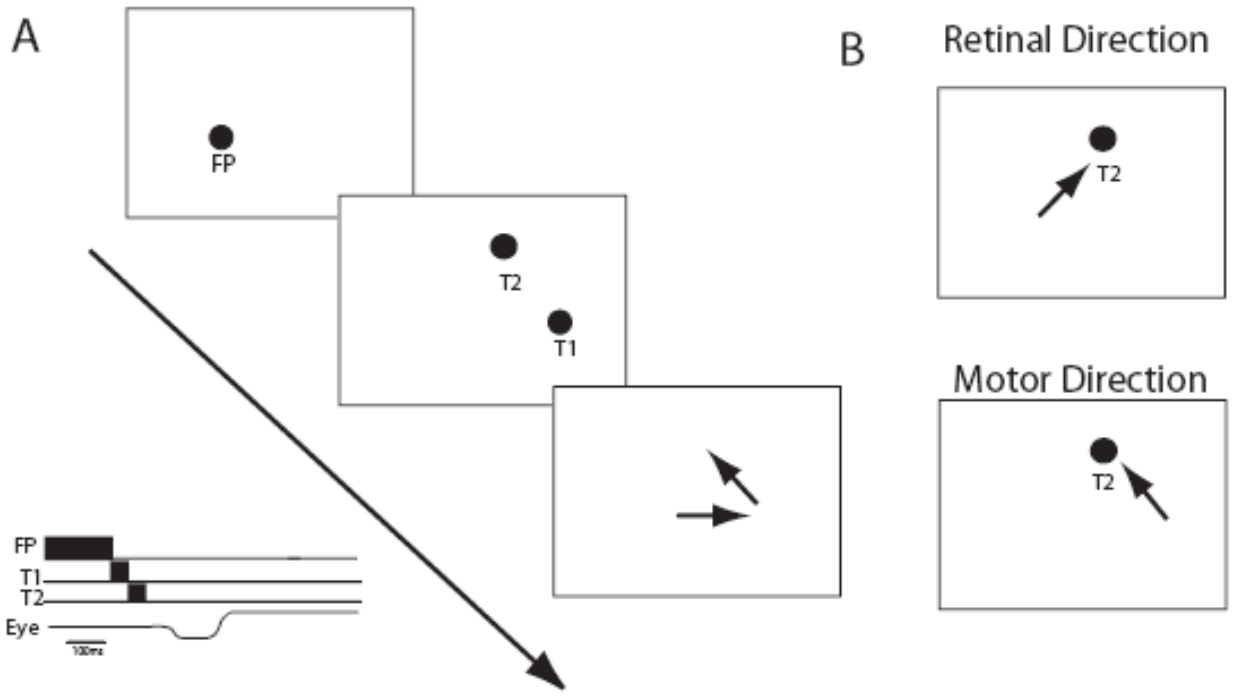


Figure 1. The configuration of the double-step task and the need for spatial constancy.

A. The spatial configuration of the double-step task. The subject begins the task fixating a central point (FP). As shown in the second panel, the fixation point is turned off and targets T1 and T2 flashed briefly in succession. The subject then makes an eye movement to the remembered location of T1 and T2. The timing of events is represented below the panels. Critically, T1 and T2 are turned off before the beginning of an eye movement. B. The top panel represents the retinal position of T2 when the subject is at the fixation point. If the subject were to make an eye movement based on retinal information alone, he would make an incorrect movement up and to the right. Instead he makes the correct motor direction, represented in the bottom panel.

performance on this task indicated that the representation of the second target depended on more than the on this task indicated that the representation of the second target depended on more than the original visual input. An accurate spatial representation also depended on information about position of the eye or the preceding eye movement. To make a correct second saccade, the brain must know that the first saccade was made.

Behavioral evidence for spatial constancy has also been found in monkeys. Monkeys trained on the identical double-step task as humans are capable of making a correct saccade to the second target (Mays and Sparks, 1980a; Baizer and Bender, 1989). In addition to the double-step task, stimulation studies demonstrate that monkeys are capable of creating stable spatial representations (Schiller and Sandell, 1983; Sparks and Mays, 1983; Sparks et al., 1987). In these studies, monkeys were trained to make a memory-guided saccade. Monkeys fixated a central location while a stimulus was flashed peripherally. Once the fixation point was turned off, the monkey made an eye movement to the remembered location. On a subset of trials, the paramedian pontine reticular formation (PPRF), the superior colliculus (SC), or the frontal eye fields (FEF) was stimulated. This evoked an eye movement away from the target. The monkeys were only rewarded when their eye landed on the location of the flashed stimulus; therefore, they made a second corrective saccade towards the remembered location. In order for the second saccade to be correct, the monkeys must take into account the evoked eye movement.

1.2 SPATIAL CONSTANCY AND COROLLARY DISCHARGE

The idea that the brain monitors our movements and uses this information to create our perceptions is an old one. In 1866, Helmholtz made a simple, but important observation. Our

vision remains clear and stable when we voluntarily move our eyes, but if we push on our eye and move it manually the visual scene appears to move. He proposed that our vision remains stable because we use information about our eye movements to adjust our perceptions. This idea was further developed in physiological terms by two research groups, Sperry (1950) and von Holst and Mittelstaedt (1950). They hypothesized that a copy of a motor command is relayed to upstream structures at the same time that the signal is sent to the muscles. Sperry termed this copy of the motor command corollary discharge.

One known pathway for corollary discharge was discovered in monkeys (Sommer and Wurtz, 2004a, b, 2006). This pathway originates in the intermediate layers of the SC, and projects to the FEF through the mediodorsal thalamus (MD). The neuronal properties of the pathway are varied. Sommer and Wurtz identified the MD neurons in the pathway by using orthodromic activation from the SC and antidromic activation from the FEF (Sommer and Wurtz, 2004a). They found MD neurons with purely visual signals, visual and motor signals, and purely motor signals. Additionally they identified SC and FEF neurons that were part of the SC-MD-FEF pathway. Response in the SC and the FEF were similar to those found in MD.

While multiple signals are passed to the FEF, Sommer and Wurtz concluded that presaccadic activity was particulary important. The majority of the neurons in the pathway contained presaccadic information, and the signal remained unchanged throughout the pathway. The importance of the presaccadic activity was even more pronounced when compared to the other signals. Visual signals from the SC arrived at the FEF after signals from extrastriate visual cortex, limiting the latter's influence. Activity during a memory delay period was drastically decreased in the MD neurons compared to that in SC neurons, sending only a small amount of

information to the FEF. Based on the signals sent to FEF, Sommer and Wurtz concluded that the activity from the SC is an ideal candidate for a corollary discharge signal.

To test their conclusion, Sommer and Wurtz interfered with the SC-MD-FEF pathway hoping to affect the corollary discharge signal (Sommer and Wurtz, 2004b). Sommer and Wurtz shut down the pathway by inactivating MD using muscimol, a $GABA_A$ agonist. To study the effects on the corollary discharge signal, they trained a monkey on the double-step task. As discussed above, in order to make a correct second saccade in the double-step task, the animal must know that the first saccade was made. Sommer and Wurtz found both saccade accuracy and precision deficits in the second saccade due to inactivation of the MD (2004b). Without accurate information about the first saccade, the monkeys were unable to complete the second saccade accurately.

1.3 PARIETAL CORTEX AND SPATIAL CONSTANCY

Behavioral evidence in both humans and monkeys demonstrates the ability to create spatial constancy across saccades. Physiological studies have built on these studies to determine the brain areas involved. In humans, the first evidence for a specific brain area playing a role in spatial constancy was in a patient with right frontoparietal lobe damage. Duhamel and colleagues (1992b) tested a patient on the double-step task similar to the one described above. She was relatively unimpaired on the double-step task when the first saccade was made to right. When the first saccade was to the right, T1 was in the affected field and T2 was in the unaffected field. She was, however, unable to make a correct second saccade in the double-step task when the first saccade was made to the left. When the first saccade is to the left, the T1 is in the

affected field and T2 was in the unaffected field. Her ability to make a first task into the affected field implies that her impairment was not due to a simple visual deficit. Presumably, the patient was unable to perform the task due to an inability to compensate for the first saccade made into the affected field. With parietal area damage, the patient was unable to calculate how the first saccade changed the target position relative to the eye position.

The above example is a single case report; the results were duplicated with a larger number of patients. Heide and colleagues (1995b) examined 35 patients with lesions in posterior parietal cortex (PPC), frontal eye fields (FEF), supplementary motor area (SMA), or the dorsolateral prefrontal cortex (PFC). PPC, PFC and FEF patients showed deficits in the double-step task; however, in PFC and FEF patients, the deficit remained even when the second target was present after the completion of the first saccade. This indicates a general inability to perform the double-step task independent of the ability to create a spatially constant percept. Only the patients with PPC damage had deficits specific to the double-step task when both targets disappeared before the initiation of the saccade. This suggests that the PPC is necessary for spatial constancy.

1.4 THEORIES OF SPATIAL CONSTANCY

How the brain combines visual information and eye position information to create stable perception remains unknown, but many theories have been proposed. One mechanism was originally proposed by Robinson (1975). He theorized that the retinal location of a target combined with eye position to create a representation of the target in space. The saccadic targets

are therefore represented in spatial coordinates as opposed to retinal coordinates. While the majority of the visual maps in the brain are retinotopic, not spatiotopic, there are a few exceptions. For example, if the supplementary eye fields are stimulated, then the eye moves to a fixed orbital position (Schlag and Schlag-Rey, 1987). The final position remained constant, independent of the initial eye position. There is also evidence that representation in parietal areas is not purely retinotopic. In several studies, the neural response in parietal areas to a stimulus at a given retinal position was affected by the position of the eye (Andersen and Mountcastle, 1983; Andersen and Zipser, 1988; Andersen et al., 1990c; DeSouza et al., 2000). Additionally, O'Dhaniel and colleagues found that reference frames for neurons recorded from the lateral intraparietal cortex (LIP) varied on a continuum between eye- and head-centered reference frames (Mullette-Gillman et al., 2005).

A second theory for spatial constancy is that the representation of the stimuli remains in retinotopic coordinates, and the representation is updated with each eye movement. In this theory, neurons use a corollary discharge signal to shift, or update their receptive fields. This theory is termed spatial updating and is based on a neural phenomenon known as remapping. Remapping refers to a neural process that shifts visual information from the coordinates of the initial eye position to the coordinates of the next eye position. Evidence for spatial updating will be discussed in the following section.

1.5 PHYSIOLOGICAL EVIDENCE FOR SPATIAL UPDATING IN MONKEYS

Research in monkeys provided the first evidence for spatial updating. Duhamel and colleagues (1992a) examined the function of lateral intraparietal cortex (LIP) by recording single neurons in

monkeys while they performed a simple eye movement task -- the single-step task (figure 2A). The task began with the monkey fixating a central fixation point (FP). A visual target (T) was illuminated while at the same time, a visual stimulus (S) was flashed briefly, outside the RF of the neuron. The fixation point was then turned off, and the monkey made an eye movement to the saccade target. The target was placed at a location so that the saccade caused the RF to move to the screen location where the stimulus was flashed. The important feature of this task was that the stimulus was turned off before the initiation of the saccade. Even though there was never a stimulus inside the RF, the neuron fired around the time of the eye movement (Figure 2B). This activity was not due to the visual stimulus alone. In a stimulus only control task, the monkey remained fixating when the stimulus was flashed; the neuron did not fire (Figure 2B). It was also true that the activity was not due to the eye movement alone. In a saccade control task, the monkey made an eye movement without the presentation of a visual stimulus; the neuron did not fire (Figure 2B). The activity of the neuron represented the memory trace of the stimulus. The response indicated that LIP neurons participate in updating an internal representation of space. This phenomenon was termed remapping, or spatial updating. While the vast majority of neurons in LIP remap, remapping is not restricted to LIP. Neurons in the FEF, the SC, and the extrastriate visual cortex exhibit remapping (Mays and Sparks, 1980a; Goldberg and Bruce, 1990; Duhamel et al., 1992a; Walker et al., 1995; Nakamura and Colby, 2002). How these different areas accomplish remapping and how the areas interact is unknown.

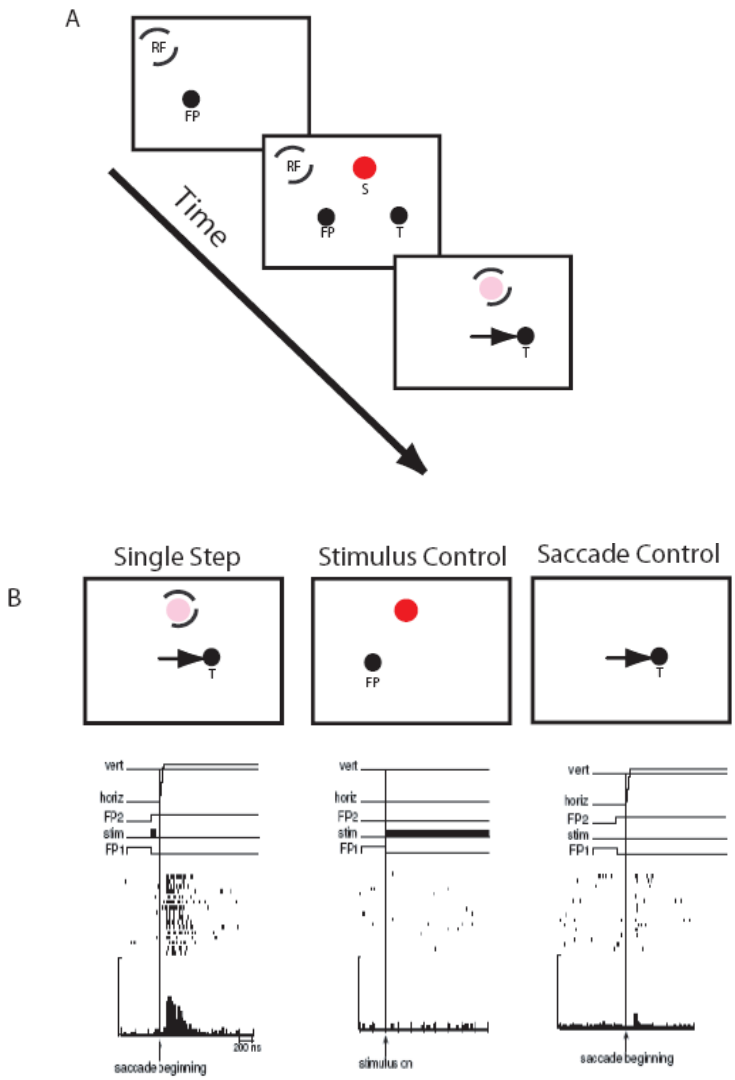


Figure 2. The configuration of the single-step task and the response in a single LIP neuron.

A. The spatial configuration of the single-step task. The neuron's receptive field (RF) is represented by a dashed circle. The monkey begins fixaing a central point (FP). A saccade target (T) is turned on while a visual stimulus (S) is flashed for 50ms. When the FP is turned off, the monkey makes an eye movement to T. The RF lands on the remembered location of S (the pink dot). There is never a visual stimulus inside the receptive field of the neuron. B. The response of a LIP neuron. In the first column the top panel represents the configuration of the single-step task; it is the same as in the A. The timing of events is represented below the panel. The visual stimulus is turned off before the eye movement begins. The response of the neuron is at the bottom. The raster represent activity, each line represents one trial, and each tick mark is one action potential. The histogram below is the sum of activity on all the trials. Each trial is aligned on the beginning of the eye movement. In the second column the configuration of the stimulus control task is represented in the top panel. The monkey remains fixating through-out the task. A visual stimulus is flashed for 50 ms in the same location as in the single-step task. The timing of the events is represented below the panel. The bottom represents the response of the neuron aligned on the stimulus onset. In the third column the configuration of the saccade control task is represented. The monkey is instructed to make an eye movement for the FP to T, no visual stimulus is presented. The timing of events is represented below the panel. The response of the neuron is at the bottom, it is aligned on the beginning of the saccade. (Adapted from Duhamel et al., 1992a)

1.6 PHYSIOLOGICAL EVIDENCE FOR SPATIAL UPDATING IN HUMANS

If humans use the same updating mechanisms as monkeys, we would expect to find remapping activity in parietal cortex. Merriam and colleagues examined remapping in humans using functional magnetic resonance imaging (fMRI) (Merriam et al., 2003, 2007). They designed an imaging experiment that closely matched the remapping experiments conducted in monkeys. In the remapping task designed for the scanner, each trial began with the subject fixating one of two points on the screen (Fig. 3A). While the subject fixated, a stimulus was presented at the center of the screen. The stimulus was irrelevant to the task, but flickered at a high contrast, making it a salient stimulus. After 2 seconds, the stimulus disappeared and a tone cued the subject to make a saccade to the other fixation point. The second fixation point was positioned so that the stimulus location was in the opposite visual field after the completion of the eye movement. As in the single-step task, the stimulus disappeared before the eye movement was initiated. In the example shown, the subject began fixating the right position. When the stimulus was presented, it was in the left visual field. After the subject moved their eyes, the screen location where the stimulus had been presented was in the right visual field.

To determine if there are neurons in the parietal cortex capable of remapping in the humans, Merriam and colleagues measured the fMRI BOLD response in both cortical hemispheres. They found that the stimulus activated visually responsive cortical areas in the contralateral hemisphere (Fig. 3B; blue curve). This result was unsurprising because the stimulus was designed to activate both low level visual areas, such as V1 and V2, as well as extrastriate and parietal areas. The critical measurement was the response in the ipsilateral cortex. Merriam et al. also found a response in the ipsilateral hemisphere; they termed it the remapped response based on three criteria (Fig. 3B; red curve).

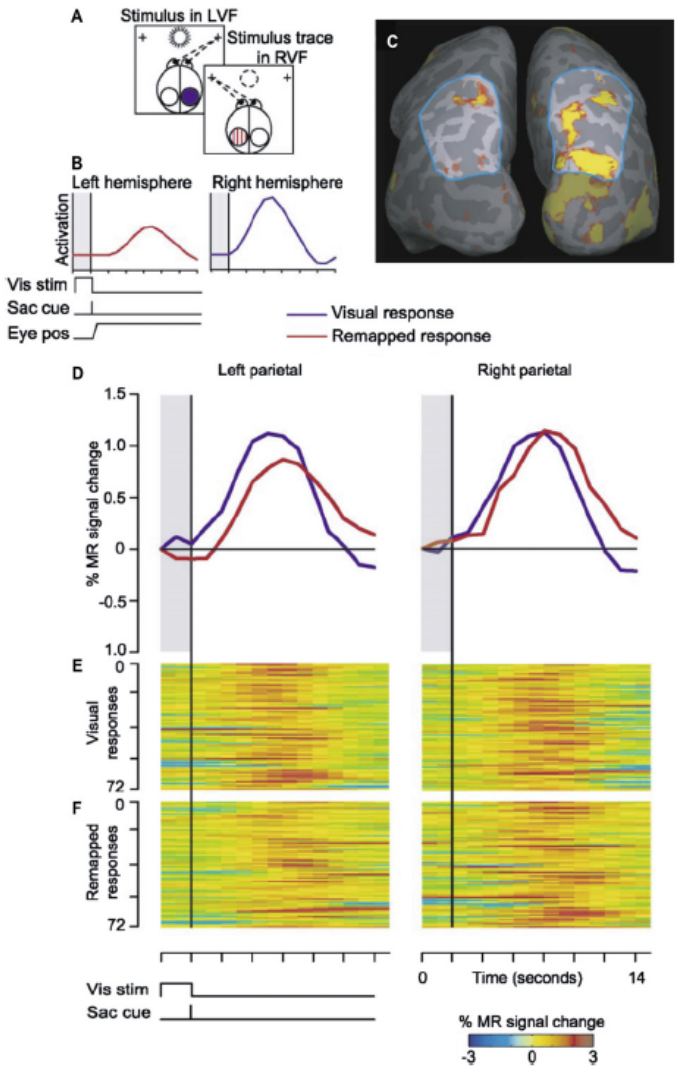


Figure 3. Remapping in human parietal cortex.

A. The single-step task for imaging. The trial begins with the subject fixating the right fixation point (first panel). The stimulus is presented at the center of the screen for 2s, activating the right hemisphere (blue circle). The subject is cued with a tone to make a saccade to the left fixation point (second panel). The memory of the stimulus trace is remapped, activating the left hemisphere (red hatched circle). B. The time course of the task and the predicted activation of the left and right hemisphere. Shaded region indicates the time that the stimulus is on. The vertical line indicates time of the auditory cue. The blue curve represents a hypothetical hemodynamic response of the right hemisphere to a visual stimulus. The red curve represents a hypothetical hemodynamic response of a remapped response. C. Activation of a single subject. The blue outlines the parietal region of interest. The stimulus elicits visually-driven activation in the contralateral (right) occipital and parietal areas. The activation in the left hemisphere indicates that the representation of stimulus was remapped in conjunction with the saccade. D. Time course of activation for the visual and remapped responses in parietal cortex for each hemisphere of a single subject. Time courses are an average of 72 trials. E and F. Bold-image raster plots of the responses from the same hemispheres for 72 successive trials, for the visual (E) and remapped (F) responses. On the y axis, each row represents a trial, and on the x axis, percent signal change is represented in pseudocolor plotted over time. Adapted from Merriam et al. (2003).

First, the response could not be explained by a visual or motor signal alone. Similar to the monkey experiments, there were two important control tasks for these imaging studies. In the stimulus control task, the subject remained fixating while the stimulus was presented, no eye movement was made. Any response in the ipsilateral hemisphere during the stimulus control task would indicate a visual response to the stimulus. This could occur if neurons in these areas had receptive fields that represent the ipsilateral visual field. In the saccade control task, no stimulus was presented and the subject made a saccade from one fixation point to the other in response to a tone. Any response in the ipsilateral field during the saccade control task would indicate a motor response to the eye movement, or an auditory response to the cue. As was the case with the monkey experiments, the remapped response was greater than the activity measured during the control tasks. Therefore, the remapped response was not a simple visual or motor signal, but represented the memory trace of the stimulus.

Second, the remapped response should occur later than the visual response. Any remapped response should be triggered by the plan to make the saccade. The cue to make an eye movement occurred after the stimulus remained on the screen for 2s. The time course of the response is illustrated in Fig. 3D and E. The visual response, represented by the blue curve occurs before the remapped response, represented by the red curve.

Third, the remapped response should be lower in amplitude than the visual response. In the monkey experiments, the remapped response was typically half the visual response. A similar result was found in the human study. In the left parietal area, the % MR change was greater for the visual response than for the remapped response. The memory of the visual stimulus activated the area to a lesser degree than the visual response.

In summary, Merriam and colleagues demonstrated that human parietal cortex had a remapped response similar to activity measured in single unit recordings in monkeys. The responses in both humans and monkeys occurred around the time of an eye movement. The responses were not due to a simple visual or motor signal, but represented the memory trace of the stimulus. Finally, the remapped responses were weaker than visual responses.

1.7 ROLE OF FOREBRAIN COMMISSURES

If remapping is the neural mechanism of spatial constancy then neurons that remap must receive information from across the entire visual field. There is evidence that this is the case even in the original Duhamel study. The task was configured so that the stimulus was flashed in the hemifield opposite the one represented by the neuron being recorded (Duhamel et al., 1992a). Visual information was updated from one visual hemifield to the other, demonstrating that information is passed between hemispheres. While this does demonstrate that information is passed from another part of the visual field, it does not completely answer the question. Do neurons in LIP receive information form multiple areas of visual space? Heiser and Colby (2005) answered the question by having monkeys perform the single-step task with different initial eye positions and saccade directions. They found that LIP, as a population, can remap independently of initial eye position and saccade direction.

An LIP neuron can receive information representing multiple areas of visual space outside its classical receptive field when remapping (Heiser and Colby, 2005). One possible source of information is through direct cortico-cortical connections. Specifically, when the updating is across-hemifields, the information is thought to be transferred through the forebrain

commissures. Berman and colleagues tested this possibility by transecting the forebrain commissures and examining the effects on a behavioral task, and on remapping activity in LIP (Berman et al., 2005; Heiser et al., 2005).

In these studies, the double-step task was used as the behavioral test for spatial updating. The monkey was initially trained on a central condition of the task, where the first saccade was a left or right horizontal saccade and the second saccade was an upward vertical saccade (Fig. 3A). To test the role of the forebrain commissures, Berman and colleagues introduced two new configurations of the double-step task. In the within version, the second saccade is offset 30° away from the midline (Fig. 3A, green). This sequence of saccades *does not* require interhemispheric transfer of visual information. In the across version, the second saccade is offset 30° towards the midline (Fig. 3A, red). This sequence of saccades *does* require interhemispheric transfer. Berman and colleagues hypothesized that when the forebrain commissures are transected, behavior in the across version of the task would be impaired, while behavior would remain normal for the within version. During the first testing session, their hypothesis was supported. Fig. 3B shows the eye traces for the first ten saccades of each of the three sequences in both monkeys. Fig. 3C shows the end points from the entire first session for both the upper field and lower fields. The monkeys made correct saccades during the within condition, but showed a deficit when making saccades during the across condition. Surprisingly, this impairment was not permanent. By the final testing session, both monkeys drastically improved their performance on the across condition (Fig. 3D). The observed impairment and subsequent recovery suggests that the forebrain commissures play an important role in spatial

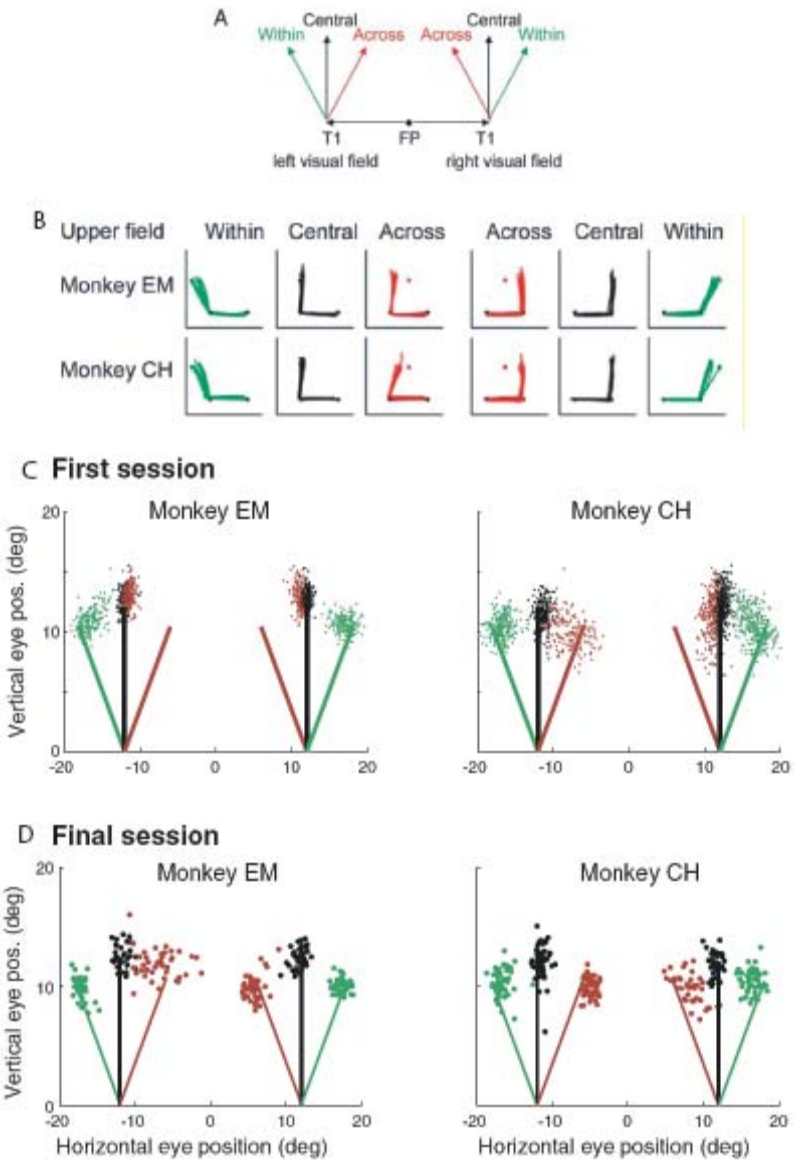


Figure 4. The double-step configuration and the performance by the split-brain monkeys, from initial testing to the final testing session.

A. The test configuration of the double-step. The start each trial at the fixation point (FP). The monkey makes a horizontal eye movement to T1, either to the right or to the left. The monkey then makes a second eye movement to one of three remembered target locations. The monkey was initially trained on the central sequences (black). On the first testing session, the within-hemifield (green) and across-hemifield (red) conditions were introduced. B. In panel B the eye traces are shown for the upper field for the first 10 trials for each sequence in both monkeys. Dots indicate the location of FP, T1 and T2. C. All the saccade end points for the first testing session for both upper and lower field are presented in panel C. The lines represent the ideal trajectories for the second saccade. The colors match those established for each condition in panel A. D. All the saccade end points for the final testing session for both upper and lower field are presented in panel C. Same conventions as in C. (Adapted from Berman et al., 2005).

updating across-hemifields, but they are not the only possible pathway for transmitting visual information.

If the forebrain commissures are not necessary for behavior dependent on spatial updating, are they necessary for remapping in LIP? Heiser and colleagues answered this question by recording LIP neurons while the monkey performed two versions of the single-step task. In the within version of the task, the representation of the flashed stimulus remained within a single hemifield (Fig. 4A). In the across version of the task, the representation of the flashed stimulus shifted across-hemifields (Fig. 4B). Heiser and colleagues found that LIP as a population is capable of remapping both within and across conditions; however, the across signal was attenuated. Fig. 4A and B is a single neuron example of this finding. There was remapping activity in both the within and across conditions, but the activity in the across condition was significantly lower compared to the within condition. The activity was not due to the stimulus alone or due to the saccade alone. Fig. 4C demonstrates the results across the population. This difference is not observed in the intact monkey (Fig. 4D).

These studies in the split brain monkeys demonstrate that the forebrain commissures may be the primary pathway of across-hemifield remapping, but they are not necessary. The goal of the current studies is to further our understanding of the circuitry of remapping in the split brain monkey.

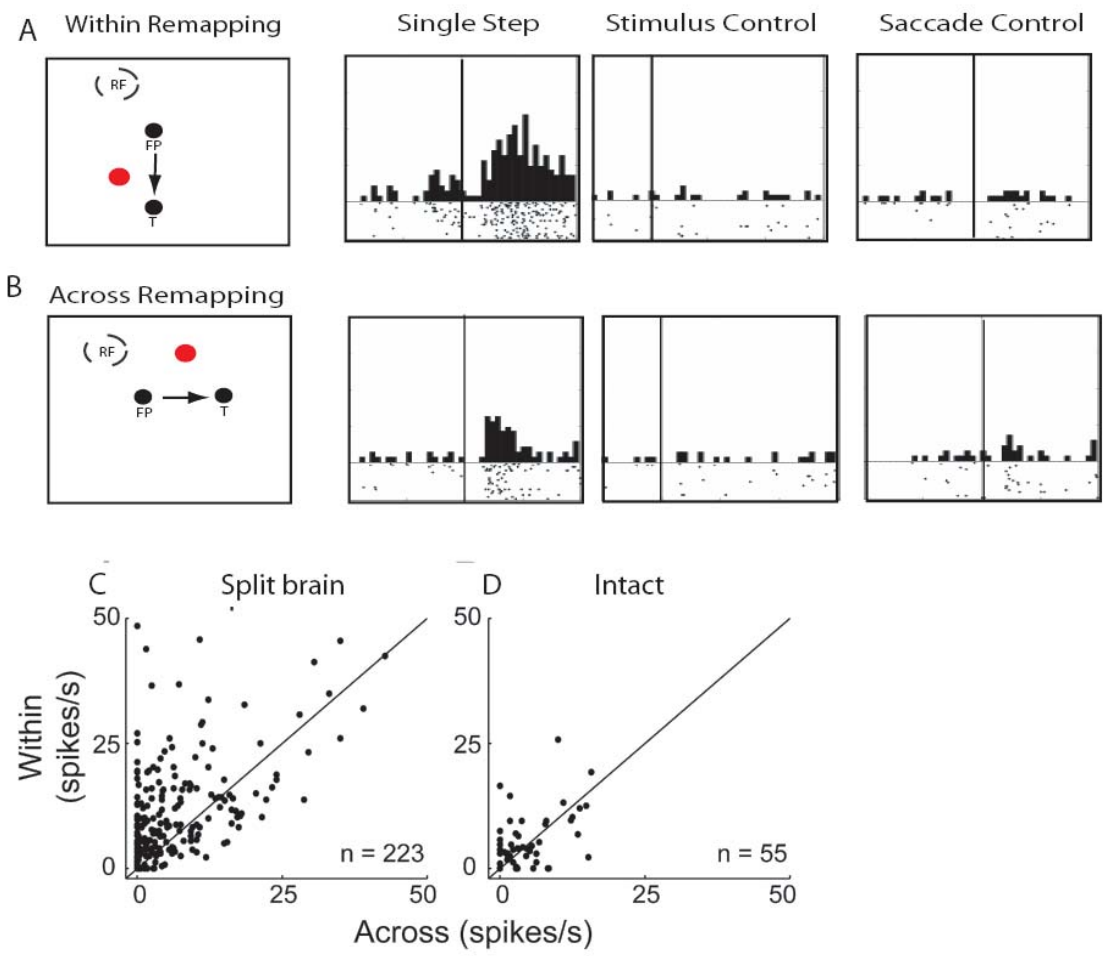


Figure 5. The activity of single neuron and population of LIP neurons while performing within and across sequences of the single-step task.

A. The first panel represents the configuration of the within sequence of the single-step task. The visual stimulus (red dot) is in the left visual field when the monkey is at FP, and the remembered location remains in the left visual field after the eye movement. The second panel represents the activity in a single neuron during the single-step task. The histogram represent the sum of activity across all trial aligned on the saccade onset. The raster below represents activity in each trial, each line is one trial, and each tick mark is an action potential. The third panel represents activity during the stimulus control task; activity is aligned on the stimulus onset. The fourth panel represents the activity in the saccade control task; activity is aligned on the saccade onset. B. The first panel represents the configuration of the across sequence of the single-step task. The visual stimulus is in the right visual field when the monkey is at FP, and the remembered location is in the left visual field after the eye movement. The convections for the second through fourth panels are the same as in A. C. Population activity in the split-brain monkeys. Activity of a neuron during the across condition is plotted against activity in the within condition, one point equals on neuron. The magnitude of activity is significantly greater for the within condition than for the across condition. D. Population activity in intact monkeys. There is no significant difference in the magnitude of remapping activity in the within condition compared to the across condition. (Adapted from Heiser et al., 2005)

1.8 EXPERIMENTAL AIMS

1.8.1 Aim 1: What is the relationship between activity in LIP neurons and spatial performance?

As described above, the forebrain commissures are the primary pathway for the transfer of visual information across hemispheres but they are not necessary for visual transfer (Berman et al., 2005). When the primary pathway through the forebrain commmissures is disrupted, alternative brain circuits can be utilized to control behavior. It is possible that these alternative circuits control behavior independent of LIP. However, LIP neurons continue to show evidence of across hemisphere transfer of remapped visual signals (Heiser et al., 2005). These results lead to a simple question: what is the relationship between neural activity in LIP and the behavior of the monkey? The goal of Chapter 2 is to test the hypothesis that LIP neural activity is correlated with the visuospatial performance.

1.8.2 Aim 2: Do LIP neurons in split brain monkeys have bilateral receptive fields?

One possible explanation for the intact across-hemifield remapping in the split brain animals is cortico-cortical connections within a single hemisphere. If this is the case, then neurons in a single hemisphere would represent visual information from both visual fields. In other words, neurons would have bilateral representations. In intact monkeys, a small number of LIP neurons have bilateral receptive fields (RF) (Andersen et al., 1990b; Barash et al., 1991b; Platt and Glimcher, 1998; Ben Hamed et al., 2001). The hypothesis is that in the absence of the forebrain

commissures the ipsilateral representation will be eliminated, leaving only contralateral RFs in LIP. In Chapter 3, we will test this hypothesis by determining the RFs of LIP neurons in split brain animals and compare them to RFs in the intact monkey.

1.8.3 Aim 3: Is there a difference in spatial updating between intact and split brain monkeys in the superior colliculus (SC)?

In addition to LIP, many other areas, including the SC, participate in remapping. It remains unknown where remapping activity originates, or how the different areas work together. The split brain monkeys give us a unique opportunity to study the circuitry of spatial updating. It is possible that the remapping activity observed in the SC is generated within the SC; however, it is also possible that the remapping in the SC is due to activity transferred from cortical areas. In Chapter 4, we test these two alternatives by recording from neurons in the superficial and intermediate layers of the SC in both intact and split brain monkeys. The hypothesis is that if remapping is generated entirely within the SC then there should be no difference in remapping activity between within and across conditions for the intact and split brain monkeys. If remapping is due to activity transferred from cortical areas then there should be a difference in activity in the intact and split brain monkeys, such that within activity is more robust than across for the split brain animal.

2.0 DYNAMIC CIRCUITRY FOR UPDATING SPATIAL REPRESENTATIONS: III. FROM NEURONS TO BEHAVIOR

2.1 ABSTRACT

Each time the eyes move, the visual system must adjust internal representations to account for the accompanying shift in the retinal image. In the lateral intraparietal cortex (LIP), neurons update the spatial representations of salient stimuli when the eyes move. In previous experiments, we found that split-brain monkeys were impaired on double-step saccade sequences that required updating *across* visual hemifields, as compared to *within* hemifield (Berman et al. 2005; Heiser et al. 2005). Here we describe a subsequent experiment to characterize the relationship between behavioral performance and neural activity in LIP in the split-brain monkey. We recorded from single LIP neurons while split-brain and intact monkeys performed two conditions of the double-step saccade task: one required across-hemifield updating and the other within-hemifield updating. We found that, despite extensive experience with the task, the split-brain monkeys were significantly more accurate for within-hemifield as compared to across-hemifield sequences. In parallel, we found that population activity in LIP of the split-brain monkeys was significantly stronger for within-hemifield as compared to across-hemifield conditions of the double-step task. In contrast, in the normal monkey, both the average behavioral performance and population activity showed no bias toward the within-hemifield

condition. Finally, we found that the difference between within-hemifield and across-hemifield performance in the split-brain monkeys was reflected at the level of single neuron activity in LIP. These findings indicate that remapping activity in area LIP is present in the split-brain monkey for the double-step task and co-varies with spatial behavior on within-hemifield compared to across-hemifield sequences.

2.2 INTRODUCTION

Visual perception is based on both incoming sensory signals and information about ongoing actions. Evidence for this idea comes from physiological studies, which have demonstrated that motor signals can influence visual representations in parietal, frontal and extrastriate cortex, and in the superior colliculus (Mays and Sparks, 1980a; Goldberg and Bruce, 1990; Duhamel et al., 1992a; Walker et al., 1995; Umeno and Goldberg, 1997, 2001a; Nakamura and Colby, 2002). In each of these areas, visual representations are updated in conjunction with eye movements, as shown in the single-step saccade task. In this task, activity of a single neuron is monitored while the monkey makes a simple saccadic eye movement. This eye movement brings the neuron's receptive field onto a location where a visual stimulus had previously appeared. The neuron fires, despite the fact that the stimulus is never physically in the receptive field. The firing represents a response to the memory trace of the stimulus, which has been updated to take the eye movement into account. Updating is presumed to involve a transfer of information from neurons that encode the stimulus location before the eye movement, to those that will encode its

location after the eye movement. This updating activity provides a mechanism for creating a stable, eye-centered map of salient locations (Colby and Goldberg, 1999).

Our central hypothesis, investigated in a series of experiments, is that updating relies on the integrity of direct cortico-cortical links. We have tested this hypothesis by examining a case in which these cortical connections are accessible to experimental manipulation. We compared updating for stimulus traces that remain within a single hemifield to updating for stimulus traces that must be transferred across-hemifields (Fig. 6). In the across-hemifield case, a visual stimulus is presented briefly in one hemifield. Following a saccadic eye movement, the trace of that stimulus is brought into the opposite hemifield. Consequently, visual representations that originate in one cortical hemisphere must be transmitted to the opposite hemisphere. The forebrain commissures – the corpus callosum and the anterior commissures – comprise the only route for direct communication between the cortical hemispheres. In two previous reports, we described separate behavioral and physiological experiments that test whether the forebrain commissures are required for interhemispheric updating (Berman et al., 2005; Heiser et al., 2005). We found that direct cortical links are an important substrate for spatial updating but are not strictly necessary. While split-brain animals showed an initial behavioral impairment on a task that requires across-hemifield updating, performance improved substantially with experience. At the single neuron level, neurons in the lateral intraparietal area (LIP) were active for both across- and within-hemifield updating, with reduced activity in the across-hemifield case.

The differences that we observed between within-hemifield and across-hemifield remapping in the split-brain monkey present an unusual opportunity to examine the relationship between updating activity and spatial behavior. In the current study, we investigated this

relationship using the double-step saccade task, which allowed us to measure simultaneously the neural activity and behavior associated with remapping. The double-step task gives insight into the ability to monitor and adjust for intervening gaze shifts (Hallett and Lightstone, 1976; Mays and Sparks, 1980a; Baizer and Bender, 1989; Goldberg and Bruce, 1990; Duhamel et al., 1992c; Mazzoni et al., 1996; Sommer and Wurtz, 2002; Baker et al., 2003; Ray et al., 2004a; Vliegen et al., 2004; Murthy et al., 2007). In this task, subjects make successive eye movements from a central fixation point (FP) to two targets, T1 and T2. The second target, T2, disappears before the eyes begin to move. This creates a mismatch between the initial retinal representation of T2 and the ultimate motor vector needed to acquire T2. For the subject to perform the sequence accurately, the representation of T2 must be updated to take the first saccade into account. Updating activity could be the mechanism for solving the spatial integration problem posed by the double-step task. Neurons in area LIP become active when the saccade to T1 brings the receptive field onto the location where T2 had appeared (Goldberg et al., 1990). This activity reflects a representation of the second target that takes the first saccade into account: T2 is encoded in coordinates that specify the vector needed to acquire T2 from the eyes' new position at T1.

In order to test the relationship between spatial updating activity and behavior, we recorded from single neurons in area LIP of split-brain and intact monkeys while they performed two conditions of the double-step task. In the across-hemifield condition, the representation of the T2 must be updated from one visual hemifield to the other, requiring interhemispheric communication of visual information (Fig. 6*A*). In the within-hemifield condition, the representation of T2 must be updated from one location to another, within the same hemifield (Fig. 6*B*).

This study had three objectives. The first was to determine whether split-brain monkeys exhibit a selective impairment in the performance of across-hemifield sequences during physiological recording sessions, even after extensive previous training and testing on the double-step task. The second objective was to determine whether activity in area LIP of the split-brain monkey is altered for double-step sequences that require across-hemifield as compared to within-hemifield updating. Our third objective was to investigate the correspondence between physiological and behavioral measures of spatial updating in the split-brain monkey.

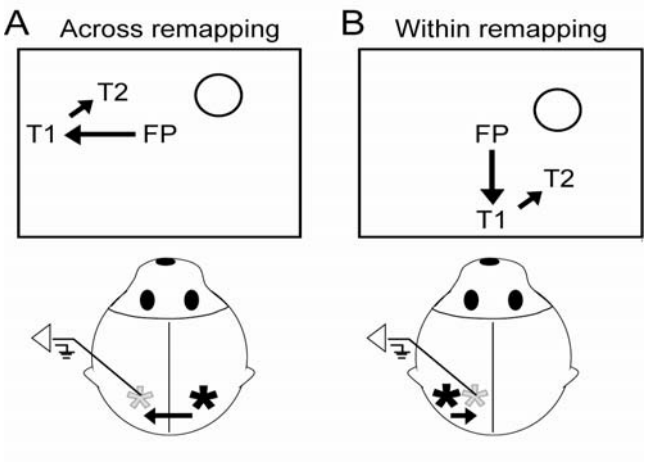


Figure 6. Assessment of behavior and neural activity during within- and across- hemifield remapping in the split-brain monkey.

The geometry of the double-step sequence is determined by the location of the neuron's receptive field. The hypothetical neuron under study is located in the left hemisphere (grey asterisk), with a receptive field (circle) in the upper right visual field. In the across-hemifield condition (A), the second target (T2) is located in the left visual field when the eyes are at central fixation (FP); its location is represented by neurons in the right hemisphere (black asterisk). When the eyes reach the first target (T1), however, the location where T2 appeared is now in the right visual field; its stimulus trace is thus represented by neurons in the left hemisphere, including the neuron under study (gray asterisk). Updating in this condition involves a transfer of visual information between neurons in opposite cortical hemispheres. In the within-hemifield condition (B) T2 appears in the right visual field when the eyes are at FP, and so is represented by neurons in the left hemisphere (black asterisk). After the saccade to T1, the stimulus trace of T2 is still represented by neurons in the left hemisphere (gray asterisk). Updating in this condition therefore involves the transfer of visual signals within the same hemisphere.

2.3 METHODS

2.3.1 General procedures

Subjects were three rhesus macaques. The forebrain commissures were intact in monkey FF; in monkeys EM and CH, the forebrain commissures were surgically transected at the outset of the experiments (Berman et al., 2005; Heiser et al., 2005). The commissurotomy is described in detail elsewhere (Vogels et al., 1994). Briefly, 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. The corpus callosum was transected along its full length using a small glass pipette with suction; the anterior commissures was fully transected. In the two weeks following the surgery, analgesics and antibiotics were administered daily.

Following completion of behavioral training and testing, monkeys were prepared for chronic physiological recording. The placement of the recording chamber (1.8 cm diameter) was determined using anatomical information from structural magnetic resonance images in conjunction with the standard stereotaxic locations for area LIP (5mm posterior and 12mm lateral in Horsley Clarke coordinates). We used MRI to verify that the chambers were located over the intraparietal sulcus. Recording began 14-21 months after the commissurotomy, and 7-11 months after the start of behavioral testing described in Berman et al. (2005). Double-step physiology data for the split-brain monkeys were collected in parallel with the single-step physiology described in Heiser et al. (2005). Animals were cared for and handled in accordance with NIH guidelines, and all experimental protocols were approved by the University of Pittsburgh Institutional Animal Care Use and Committee.

During recording sessions, the monkey sat in a darkened room with its head fixed in a primate chair, facing a tangent screen. Visual stimuli were back-projected on the tangent screen using a LCD projector. Stimulus presentation was under the control of two computers running a C-based program, CORTEX, made available by Dr. Robert Desimone. Eye position was monitored using scleral search coils (Judge et al. 1980), with a sampling rate of 250 Hz.

2.3.2 Physiological methods

Neural activity was recorded using tungsten microelectrodes (Frederick Haer, Bowdoinham, ME) 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. The grid system permitted parallel penetrations along the bank of the intraparietal sulcus (IPS) with a resolution of 1 mm. 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. Individual neurons were isolated by means of an on-line spike-sorting system using a template-matching algorithm (Signal Processing Systems, Prospect, Australia).

2.3.3 Behavioral paradigms

2.3.3.1 Memory guided saccade task.

We used the memory guided saccade task to search for neurons and assess their visual, memory and saccade-related response properties. In this task, the monkey began by fixating on a central fixation point. After an initial delay of 300-500 ms, a stimulus appeared in the receptive field for 50 ms. After a second delay of 400-800 ms, the fixation point was extinguished, which

cued the monkey to make a saccade to the location of the flashed stimulus. After the saccade, the stimulus re-appeared and the monkey maintained fixation on it for an additional 300-500 ms. We used standard mapping procedures to determine the location of a neuron's receptive field (Barash et al. 1991).

2.3.3.2 Double-step task.

This task provides a measure of both the neural activity and behavior associated with spatial updating. At the start of each trial, the monkey maintained fixation on a central fixation point (FP) for 300-500ms. The first saccade target (T1) then appeared and remained illuminated. The second target (T2) appeared 100 ms later, and was extinguished after 50 ms. The fixation point was extinguished simultaneously with the disappearance of T2, cueing the monkey to initiate the double-step sequence. The monkey made a visually-guided saccade to T1 (T1 was extinguished upon completion of the first saccade), followed by a memory-guided saccade to T2. The second target then re-appeared, and the monkey fixated this target location for an additional 300-500 ms before receiving juice reward.

2.3.3.3 Single-step task.

Stimuli in the single-step task have the same configuration as the double-step task. The important difference is that in the single-step task, the stimulus to be updated is not the target of an eye movement, and is irrelevant to the monkey's behavior. The monkey attained central fixation and maintained gaze there for 300-500 ms. Two events then occurred simultaneously: a peripheral stimulus appeared outside of the neuron’s receptive field, and a new fixation point (T1) was illuminated. The peripheral stimulus was extinguished 50 ms later, simultaneously with the disappearance of FP. This was the monkey's cue to make a visually guided saccade to

T1. The saccade to T1 moved the neuron's receptive field onto the location of the now-extinguished stimulus. The monkey maintained gaze on T1 for an additional 500-700 ms to receive juice reward.

2.3.3.4 Saccade control task.

This visually-guided saccade task was used to determine whether activity in the single-step task could be attributed to the generation of the saccade alone. Task events and timing were identical to the single-step task, except that no peripheral stimulus was presented.

2.3.3.5 Stimulus control task.

The stimulus control task was used to ensure that the stimulus location used in the single-step task was outside of the receptive field and did not drive the neuron. In this task, the monkey maintained central fixation for 300-500 ms. The peripheral stimulus was flashed for 50 ms, and the monkey was required to maintain fixation for an additional 1200-1500 ms.

2.3.4 Experimental design

We initially assessed neurons in the MGS task, and then began the experimental protocol. This protocol consisted of eight types of trials for each neuron: four tasks (stimulus control, saccade control, single-step and double-step) x two conditions (within-hemifield, across-hemifield). We collected 12-20 trials for each trial type. The tasks were run in separate blocks, always in the same order: stimulus control, saccade control single-step, double-step. We collected data in this order because previous experiments have demonstrated that long-term inter-trial memory responses can persist after experience with updating tasks (single-step or double-step) and can

lead to activity in subsequent saccade control trials (Ray et al., 2004b; Vliegen et al., 2004). In each block, the within and across conditions were randomly interleaved. This interleaving was critical to the design, as each neuron served as its own control.

The exact geometry of the within-hemifield and across-hemifield conditions was tailored for each neuron, based on the location of the receptive field (Fig. 6). By definition, different spatial configurations are required for remapping stimulus traces within and across hemifields. We held saccade amplitude constant and varied only the direction of the first saccade of the within and across conditions. The second saccade always had the same direction and amplitude for the two conditions, as it was described by the vector between central fixation and the neuron's receptive field. We used two standard configurations for most neurons. In the within-hemifield condition, a vertical saccade kept the representation of the second target within the same hemifield both before and after the first saccade. In the across-hemifield condition, a horizontal ipsiversive saccade moved the representation of T2 from one hemifield to the other. For the remaining neurons, we used diagonal saccades for one or both conditions. For the first saccade, average amplitude was 21.3° (± 3.4° s.d.). For the second saccade, average amplitude was 15.1° (± 5.1° s.d.).

2.3.5 Analysis

2.3.5.1 Analysis of double-step saccade data.

We quantified the accuracy of the second saccade by calculating distance error, which describes the absolute difference between the saccade endpoint and the target. Latency of the first saccade was defined as the time between the disappearance of the central fixation point and the initiation of the first saccade (velocity above 50°/s). Latency of the second saccade was

defined as the time between the end of the first saccade (velocity below 20°/s) and the initiation of the second saccade.

2.3.5.2 Selection of double-step saccade data.

We screened the behavioral data at two stages of analysis in order to ensure that the neural and behavioral findings were representative and uncontaminated by inattentive performance of the task. First, for an individual trial to be considered valid, the latency of the first saccade had to be between 50 and 350 ms, and this saccade had to reach the first target accurately. We assessed accuracy using a measure of saccade gain, where gain had a maximum value of one, and was equal to the absolute difference between target amplitude and distance error, divided by target amplitude. We required that first-saccade gain be at least 0.75 for each individual trial (upper limit of the gain measure was, by definition, 1). Second, the average saccade data associated with a given neuron (a "session") were included only if there were a minimum of 10 valid trials for each condition (of the 12-20 total trials collected), with an *average* first-saccade gain of at least 0.85 for each condition. In the final datasets for split-brain and intact animals, the accuracy of the first saccade was not significantly different for the within-hemifield and across-hemifield conditions ($p>.05$, Wilcoxon signed rank). Therefore, conditional differences in the accuracy of the *second* saccade could not be attributed to differences in the first saccade. The landing point of the second saccade is the critical measure, as correct performance requires spatial updating; the first saccade was visually guided and could be completed using simple retinal information. We tested for significant differences between within- and across-hemifield behavior using the nonparametric Wilcoxon signed rank test.

2.3.5.3 Selection of neurons.

Our initial database (n=277) included all single neurons recorded in the lateral intraparietal sulcus that exhibited a significant visual response in the memory-guided saccade task (t-test comparing a visual epoch, 100ms following the onset of the stimulus response, and a baseline epoch, 200-300ms after attainment of fixation). Neurons were then excluded on the basis of insufficient behavioral data (see above). Our remaining physiological criteria focused on ensuring a clear interpretation of activity in the single-step and double-step tasks. In these tasks, updating activity occurs when the monkey makes a saccade to the first target (T1), which brings the memory trace of the stimulus into the receptive field. Updating activity is not attributable either to the stimulus alone or to the saccade alone. It was therefore critical that we take into account any activity due simply to the stimulus or saccade alone. We adjusted for saccade-alone activity using a subtraction method, described below. For stimulus-alone activity, we analyzed the activity in the stimulus control task to be certain that the response in the single-step task could not be attributed to the presence of the stimulus alone. We compared firing rate in a visual epoch of the stimulus control task (50-250 ms after stimulus onset) to that in the baseline epoch (200-300 ms after fix attain). We excluded neurons if they had a significant visual response in either stimulus control condition (t-test, $p<0.05$). Approximately one quarter of all LIP neurons recorded had such a response – in other words, the receptive fields were large enough that the to-be-remapped stimulus evoked a response even when the monkey was fixating centrally. These cells were not analyzed further. Our final database was comprised of 181 cells with sufficient behavioral data and no significant activity in the stimulus-alone control.

2.3.5.4 Assessment of updating activity.

We use the term 'updating activity' to refer to the neuron's response to a stimulus trace that has been updated in conjunction with an eye movement. We measured updating activity in the epoch beginning at the initiation of the first saccade, and ending at the initiation of the second saccade. This epoch was computed individually for each trial of the double-step task. On average, the duration of this epoch was 174ms (s.d. = 34ms). We chose this epoch so that remapping was measured during a time-window that was identical from trial to trial with respect to the eye movements. If, for example, we had measured remapping solely in relation to the second saccade, the remapping epoch would include variable amounts of time before or after the first saccade. We therefore measured remapping in relation to *both* S1 and S2 to minimize the effects of variability in first saccade latencies. It is important to note that, although the epoch is variable in its duration, the measure of firing rate (spikes per second) is inherently independent of epoch duration.

It is essential that our measure of updating activity does not reflect firing related simply to the presence of the stimulus alone or to the saccade alone. As described above, we excluded at the outset any neurons that had a significant response to the stimulus alone. A number of the included neurons exhibited some response in the saccade control task. This activity typically occurred for spatial configurations in which the saccade alone (saccade to T1) brought the neuron's receptive field onto the location where the central fixation point had appeared. Given this and earlier observations in our lab, the most parsimonious explanation for this activity in the saccade-alone task is that it represents remapping of the fixation point (Heiser and Colby, 2005). We adjusted for this saccade-alone activity by computing the average firing rate in the saccade-alone task, in an epoch that was identical to the *average* double-step remapping epoch for the

individual neuron. We did this for all neurons, for both the within and across conditions, regardless of whether there was significant activity in the saccade-alone task. The average double-step remapping epoch was computed separately for within and across conditions, because each condition required a different first saccade. This computation ensured that the saccade-alone epoch for each condition corresponded to the same time window as used for the double-step task. For example, if a neuron had an average across-hemifield remapping epoch of 190ms (beginning at the start of the first saccade), then the across-hemifield saccade-alone epoch was also 190ms, beginning at the start of the first saccade. We report updating activity as the average firing rate in the double-step remapping epoch *minus* the average firing rate in the corresponding epoch of the saccade control task. Throughout the paper, the phrase "updating activity" refers to this adjusted firing rate. If activity in the saccade control exceeded activity in the double-step task, updating activity takes on a negative value. Updating activity in the double-step task was deemed significant when the firing rate in the remapping epoch exceeded that in the corresponding saccade control epoch at a significance level of $p<.05$ (t-test).

We computed a neural Within:Across (WA) index to quantify the strength of the neuron's preference for either the within-hemifield or across-hemifield condition. As described previously (Heiser et al. 2005), this index normalizes the updating activity observed in the double-step task to the total activity observed in the double-step and saccade control tasks, using the following formula: WA Index = (DS*w*-SAC*w*)-(DS*a*-SAC*a*) / (DS*w*+SAC*w*)+(DS*a*+SAC*a*). In this formula, DS*w* and DS*a* represent the firing rates measured in the within and across conditions of the double-step task, and SAC*w* and SAC*a* represent the firing rates measured in the corresponding saccade control conditions. The denominator of this formula accounts for the fact that the saccade-alone activity exceeded double-step activity for at least one condition in

some neurons. The formula ensures that the index has a range of –1 to +1. Positive values indicate that activity was stronger for within-hemifield updating, whereas negative values indicate that activity was stronger for across-hemifield updating.

We used two analyses to assess the effect of task (double-step versus single-step) on the strength of LIP activity. In the first, we compared average firing rates directly. Activity in the single-step task was measured in a remapping epoch, aligned on the start of the first saccade. The duration of this epoch was identical to the average epoch used for the double-step task for each condition (within and across). We directly compared the double-step and single-step firing rates, without subtracting any saccade control activity, as the contribution of saccade-alone activity would be equivalent for the two tasks. The same logic applied for our second analysis, where we also used average firing rates without subtracting saccade control activity. In this second analysis, we measured the average difference between within-hemifield and across-hemifield activity for each of the tasks (single-step and double-step) and then compared the within:across differences for the two tasks.

2.3.5.5 Measuring neural latency.

We measured the latency of the remapped response relative to the beginning of the first saccade. Neural latency can only be reliably defined with the method described below if all of the activity present in the double-step task is attributable to remapping the stimulus, rather than simply to the generation of the saccade. In contrast to the analysis of the strength of the remapped responses described above, there was no method to account for saccade control activity in the analysis of neural latency. Therefore, if there was any significant activity in the saccade control associated with a particular double-step condition, we excluded it from latency analyses.

Previous studies have shown that remapping can occur over a broad range of latencies (Goldberg et al., 1990). We used the following method to measure neural latency in individual neurons (Berman et al., 2005; Heiser et al., 2005). We searched for the onset of the neural response in the time window from 100 ms before saccade onset to 300 ms after saccade onset. We used a sliding window to find the time when the firing rate first began to differ significantly from activity during the baseline epoch (200-300 ms after attainment of fixation). Specifically, we measured activity in a 20 ms response window beginning 100 ms before saccade onset. We used a t-test ($p < 0.05$) to assess whether activity in the response window differed significantly from baseline activity. If there was no significant difference, the window was shifted forward 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 occurrence 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 within 300 ms after saccade onset, we concluded that there was no response associated with remapping the stimulus trace. We used an analogous method to determine the visual response latency in the memory guided response task. The calculated latency was verified by inspection. For all matched comparisons of neural activity (within-hemifield versus across-hemifield, single-step versus double-step) or neural latency, we used the Wilcoxon signed rank test.

2.3.5.6 Trial-by-trial analysis in single neurons.

Our assessment of the relationship between neurons and behavior included an analysis of the trial-by-trial correlation between updating activity in single neurons and double-step saccade performance. As stated above, one of the challenges in measuring updating activity is that we must remove the contributions of saccade-alone activity. When we consider individual trials,

there is no principled way to match individual saccade-alone trials to individual double-step trials for this subtraction. We used the following method to remove the contributions of saccade-alone firing from double-step activity on single trials. For a given neuron, we computed the double-step firing rate for each trial as described above, measuring the spikes per second in the epoch from the beginning of the first saccade to the beginning of the second saccade. From each individual-trial double-step firing rate, we then subtracted the *average* saccade-alone firing rate for that condition (within or across). The average saccade-alone firing rate was computed using the epoch corresponding to the average double-step epoch for that neuron and condition. This method allowed us to remove the contributions of saccade-alone activity while maintaining information about updating activity on individual trials. We assessed the relationship between updating activity and behavior (accuracy or latency) by performing a Pearson's correlation analysis.

2.4 RESULTS

The goal of these experiments was to characterize the behavioral and physiological correlates of spatial updating in split-brain monkeys. We recorded from a total of 277 single neurons in the lateral intraparietal cortex of two split-brain monkeys (n=216) and an intact monkey (n=61) during performance of this task. Of these, we describe the neural activity and associated saccadic data from recording sessions that met a series of physiological and behavioral criteria (see Methods). The results focus on a final dataset of 139 neurons from the split-brain animals, and 42 neurons from the intact animal. We monitored each neuron's activity while the monkeys performed two conditions of the double-step saccade task, which required spatial representations

to be updated either across or within visual hemifields (Fig. 6). The results are presented in three sections. In the first section, we characterize the behavioral performance of the split-brain and intact monkeys during these physiological recording sessions. In the second section, we describe the accompanying neural activity in area LIP. This section focuses on the comparison between within-hemifield and across-hemifield remapping, and subsequently addresses the comparison of the single-step and double-step tasks. In the third section, we investigate the relationship between behavior and neural activity.

2.4.1 Performance on the double-step task

In behavioral studies described previously, we discovered that split-brain monkeys were initially impaired in performance on a set of standard across-hemifield double-step sequences, but were ultimately able to perform these sequences well (Berman et al. 2005). Nonetheless, the monkeys' performance of across-hemifield sequences remained less accurate than that of within-hemifield sequences. This inaccuracy was most evident when we introduced a novel spatial configuration. In the recording sessions described here, the spatial configuration of the task was necessarily determined by the location of the response field of each neuron. As a result, the monkeys were commonly presented with new spatial configurations of the double-step task. We therefore predicted that, during physiological recording, the split-brain monkeys would continue to demonstrate a behavioral impairment for the across-hemifield sequences as compared to the within-hemifield sequences.

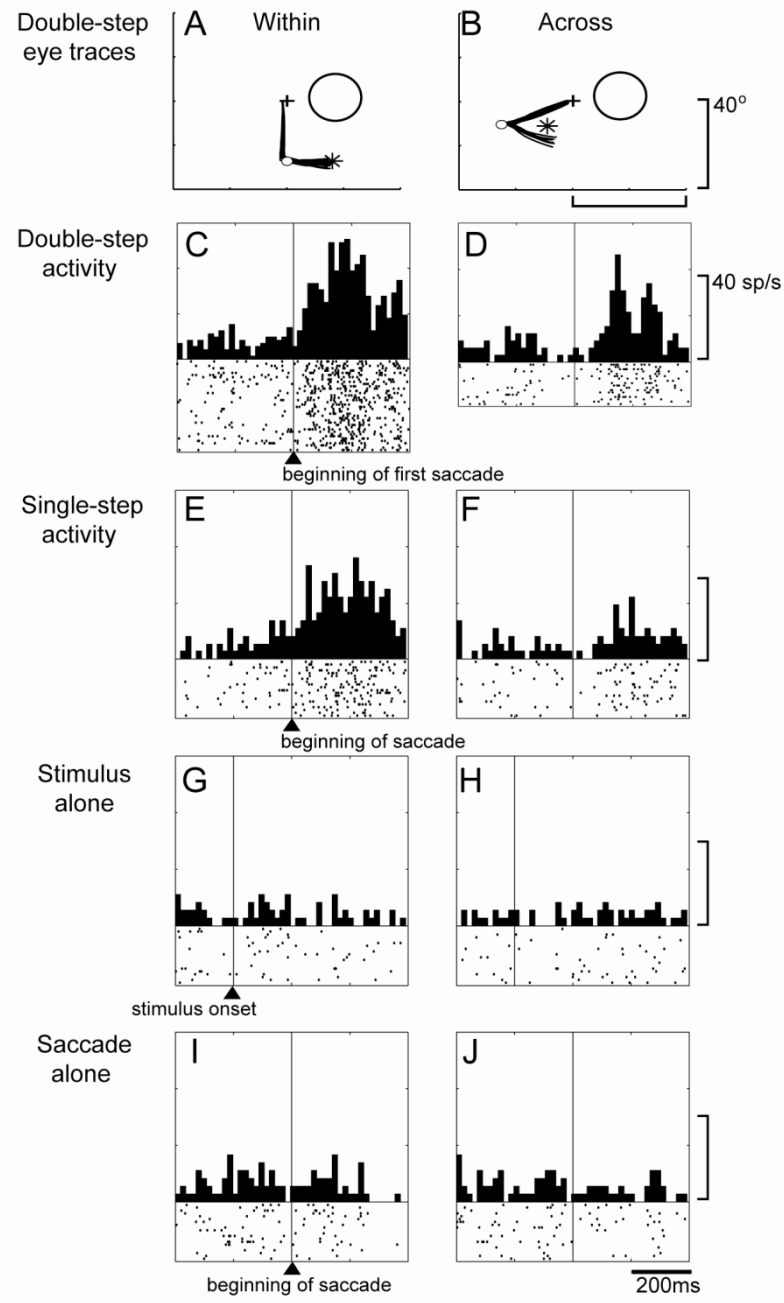


Figure 7. Activity in a single neuron that remaps both within and across hemifields in the double-step task.

The monkey makes sequential saccades from fixation (crosshair) to the first target (dot) and second target (asterisk). The first saccade brings the neuron's receptive field onto the location where the second target had appeared. Eye position traces from the first ten trials are shown for the within (A) and across (B) conditions. Recording during the double-step task shows neural activity during the within (C) and across (D) conditions. Recording during the single-step task likewise shows that activity in both the within (E) and across (F) conditions is greater than in the control tasks (G-J).

2.4.1.1 Performance of across-hemifield sequences is moderately compromised in the split-brain monkey

We found that the split-brain monkeys were selectively impaired in the across-hemifield condition of the double-step saccade task during physiological recording sessions. An example of double-step performance during recording from a single neuron is shown in Fig. 7. The split-brain monkey was very accurate on the within sequence (*A*) but less accurate on the across sequence (*B*). For this and every recording session, we quantified the accuracy of the monkeys' double-step performance by computing the distance error of the second saccade, using all trials in which the monkey accurately reached the first saccade target (T1).

The behavioral results from all recording sessions were consistent with the pattern of double-step performance seen in Fig. 7. On average, error on the second saccade was significantly greater for the across as compared to the within condition (Fig. 8*A*: across error = 3.90±0.26° (SE); within error = 1.92±0.077°, $p<.0001$, Wilcoxon signed rank test). We observed no significant difference between within- and across-hemifield accuracy in the intact monkey (Fig. 8B: across error = 2.67±0.14; within error = 2.54±0.15°, $p>.05$, Wilcoxon signed rank).

We next asked whether impairment of the across-hemifield sequences would also produce prolonged saccadic latencies. In our initial behavioral testing on a set of standard sequences, the split-brain monkeys exhibited moderate increases in latency on the first and second saccades of the across-hemifield sequences. By the end of many months of behavioral testing, however, the monkeys were no longer delayed in saccade initiation in the standard across-hemifield sequences (Berman et al. 2005). Further, across-hemifield latencies were not consistently prolonged when we introduced a new spatial arrangement of the double-step targets,

even though accuracy could again be impaired. We therefore predicted that across-hemifield latencies would not be slowed during the physiological recording sessions.

In the present study, we indeed found that saccadic latencies were not uniformly prolonged for the across-hemifield as compared to the within-hemifield condition, in either the split-brain or intact animal (Fig. 8*C-F*). In the split-brain monkeys, average S1 latencies were slightly prolonged for the across-hemifield condition (Fig. 8*C*, 123.8±3.3 ms (SE), compared to 115.9±2.1 ms for within-hemifield). This difference approached but did not reach significance (p=0.06, Wilcoxon signed rank). By contrast, average S2 latencies were significantly *faster* for the across-hemifield condition (Fig. 8*E*, 108.4±3.1ms, compared to 120.3±2.8ms for within-hemifield; p<.001, Wilcoxon signed rank). This observation is in keeping with our findings at the end of the initial behavioral testing: S2 latencies for the across-hemifield condition were no longer delayed, and were actually faster than those for the within-hemifield condition (Berman et al. 2005). In the intact monkey, we found no significant differences between within- and across-hemifield saccade latencies for either saccade (Fig. 8*D,F*: S1 across: 177.5±4.5 ms, S1 within: 174.1±6.3 ms, p=.29; S2 across: 143.6±2.9 ms, S2 within: 145.8±4.5 ms; p=.70, Wilcoxon signed rank). Overall, the split-brain monkeys had faster average saccade latencies than the intact monkey. This may reflect the very extensive experience of the split-brain monkeys on the double-step task. Each of the split-brain monkeys had more than 1.5 years of experience with the task before recording began. In contrast, the intact monkey had less than six months of experience.

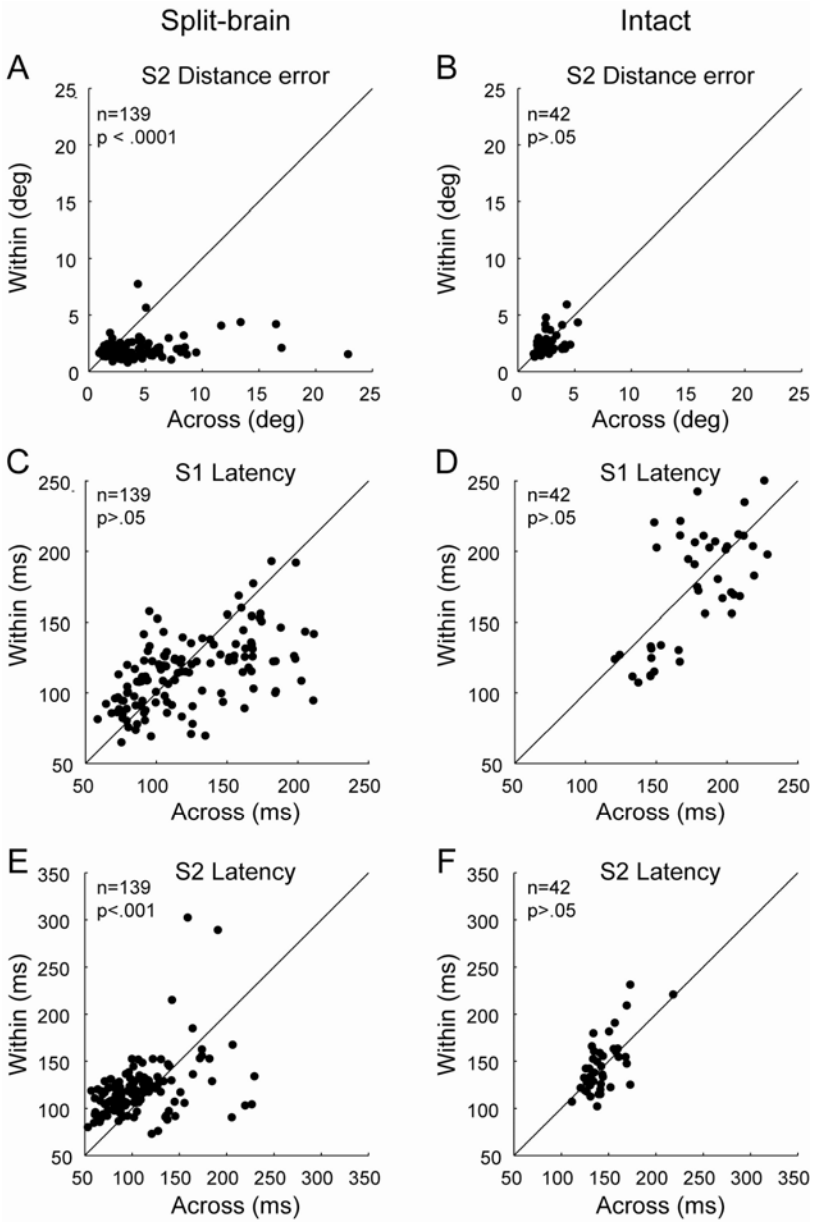


Figure 8. Accuracy and latency of double-step performance.

Panels in the left column represent data from the two split-brain monkeys; those in the right column are from a monkey with commissures intact. Each point represents average double-step behavior during the recording of a single neuron, for the within-hemifield (y axis) and across-hemifield condition (x axis). Distance error of the second saccade (S2) was significantly greater for across-hemifield updating in the split-brain (A) but not the intact animal (B). For latency (C-F), both the first and second saccades were faster overall for the split-brain monkeys, who were highly experienced on the task as compared to the intact monkey. For the first saccade (S1), within-hemifield and across-hemifield latencies were not significantly different for either split-brain or intact (C,D). For the second saccade, overall latencies were significantly faster for the across-hemifield condition in the split-brain (E) but did not differ in the intact monkey (F).

These data show that S2 latencies in the split-brain monkeys were faster for across-hemifield as compared to within-hemifield sequences. We considered the possibility that this finding reflected a trade-off between speed and accuracy, in which faster saccade latencies were associated with greater error. Accordingly, we plotted average S2 accuracy and latency against each other for all recording sessions (Fig. 9). Correlation analyses showed that the faster latencies were slightly but significantly related to *smaller* errors, both in the split-brain monkeys (Fig. 9*A*, slope = .013, r =.18, $p<.05$) and in the intact monkey (Fig. 9*B*, slope = .010, r = .26, $p<.05$; Pearson's correlation). This association between faster latencies and smaller errors remained significant when we focused solely on the across-hemifield condition for the split-brain monkeys (slope = .023, r = .27 $p<.001$). These findings indicate that the rapid latencies were not due to a speed-accuracy trade-off. In general, these very fast latencies likely reflect the fact that the split-brain monkeys were highly practiced as compared to the normal animal. The rapid across-hemifield latencies in the split-brain monkeys further suggest that they may have adopted a more automatic strategy for performing these sequences as they gained experience. In summary, the present findings demonstrate that the split-brain monkeys were only moderately impaired on performance of the across-hemifield double-step sequences. The monkeys exhibited greater errors for new across-hemifield sequences, though these errors were smaller than those observed in initial behavioral testing on the standard sequences (Berman et al. 2005). Latencies were not systematically prolonged for new across-hemifield sequences and were in fact faster in the case of the second saccade. These behavioral data reinforce the conclusion that spatial representations can be updated effectively across hemifields in the absence of the forebrain commissures.

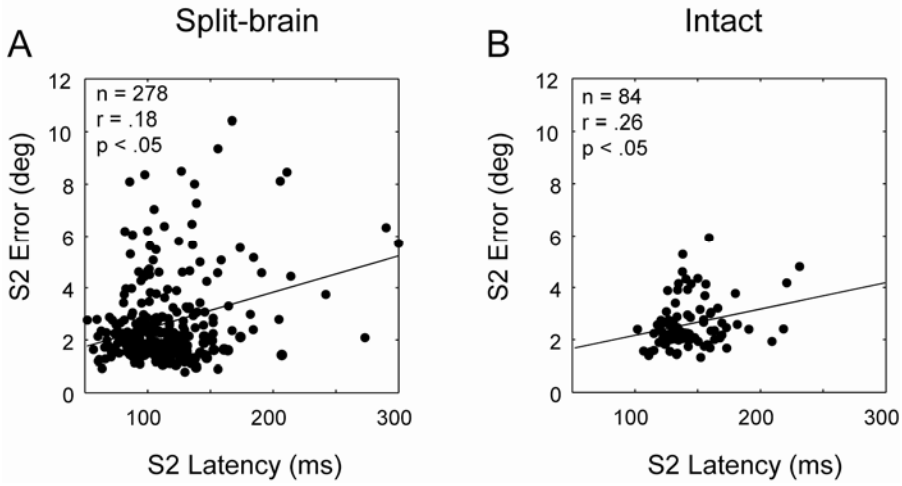


Figure 9. Relationship between speed of saccade initiation and accuracy for the second saccade of the double-step task.

Each point represents the spatial error (y axis) and average saccade latency (x axis) from a given neural recording session. Each session contributes two datapoints, one from within-hemifield trials and one from across-hemifield trials. The regression line is indicated by the thin black line. For both the split-brain (A) and intact (B) monkey, the overall slope of the relationship between speed and accuracy is positive: as latency increased, so did spatial error.

2.4.2 Neural activity during performance the double-step task

2.4.2.1 Within-hemifield and across-hemifield updating

LIP NEURONS IN THE SPLIT-BRAIN MONKEY REMAP STIMULUS TRACES ACROSS HEMIFIELDS IN THE DOUBLE-STEP TASK. Our second objective was to determine whether neurons in area LIP can remap spatial representations across visual hemifields in the double-step task in the absence of direct links between the cortical hemispheres. At the outset of our experiments in the split-brain monkey, our expectation was that LIP neurons would not exhibit remapping when the stimulus trace needed to be updated from one visual field to another. Results from recording during the single-step task, however, revealed that updating signals were present in area LIP of the split-brain monkey, even for the across-hemifield case (Heiser et al., 2005). We therefore expected that across-hemifield remapping would likewise be present in the double-step task.

Our central observation here is that neurons in area LIP of the split-brain monkey can update stimulus representations both within and across visual hemifields in the double-step saccade task. An example of this activity is shown for a single neuron in Figure 7. In the double-step task, the monkey made sequential saccades to two targets, T1 and T2 (Fig. 7*A,B*). The neuron responded vigorously for both the within-hemifield and across-hemifield conditions of this task (Fig. 7*C,D*). The neuron's response was negligible in the corresponding stimulus-alone (Fig. 7*G-H*) and saccade-alone control tasks (Fig. 7*I-J*). The minimal activity in these control tasks demonstrates that activity in the double-step task is not attributable to the generation of the saccade alone, or to the presentation of the T2 stimulus alone. Rather, the activity represents the cell's response to a stimulus trace of T2, which has been remapped in conjunction with the saccade to T1. This single neuron responded not only when the stimulus trace was updated within the same hemifield, but also when it was updated across hemifields. We asked whether this observation was evident in the population of LIP neurons, focusing on the prevalence, magnitude, and latency of updating activity.

MOST LIP NEURONS EXHIBIT BOTH WITHIN-HEMIFIELD AND ACROSS-HEMIFIELD REMAPPING. We first assessed the likelihood of observing significant updating activity in the across-hemifield condition of the double-step task (Fig. 10). We expected that across-hemifield remapping might be less prevalent than within-hemifield remapping in the absence of the forebrain commissures. In the split-brain monkeys, we found that 85% of neurons (119/139) exhibited significant remapping in at least one condition. Of these neurons, the vast majority had significant updating activity in both the across-hemifield and within conditions (70%, n=83, Fig. 10*A*). Some neurons had a significant response only for the within-hemifield condition (24%, n=29), and a

few were significant for the across-hemifield condition alone (6%, n=7). In the intact monkey, we found that the majority of neurons exhibited significant remapping in at least one condition (64%, 27/42, Fig. 10*B*). Of these, the majority had significant updating activity in both conditions (56%, n=15). The remaining neurons were more likely to show significant remapping for the across-hemifield condition only (37%, n=10) than for the within-hemifield condition only (7%, n=2). The salient observation here is that, among neurons with significant remapping, a substantial majority of neurons had significant across-hemifield remapping in both split-brain and intact animals (76% and 92%, respectively). We conclude that even in the absence of the forebrain commissures, the majority of LIP neurons can respond to the updated representations of T2 that originate in the opposite hemisphere.

WITHIN-HEMIFIELD REMAPPING IS STRONGER THAN ACROSS-HEMIFIELD REMAPPING IN THE SPLIT-BRAIN MONKEY. We next asked whether the magnitude of remapping activity in the double-step task was similar for across-hemifield and within-hemifield conditions. The example neuron from the split-brain monkey (Figure 7) fired strongly in both conditions of the double-step task, though less for the across-hemifield condition. Our data from single-step experiments in these split-brain monkeys demonstrated that LIP activity was stronger for within-hemifield updating (Heiser et al. 2005). In the present study, we observed the same pattern for updating activity in the double-step task. On average, neurons in the split-brain monkey exhibited significantly stronger updating activity for the within-hemifield condition as compared to the across-hemifield condition (Fig. 10*C*; within-hemifield: 18.2±1.5 sp/s (SE); across-hemifield:, 13.12±1.3 sp/s; $p<.0001$, Wilcoxon signed rank). No difference was observed in the intact

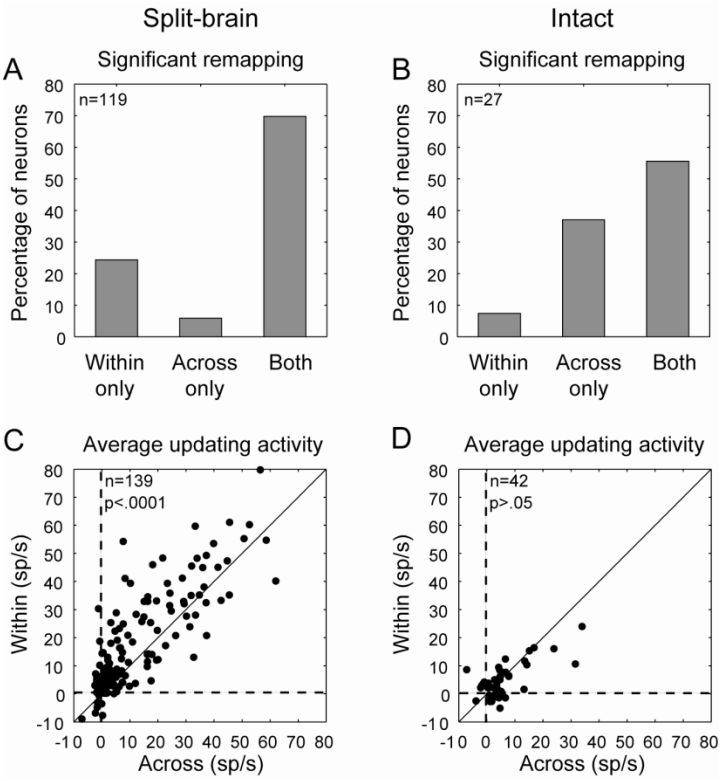


Figure 10. In the split-brain monkey, updating activity in LIP is stronger for the within-hemifield than the across-hemifield condition.

This difference was not observed in the intact monkey. Bars represent the percentage of neurons with significant remapping for Within only, Across only, or both conditions in the split-brain (A) and intact monkey (B); neurons with no significant remapping are excluded. For all single neurons in the split-brain (C) and intact monkey (D), average updating activity in the within-hemifield condition (y axis) is plotted against that in the across-hemifield condition (x axis). Updating activity is adjusted to take saccade-alone activity into account (see Methods); negative updating activity (below or to the left of the dotted lines in C,D) indicates that saccade-alone activity exceeded activity in the double-step task.

monkey (Fig. 10*D*; within-hemifield: 4.57±0.95 sp/s; across-hemifield:, 5.98±1.2 sp/s, p=.14, Wilcoxon signed rank). These data indicate that across-hemifield remapping, while clearly present in the split-brain monkey, is less robust than within-hemifield remapping.

We considered whether the difference between across-hemifield and within-hemifield activity in the split-brain monkey might reflect a difference in anticipated reward. Activity in area LIP may be modulated by reward or motivational signals (Dorris and Glimcher 2004; Platt and Glimcher 1999; Sugrue et al. 2004). In the present experiment, the split-brain monkeys

performed the across-hemifield double-step sequences less accurately, and thus were rewarded less frequently on these trials. We reasoned that if reward modulation were responsible for the difference between within- and across-hemifield updating in the double-step task, then the difference would disappear if reward amounts did not differ. We analyzed a subset of neurons recorded in sessions where the split-brain monkeys received reward on at least 90% of trials, for both the within- and across-hemifield sequences. For this subset (n=22), there was no significant difference in the amount of reward received for the two conditions ($p=.29$, Wilcoxon signed rank test). There was, however, a significant difference in updating activity between conditions (within-hemifield: 26.9 sp/s; across-hemifield, 21.4 sp/s, $p<.05$, Wilcoxon signed rank). We conclude that stronger within-hemifield updating in the split-brain monkeys is not attributable simply to differential reward.

LATENCY OF REMAPPING IN THE WITHIN- AND ACROSS-HEMIFIELD CONDITIONS. In our earlier study of the split-brain monkey, we found that across-hemifield updating activity began later than within-hemifield updating in the single-step task (Heiser et al. 2005). Might the same be true in the double-step task? We investigated this question in a subset of single neurons that had detectable neural latencies in both the within and the across condition. In order to detect the latency of updating accurately, it was necessary that the neurons have no significant saccade-alone activity for either condition, as this would interfere with the measure of the onset of updating activity. In the subset of neurons that met these criteria for both conditions (split-brain, N=22; intact, N=14), we could directly compare the neural latencies for within-hemifield and across-hemifield updating in the double-step task.

We found that the onset of updating activity was significantly later for the across-hemifield condition as compared to within-hemifield in the split-brain monkey, but not in the intact monkey. For each neuron, we compared the latency of within-hemifield remapping to that of across-hemifield remapping (Fig. 11). Points that fall along the unity line indicate that remapping began at the same time for the two conditions. In the split-brain monkeys, most points fall below the line, indicating that across-hemifield remapping began later than within-hemifield remapping in single cells (Fig. 11*A*, $p<.05$, Wilcoxon signed rank). In the intact monkey, neural latencies did not differ significantly for within-hemifield and across-hemifield conditions (Fig. 11*B*, $p=.54$, Wilcoxon signed rank). It is worth noting that there are several neurons in both the split-brain and intact monkeys in which updating activity begins even before the start of the eye movement (unshaded areas in Fig. 11*A,B*). This presaccadic activity is an example of predictive remapping and provides an updated representation before the eye movement is initiated. In the split-brain monkeys, a small number of neurons exhibit presaccadic remapping even in the across-hemifield condition (dots to the left of the dashed vertical line), although they are less common than neurons that exhibit presaccadic within-hemifield remapping (dots below the dashed horizontal line). These neural latency data lend further support to the conclusions from our firing rate analyses: in the split-brain monkey, neural signals associated with across-hemifield updating are common but are modified relative to within-hemifield signals.

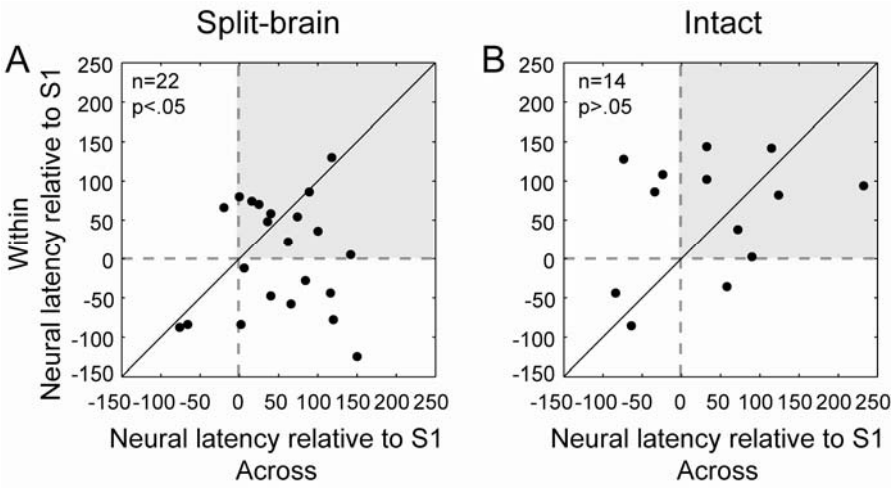


Figure 11. In the split-brain monkey (A), neural activity begins earlier for within-hemifield than across-hemifield updating.

This difference was not observed in the intact monkey (B). Analysis was conducted on a subset of neurons with detectable neural latencies for both within and across conditions (see RESULTS). For each neuron, the neural latency in the within-hemifield condition (y axis) is plotted against that in the across-hemifield condition (x axis). Neural latency is determined relative to the beginning of the first saccade (S1). Grey shading represents the region in which both within-hemifield and across-hemifield neural latencies were after the start of S1; unshaded areas indicate neural activity that began even before the start of S1. This activity reflects predictive updating, which was more frequent in the split-brain monkey for the within than the across condition. This is consistent with delayed across-hemifield updating activity in the absence of the forebrain commissures.

2.4.2.2 Task-related differences in updating activity

NEURAL ACTIVITY IS STRONGER IN THE DOUBLE-STEP TASK THAN IN THE SINGLE-STEP TASK. In the double-step task, LIP neurons update the representation of a stimulus that is highly relevant to the animals' behavior – the stimulus is the target for the second saccade. Does this behavioral relevance influence neural activity? We addressed this question by comparing activity in the double-step and single-step tasks. In the single-step task, the monkey makes a single saccade from fixation to the first target (T1). This saccade brings the neuron's receptive field onto the location where the stimulus had appeared. The stimulus, while salient due to its sudden onset, is not the target of the monkey's second eye movement as it is in the double-step task.

We found that activity in LIP is influenced by behavioral demands: activity is clearly increased in the double-step task as compared to the single-step task. In Fig. 7, we show activity in the double-step (*C*,*D*) and single-step tasks (*E*,*F*) for the representative LIP neuron from a split-brain monkey. In both tasks, the neuron exhibited updating activity in the within-hemifield and across-hemifield conditions. What is striking is that the neuron's activity increased sharply for the double-step task, irrespective of condition. We asked whether this task-related increase was also apparent in the population of LIP neurons. For each cell, we plotted average activity in the double-step task against activity in the single-step task for each of the conditions, for split-brain (Fig. 12*A*) and intact (12B) monkeys. The vast majority of points fall above the unity line, indicating stronger activity in the double-step task than in the single-step task. This increase was highly significant for the split-brain monkeys and for the intact monkey ($p<.0001$ for each group, Wilcoxon signed rank). These data indicate that activity is heightened when the stimulus to-be-updated is relevant for the monkey's behavior.

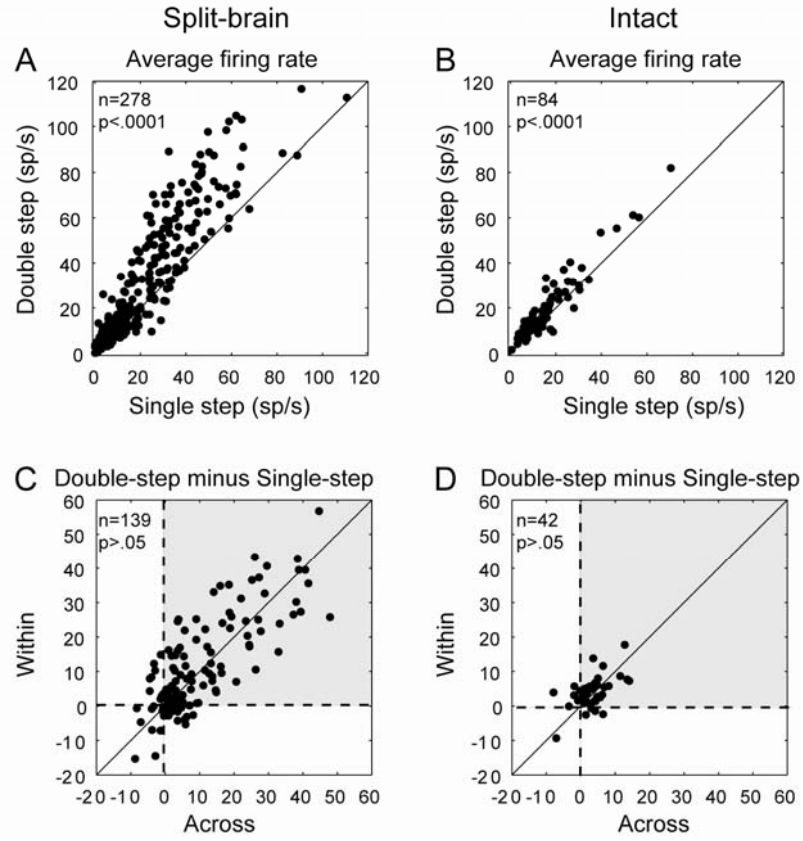


Figure 12. Comparison of neural activity in the single-step and double-step tasks.
For the split-brain (A) and intact animal (B), average firing rate is greater in the double-step as compared to the single-step task. Each dot represents the average firing rate for a single neuron for the double-step task (y axis) plotted against that for the single-step task (x axis). Each neuron contributes two data points, one for within and one for across. For the split-brain (C) and intact monkey (D), increased activity in the double-step task is present for both within-hemifield and across-hemifield updating. Each point represents the differential activity for the two tasks (Double-step minus Single-step, in sp/s). The average differential activity for each neuron is shown for the within condition (y axis) and across condition (x axis). The shaded square shows the region in which double-step activity is greater than single-step activity for both within-and across- hemifield conditions.

INCREASED ACTIVITY IN THE DOUBLE-STEP TASK OCCURS FOR BOTH UPDATING CONDITIONS. We next asked whether this task-related increase in neural activity occurred differentially for the within-hemifield as compared to the across-hemifield condition. We reasoned that, in the split-brain monkeys, the behavioral relevance of the stimulus might be conveyed more strongly when updating took place within the same hemifield. If so, we would observe a larger task-related increase in activity for the within-hemifield condition. In order to test this possibility, we computed the difference between average double-step and single-step activity for the within-

hemifield condition for each neuron, and compared this to the same difference computed for the across-hemifield condition.

We found that increased activity in the double-step versus single-step task did not occur preferentially for the within-hemifield condition. In Fig. 12*C* and *D*, we plotted the task-related difference in average firing rates from each cell, for the within condition (y axis) and across condition (x axis). If the task-related increase had been stronger for the within condition, more points would fall above the unity line. Instead, the points are centered on the unity line, and do not differ significantly by condition; this was true for the split-brain animals and for the intact animal (p=.34 and p=.27, respectively; Wilcoxon signed rank test). In other words, when the split-brain monkeys performed the double-step task, the activity of LIP neurons did not increase preferentially for the within-hemifield condition as compared to the across-hemifield condition. This finding indicates that the behavioral relevance of the stimulus can strengthen neural activity for both within-hemifield and across-hemifield updating in the split-brain monkey.

In summary, we made three key observations regarding neural activity in area LIP during the double-step task. First, the majority of LIP neurons in the split-brain monkey exhibit updating activity in the double-step task, even when the second target must be updated from one visual hemifield to the other. Second, across-hemifield remapping is less robust than within-hemifield remapping in the split-brain monkey, as evidenced in reduced magnitude and delayed onset of activity. Finally, in both the intact and split-brain monkeys, neural activity is increased for the double-step as compared to the single-step task, whether updating is within or across visual hemifields.

2.4.3 Is updating activity related to behavior in the split-brain monkey?

The goal of this final section is to determine whether there is a correspondence between updating activity and double-step performance. This possibility is of particular interest in the split-brain monkey, where we observed conditional differences in both neural activity and behavior. Our focus is the generation of the second saccade in the double-step task, which requires spatial updating. Specifically, we asked whether the accuracy or latency of this saccade is related to the updating activity that precedes it. We first investigate the relationship between neural activity and behavior at the level of the population, and then ask whether updating activity in single LIP neurons is related to spatial behavior.

2.4.3.1 Population activity in LIP corresponds to double-step performance

Our first analysis focused on the correspondence between the neural population and behavior. For this analysis, we characterized the relative bias toward within-hemifield or across-hemifield updating. We used indices that capture the differences in neural activity and behavior between within-hemifield and across-hemifield updating. The Within:Across neural index is computed for each cell, on the basis of updating activity in the remapping epoch (see Methods). The Within:Across behavioral indices are computed by taking the difference between measures of within-hemifield and across-hemifield performance (e.g., error across – error within) and dividing by the sum of the two. For all indices, values range from –1 to +1; this normalization allowed us to assess data from different sessions and monkeys on a comparable scale. Positive values always denote a bias for within-hemifield updating, manifest in stronger updating activity or greater accuracy or more rapid performance on the within-hemifield as compared to the across-hemifield condition. Using this approach, we asked whether the relative difference

between within-hemifield and across-hemifield updating was similar for neural activity and behavior.

We observed key similarities between updating activity in the population of LIP neurons and overall behavior. In the split-brain monkey, the distributions for both the neural indices and the accuracy indices were skewed positively ($p < .0001$, sign test, Fig. 13*A*,*C*), indicating that the within-hemifield bias in LIP activity was aligned with the bias in spatial accuracy. The latency index, by contrast, was skewed negatively ($p < .0001$, Fig. 13*E*), representing the overall bias for *faster* saccade initiation in the across-hemifield as compared to the within-hemifield condition. In the intact monkey, the distributions of all three indices did not differ significantly from zero (Fig 13*B*,*D*,*F*; $p > .05$). When we compared the index distributions from the split-brain monkeys to those of the intact monkey, we found that the distributions differed significantly from each other on all three measures (neural indices, $p < .0001$, error indices, $p < .00001$; latency indices, $p < .001$; Wilcoxon rank sum test). These normalized indices confirm our earlier analyses and provide a concise synopsis of the similarities and differences between LIP population activity and average behavior.

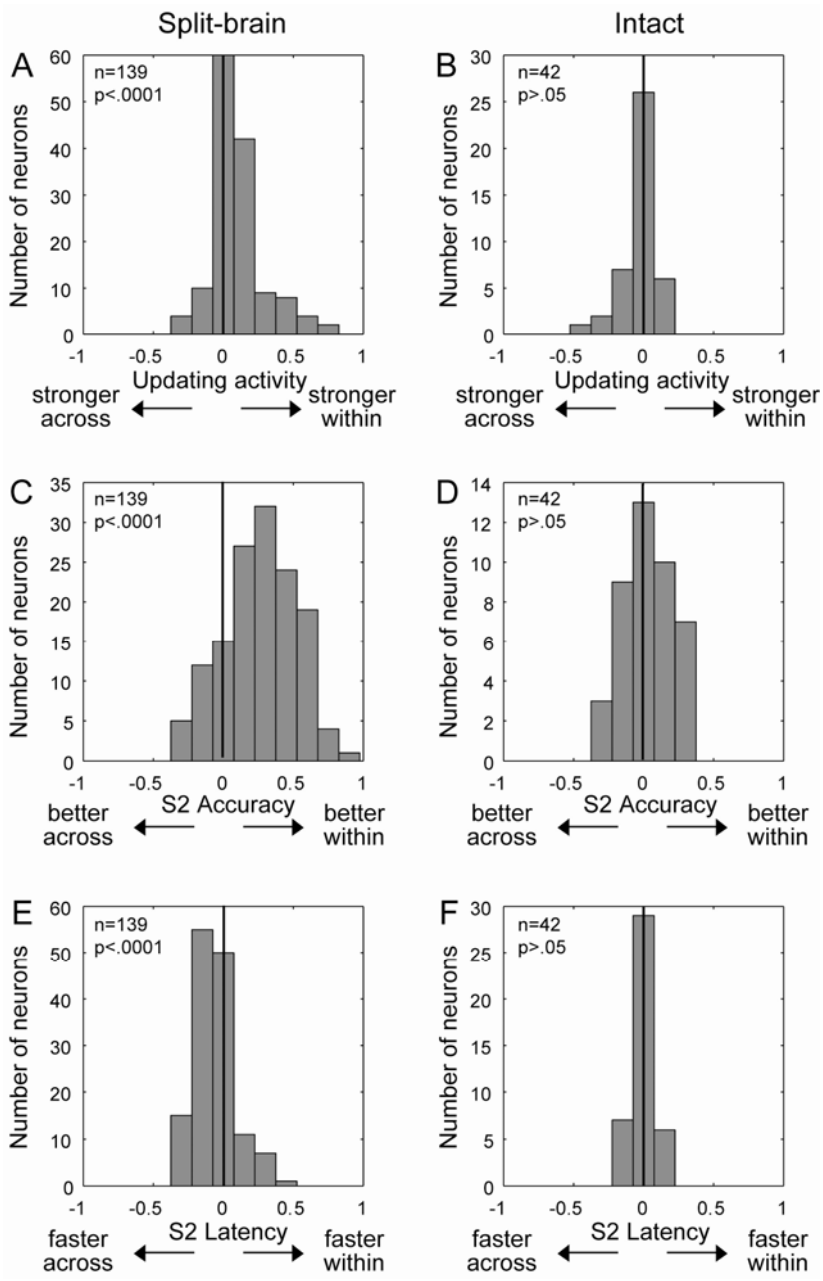


Figure 13. Population measures of updating strength and behavioral accuracy and latency.
Each panel shows the distribution of Within:Across (WA) index values from all neurons (single recording sessions). The index represents a bias for within-hemifield updating (positive values) or across-hemifield updating (negative values). The vertical line indicates no difference between within- and across-hemifield updating. In the split-brain monkey, the WA index is positively skewed for neural activity and distance error (A,C), but is negatively skewed for saccade latency (E). In the intact monkey, the WA index distribution does not differ from zero for neural activity (B), accuracy (D), or latency (F). Thus, at the population level, saccade accuracy parallels neural activity for both split-brain and intact monkeys. Saccade latency, by contrast, parallels neural activity in the intact monkey but not in the split-brain monkeys.

2.4.3.2 Trial-by-trial relationship between updating activity and behavior

Our second analysis emerges from the basic observation that the split-brain monkeys exhibited differences between within-hemifield and across-hemifield updating, in both activity and behavior. These differences in the split-brain monkey present an opportunity to ask whether the activity of single LIP neurons is related to performance of the double-step task. The objective of this second analysis is to determine whether remapping in single neurons bears any relationship to behavior on a trial-by-trial basis. For example, if a single neuron has stronger updating activity on certain trials than on others, is the monkey's performance likely to be more accurate on those same trials? We examined this possibility by conducting a correlation analysis across trials. We asked whether the accuracy or latency of the second saccade was significantly related to updating activity on a trial-by-trial basis. For each neuron, we obtained the Pearson's correlation coefficient, *r*, for the relationship between the saccade behavior (accuracy or latency) and updating activity (see Methods). We then assessed the distribution of *r* values from the population of LIP neurons. If remapping in single LIP neurons is systematically related to double-step performance on a trial-by-trial basis, then the distribution of *r* values will be significantly shifted away from zero.

We conducted this trial-by-trial analysis in two ways. In the first analysis, we analyzed the data from all trials, combining both within-hemifield and across-hemifield conditions. In the split-brain monkey we knew from preceding analyses (e.g., Figs 8 and 10) that there were systematic differences between the within and across conditions for updating activity and for performance. The first analysis allowed us to determine whether such differences in behavior and updating activity co-occur when measured at the level of single neurons. In the second

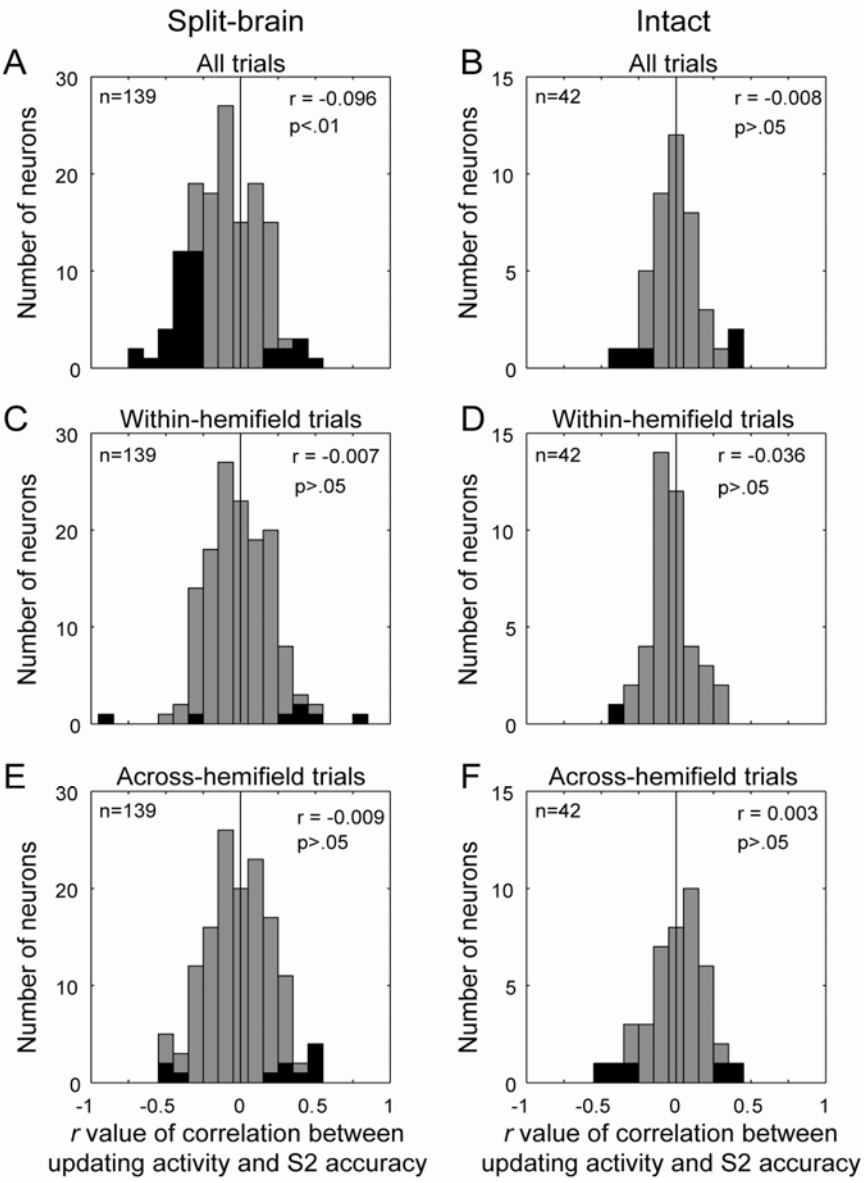


Figure 14. Trial-by-trial analysis for single-neuron updating activity in LIP and the accuracy of double-step performance.

Panels show the distribution of *r* values for the trial-by-trial correlation between updating activity and error of the second saccade. The left column shows data from the split-brain monkeys, right column from the intact monkey. Top row (A,B) shows data for all trials (within and across combined), middle row (C,D) shows data for within-hemifield trials only, and bottom row for across-hemifield trials only (E,F). Black shading indicates single neurons for which the trial-by-trial relationship was significant at $p<.05$. Vertical line indicates zero; x axis is identical for all panels. Negative *r* values indicate that greater updating activity was associated with smaller error. In the split-brain monkey, the population of *r* values had a significant negative skew only when all trials were combined (A), due to the differences between within and across-hemifield updating. The distributions were not significantly skewed for separate within (C) or across (E) trials in the split-brain monkey. In the intact monkey, there was no relationship between updating activity and second-saccade error on the double-step task whether trials were combined (B) or separate (D,F).

analysis, we computed the trial-by-trial correlations separately for the within and across conditions. If we observed a relationship for a single condition, it would indicate that the trial-by-trial variability in updating activity was significantly linked to behavioral performance, irrespective of any overall differences between within- and across-hemifield updating.

When data from both within-hemifield and across-hemifield conditions were combined, we found that the strength of remapping in LIP neurons in the split-brain monkeys was significantly related to the accuracy of the second saccade. The distribution of *r* values for the population was skewed negatively and was significantly different from zero (Fig. 14*A*; mean r = -0.096, $p<.01$, sign test). When we considered individual neurons, we found that nearly 30% exhibited a significant trial-by-trial correlation between remapping strength and accuracy (39/139; shaded in black in Fig. 14A). Of these, the majority had a negative correlation (31/39). These findings from the split-brain monkey demonstrate that stronger updating activity was slightly but significantly associated with smaller errors in individual recording sessions. We expected, however, that this association emerged from the differences between the within and across conditions. Was a trial-by-trial relationship present, independent of the conditional differences?

When we conducted the trial-by-trial analyses separately for the two conditions, we found no significant relationship between updating activity and second-saccade accuracy. Neither distribution of *r* values differed significantly from zero (within, Fig. 14*C*, mean r = -.007, $p = .73$; across, Fig. 14*E* mean r = -.009, $p = .31$, sign test). Further, only a small number of individual neurons exhibited a significant relationship (7/142 for within alone, 11/142 for across alone). These data indicate that, once conditional differences are removed, there is no

systematic relationship between the trial-by-trial variability in updating activity in single LIP neurons and the monkeys' accuracy on the double-step task.

In the intact monkey, we did not observe a significant trial-by-trial relationship between the strength of updating activity and the accuracy of performing the second saccade, whether the within and across data were combined or analyzed separately. When the two conditions were combined, the distribution of *r* values for trial-by-trial correlations did not differ significantly from zero (Fig. 14*B*, mean $r = -.007$, $p = .64$, sign test). A small proportion of individual neurons exhibited a significant correlation between remapping strength and accuracy (5/42, 12%), but these showed no trend toward a negative (n=3) or positive (n=2) correlation. The absence of a significant relationship for the combined data in the intact animal is not surprising. Saccade accuracy was considerably less variable in the intact animal than in the split-brain animals, where greater variability was introduced by the difference between within-hemifield and across-hemifield updating. As expected, when we analyzed data from the within and across conditions separately, the distributions of *r* values for the intact monkey were not significantly shifted from zero (within, Fig. 14*D*, mean $r = -.036$, $p = .09$; across, Fig. 14*F* mean $r = .003$, $p = .88$, sign test). These data constitute further evidence that trial-by-trial variability in updating activity is not significantly related to the accuracy of double-step performance.

We next examined the relationship between updating activity in single neurons and the latency of the second saccade in the double-step task. For the split-brain animals, the distribution of *r* values had a slight positive shift which approached significance when the within and across trials were combined (Fig. 15A; mean $r = .062$, $p=.09$, sign test). When we considered the strength of the correlation in individual neurons, we found that about a third of single neurons in the split-brain monkey showed a significant relationship between updating

activity and S2 latency (41/139). Here, a majority had a positive correlation (30/41), indicating a link between stronger activity and longer latencies. This counterintuitive relationship likely reflects the general tendency for LIP neurons in the split-brain monkey to have weaker updating activity in the across-hemifield condition, while saccade latencies were often *faster* in this condition. Consistent with this interpretation, we found that there was no relationship between updating activity and latency once the conditional differences were removed. When we conducted the analyses separately, the distribution of *r* values did not differ significantly from zero for either condition (within, Fig. 15*C*, mean $r = .013$ $p = .73$; across, Fig. 15*E*, mean $r = .057$, $p = .18$, sign test). We conclude that there is no significant trial-by-trial relationship between updating activity and saccade latency in the split-brain monkey.

Latency results for the intact monkey were virtually identical to those for the split-brain monkeys when the within and across trials were combined: the distribution of *r* values had a slight positive shift that approached significance (Fig 15*B*; mean $r = .062$, $p=.09$, sign test). In this combined analysis, a small proportion of single neurons showed significant trial-by-trial correlations (7/42, 17%), with most showing a positive relationship (5/7). We then conducted the trial-by-trial analysis separately for the two conditions. For the within condition, the distribution had a small but significant positive shift (Fig 15*D*; mean $r = .105$, $p<.01$, sign test), though the number of individual neurons with a significant correlation was very small (2/42, <1%, both positive). For the across condition, we found that the distribution of *r* values did not differ significantly from zero (Fig 15*F*; mean $r = .056$, $p=.64$, sign test).

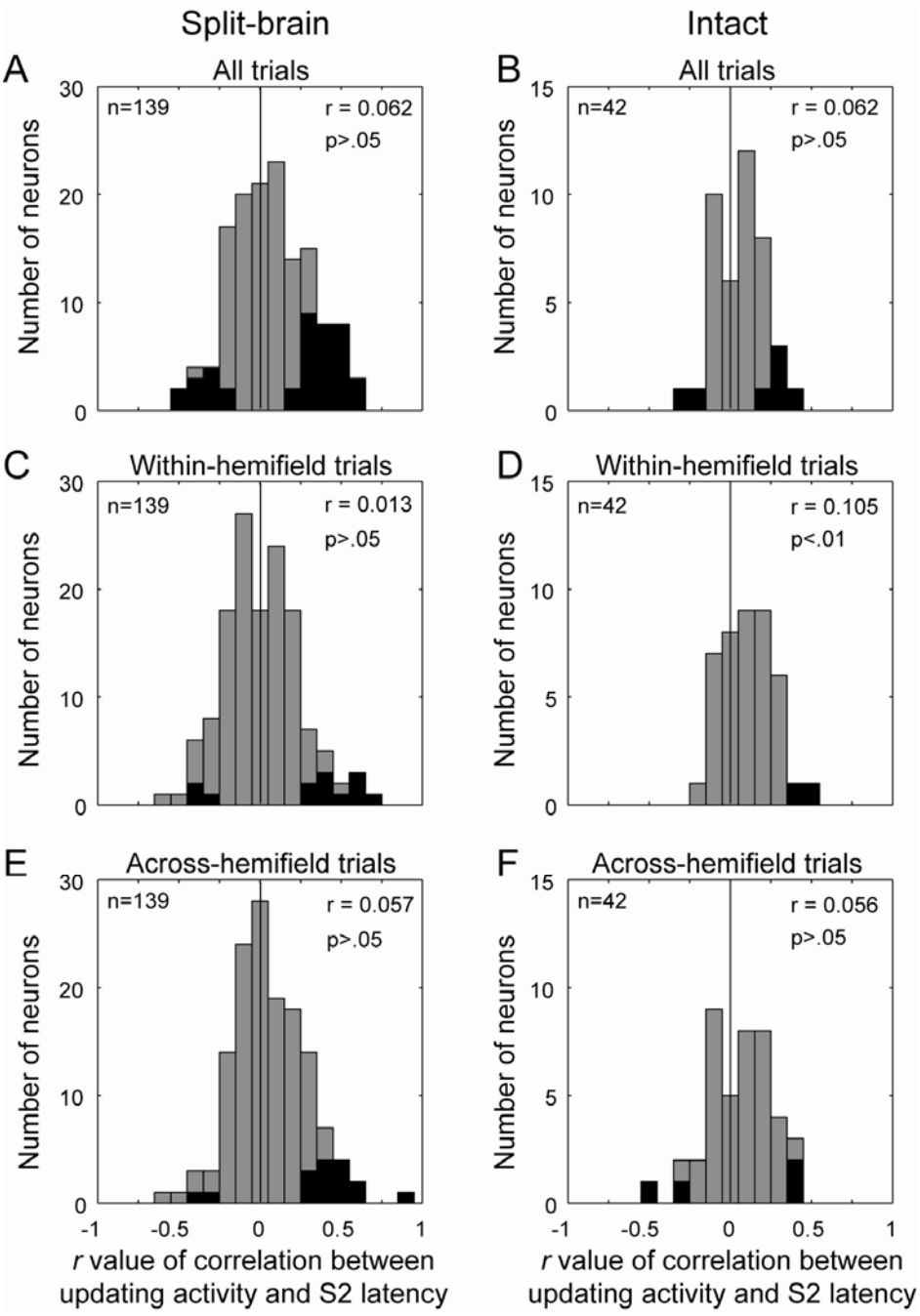


Figure 15. Trial-by-trial analysis for single-neuron updating activity in LIP and the latency of double-step performance.

Panels show the distribution of *r* values for the trial-by-trial correlation between updating activity and latency of the second saccade. Conventions as in Fig. 14. For all trials combined (A,B) the distribution had a slight but nonsignificant positive skew for both split-brain and intact monkey, indicating that stronger updating activity was associated with longer latencies. This positive skew was significant in the intact monkey for within-hemifield trials alone (D). For all other cases in the split-brain (A,C,E) and intact monkey (B,F), there was no significant trial-by-trial relationship between updating activity and second-saccade latency on the double-step task.

In summary, these analyses indicate that updating activity in single LIP neurons is related to performance on the double-step task insofar as there are differences between within-hemifield and across-hemifield updating in the split-brain monkey. Independent of the conditional differences, however, we found no clear evidence that updating activity in single LIP neurons is correlated with behavioral performance on a trial-by-trial basis, in either the split-brain or the intact monkey.

2.4.3.3 Experience-dependent changes in behavior and neural activity

This extensive dataset gave us the opportunity to ask how double-step performance and neural activity in the split-brain monkey changed with experience. One of the most intriguing findings from our previous behavioral studies was that the split-brain monkeys exhibited initial impairments in performance on the across-hemifield condition but improved substantially as the animals gained experience with specific test sequences (Berman et al. 2005). In the present study, the spatial arrangement of double-step targets was determined by the location of the receptive field, and as a result, the monkeys were often presented with new double-step sequences. For one monkey, however, we had multiple testing sessions (n=35) in which the receptive field was placed at the same angle (45°) relative to central fixation (Fig. 16*A*). Consequently, the monkey had repeated experience with the same geometric arrangement of double-step targets. This allowed us to investigate the impact of experience on both the behavior and neural activity associated with spatial updating. We were interested in two questions. First, could we detect any experience-dependent change in the monkeys' double-step performance on the across-hemifield and within-hemifield conditions? Second, if so, would these behavioral changes be accompanied by parallel changes in neural activity? We addressed these questions by looking at the Within:Across indices for the sessions in which the monkey performed the

same configuration of the double-step task. These indices, described above, capture the relative bias toward within-hemifield updating (positive values) or across-hemifield updating (negative values). We reasoned that if experience improved the monkey's performance on the across-hemifield as compared to the within-hemifield sequence, we would observe a shift in the behavioral Within:Across indices, with values becoming less positive.

We found that the monkey initially performed the across-hemifield sequence less accurately than the within-hemifield sequence: in the first few sessions, the values for the Within:Across accuracy index were +0.4 or greater (Fig. 16*B*), consistent with more accurate performance on the within-hemifield condition. With experience, however, there was a decreasing difference in accuracy for the across-hemifield as compared to the within-hemifield condition. This is evident in the index values, which became more negative over sessions (Fig. 16*B*). We found a significant correlation between the Within:Across accuracy index and session ($r=-0.602$, $p<.001$, Pearson's), indicating that experience led to improved accuracy on the across-hemifield as compared to the within-hemifield double-step task. The effect of experience was even more apparent for saccade latency (Fig. 16*C*). In initial sessions with this specific double-step configuration, the monkey initiated the second saccade at about the same time for the across-hemifield and within-hemifield conditions (index values near zero). With experience, the monkey's second saccade latencies became increasingly faster for the across-hemifield condition as compared to the within-hemifield condition (index values became more negative). The Within:Across latency index was significantly correlated with session ($r=-0.679$ $p<.0001$, Pearson's). These accuracy and latency data show that experience was associated with improved behavioral performance on the across-hemifield condition as compared to the within-hemifield condition.

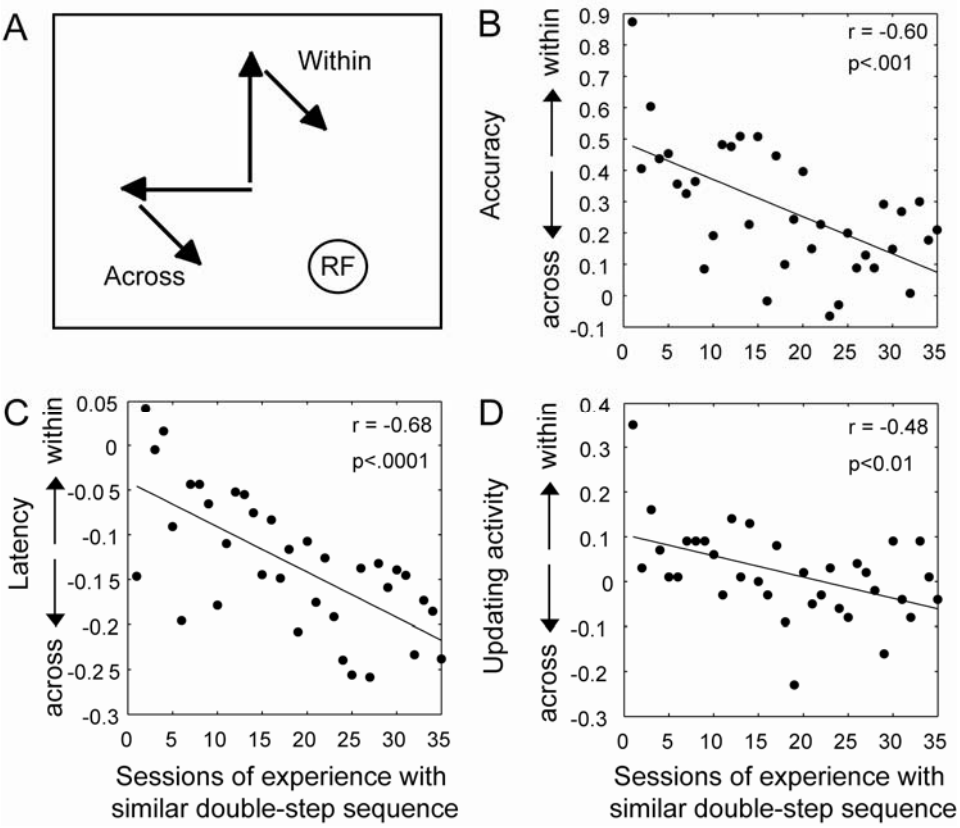


Figure 16. Changes in behavior and neural activity over multiple sessions of testing with the same spatial geometry of the double-step saccade task.

Each point represents data from a single recording session (one cell) in which the receptive field (RF) was located at the same angle, 45°, from fixation (A). In panels B-D, Within:Across indices (y axis) are plotted as a function of session (x axis); regression lines are indicated by the thin black lines. Positive index values denote greater accuracy (B), faster latency (C), or stronger updating activity (D) for the within-hemifield sequence. For accuracy and updating activity, index values approached zero over sessions, indicating that within and across updating became more alike as the monkey gained experience. For latency, index values became increasingly more negative, indicating that across-hemifield latencies became even shorter relative to within-hemifield latencies as the monkey gained experience.

The second question we asked was whether we observed a similar experience-dependent change in neural activity. For example, does activity in area LIP neurons shift from being stronger for the within-hemifield condition (positive index values) to being more equivalent for the two conditions (index values near zero)? We found that neural activity indeed exhibited a trend that matched what we observed in the behavioral data: the Within:Across neural index became more negative over sessions and was significantly correlated with session (Fig. 16*D;* r=-0.482, p<.01, Pearson's). Finally, we found a significant relationship between a single neuron's

Within:Across index and both of the behavioral Within:Across indices (neural index vs. accuracy index, $r=.526$, $p<.01$; neural index vs. latency index, $r=.415$, $p<.05$, Pearson's). These results indicate that updating activity in area LIP changes in concert with behavior as the monkey gains experience with specific double-step sequences.

2.5 DISCUSSION

Our central hypothesis is that direct cortico-cortical links are integral to updating spatial representations when the eyes move. We have investigated this hypothesis in a series of experiments that assess the behavioral and physiological correlates of remapping in the split-brain monkey (Berman et al., 2005; Heiser et al., 2005). In the present study, we examined the split-brain monkeys' performance on the double-step saccade task and the accompanying neural signals in parietal cortex. Three key observations emerge from this study. First, we found that split-brain monkeys continued to exhibit moderate impairment in the double-step task when across-hemifield updating was required, despite extensive training and experience with the task. This impairment was evident in increased spatial error on the across-hemifield condition. Second, we found that neural activity associated with across-hemifield updating in the double-step task was altered but by no means abolished in the absence of the forebrain commissures. In area LIP of split-brain monkeys, average updating activity was diminished and delayed in the across-hemifield condition but was nevertheless present in a majority of neurons. The double-

step task elicited heightened activity compared to the single-step task, demonstrating an influence of behavioral relevance for both within-hemifield and across-hemifield conditions. Third, we found evidence that remapping in area LIP, when considered at the level of the population, corresponds to the accuracy of performance on the double-step task in the split-brain monkey. We discuss the implications of these new findings for the neural circuitry of spatial updating and the representation of space in area LIP.

2.5.1 The role of direct cortical links in spatial updating

Our present findings, together with our earlier behavioral and physiological studies, demonstrate that direct cortico-cortical links are an important part of the circuitry for spatial updating. In the absence of the forebrain commissures, spatial updating was less robust for double-step sequences that required the stimulus trace of the second target to be remapped across hemifields as compared to within the same hemifield. This was evident both in the monkeys' performance of the double-step task and in the pattern of activity in area LIP. During these physiological recording sessions, the monkeys generated less accurate saccades in the across-hemifield condition as compared to the within-hemifield condition, despite many months of experience with both conditions of the task. Furthermore, single neuron activity in LIP was diminished in the across-hemifield condition, despite an increase in firing rate for the double-step as compared to the single-step task. These findings point toward the conclusion that direct cortico-cortical communication provides the most robust and rapid pathway for updating stimulus traces when the eyes move.

2.5.2 Subcortical pathways and recovered function

Our findings demonstrate that while direct cortico-cortical connections via the forebrain commissures are the primary pathway for remapping, they are not the only route by which remapped information can be transferred (Berman et al., 2005). Both split-brain monkeys were able to perform the across-hemifield double-step sequences, despite some inaccuracy, and showed no significant slowing of saccade latency. The majority of LIP neurons in the split-brain monkeys had significant updating activity in the across-hemifield condition of the double-step task. Furthermore, when we compared remapping for the double-step and single-step tasks, we found that the behavioral relevance of the to-be-updated stimulus was conveyed for both within-hemifield and across-hemifield conditions. These behavioral and neural data point toward an unexpected outcome of this series of experiments: spatial updating across visual hemifields is remarkably effective in the absence of the forebrain commissures.

What structures contribute to across-hemifield updating in the split-brain monkey? In the absence of the forebrain commissures, the SC may be a critical node for relaying remapped visual signals when across-hemifield updating is required. Neurons in the SC carry a range of visual, oculomotor, and cognitive signals, and can dynamically update visual representations in conjunction with eye movements (Munoz and Everling, 2004; Schiller and Stryker, 1972; Walker et al. 1995; Wurtz and Goldberg, 1971). In the normal monkey, the remapped visual signals observed in SC are thought to originate in cortex (Quaia et al. 1998). The frontal eye field sends remapped visual information to the SC (Sommer and Wurtz, 2003); area LIP is another likely source of these signals as it also projects directly to neurons in the intermediate layer of the SC (Ferraina et al. 2002; Pare and Wurtz, 1997, 2001). In addition to the SC, the pulvinar and cerebellum have been implicated as important pathways for interhemispheric

transfer in the absence of the forebrain commissures (Corballis, 1995; Glickstein, 1990). Furthermore, there is considerable interest in the proposal that thalamic nuclei may serve to mediate cortico-cortical communication (Guillery and Sherman 2002). These findings underscore the likelihood that a broad network of regions work together to carry out across-hemifield updating when the predominant pathways – the forebrain commissures – are absent.

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 of the superior colliculus or frontal eye field induce deficits in saccadic eye movements, but these deficits are transient unless both structures are removed (Schiller et al. 1979). If either the SC or FEF remains intact, voluntary saccade generation recovers spontaneously within several weeks. These findings have been interpreted as evidence of parallel pathways (Schiller et al. 1980), and more recently as evidence of reorganization in the oculomotor system (Hanes and Wurtz, 2001). Our results show that spatial updating is likewise subserved by a flexible cortical and subcortical network. Plasticity is not limited to the circuit for generating eye movements but is also present in the circuit responsible for the *perceptual consequences* of eye movements. These findings highlight the importance of the neural systems that use motor signals to modify sensory representations in the primate brain.

In keeping with these findings, we recently reported that the communication of *corollary discharge* information does not rely on direct cortico-cortical links (Colby et al. 2005). Corollary discharge, a copy of the motor command to move the eyes, is presumed to initiate the updating of visual representations (Duhamel et al. 1992a; Quaia et al. 1998), and recent experiments provide direct evidence that this is the case (Sommer and Wurtz 2006). Our observations indicate that corollary discharge signals, presumably originating in one hemisphere,

can initiate spatial updating in the opposite hemisphere. This conclusion is consistent with recent evidence that subcortical structures play an important role in conveying corollary discharge information to cortex (Bellebaum et al. 2005; Crapse and Sommer, 2006; Sommer and Wurtz, 2002, 2006). Further delineation of these pathways will be essential to understanding both the behavioral and physiological correlates of remapping.

2.5.3 Modulation of neural activity in area LIP by behavioral relevance

One of the most striking features of LIP activity in the double-step saccade task is that firing rates are increased relative to the single-step task (Goldberg et al., 1990). This increase presumably reflects the added contributions of both oculomotor and attentional factors. The oculomotor contribution follows from the observation that many neurons in LIP have saccade-related activity, as measured in the memory-guided saccade task (Barash et al., 1991a; Colby et al., 1996). In the double-step task, the second saccade is directed into the neuron's response field, eliciting activity that could add to the remapped response. These eye movement signals alone, however, cannot account for increased responsivity in the double-step task; neurons are active in the double-step task even when they have no saccade-related activity (Goldberg and Bruce, 1990; Goldberg et al., 1990; Walker et al., 1994). Attention also contributes to the intensified activity in the double-step task. Remapping in LIP is modulated by the salience of the stimulus to be updated (Gottlieb et al., 1998). This attentional modulation is consistent with multiple lines of evidence that suggest a role for area LIP in encoding salient visual stimuli (Assad, 2003; Bisley and Goldberg, 2003; Wardak et al., 2004). Together, these findings indicate that the heightened neural activity in the double-step task represents a concatenation of visual, oculomotor, and attentional signals.

In the split-brain monkey, we observed heightened activity in the double-step task both for updating within hemifields and updating across hemifields. Without direct cortical links, it seemed possible that the system would be less effective in relaying the behavioral relevance of the to-be-updated stimulus from one hemisphere to the other (Reuter-Lorenz and Fendrich, 1990; Hines et al., 2002). We found, however, that the behavioral relevance was conveyed well for both within-hemifield and across-hemifield updating. This finding is consistent with earlier studies in split-brain patients, which indicate that subcortical structures can mediate the interhemispheric communication of attentional signals (Corballis, 1995).

2.5.4 Area LIP and spatial behavior

Parietal cortex has long been known to be essential to the performance of spatial tasks ((Andersen, 1987; Rizzolatti et al., 1997; Colby and Olson, 1999; Li and Andersen, 2001). More recently, physiological studies have begun to ask how neural activity within parietal cortex relates to behavior. A number of studies have focused on decision processes, and suggest that activity in area LIP can predict perceptual choice or the monkey's preference among competing actions (Platt and Glimcher, 1999; Shadlen and Newsome, 2001; Williams et al., 2003; Dorris and Glimcher, 2004; Sugrue et al., 2004). Recent studies have investigated whether single neuron activity in LIP relates in any systematic way to the generation of saccadic eye movements. For example, several experiments have shown a significant correlation between saccade latencies and the time of saccade selection signals in LIP in a visual search task (Ipata et al. 2006, Thomas and Pare 2007). Our experiment differs from these recent studies in two important ways. First, we have focused on a specific aspect of LIP function – updating activity – and have asked if it is related to the monkeys' ability to perform the second saccade in the

double-step task. Second, our investigation focused not on the normal animal, but on split-brain monkeys. In the present study, we capitalized on the variability in LIP updating activity and behavioral performance in the split-brain monkeys, and asked whether the two are related.

Our results indicate a parallel between the strength of updating activity in LIP neurons and the accuracy of double-step performance in the split-brain monkey. In single neurons, stronger updating activity in LIP was associated with more accurate performance of the second saccade when within and across trials were analyzed together. When within and across trials were analyzed separately, however, we found no trial-by-trial relationship between updating activity and accuracy. Rather, the relationship in single cells reflects the conditional differences between within-hemifield and across-hemifield updating. In our population analysis, we focused on the relative difference between within-hemifield and across-hemifield updating. Average updating activity in area LIP was stronger for within-hemifield than across-hemifield updating, and, in parallel, the monkeys were more accurate for within-hemifield than across-hemifield updating. These findings imply that the spatial coordinates for the second saccade in the double-step task may be extracted from the remapped responses of an ensemble of LIP neurons. This is compatible with the suggestion that population activity in LIP can guide the direction of saccades generated in the antisaccade task (Zhang and Barash, 2000), and is consistent with other findings of population coding in the oculomotor system (Lee et al. 1988).

We observed an unanticipated relationship between updating activity and second-saccade latency in the split-brain monkeys: stronger updating activity was associated with prolonged saccade latencies instead of faster latencies as might be expected. At the level of single neurons, we found that some cells had significant, positive trial-by-trial correlations between updating activity and latency when within- and across-hemifield trials were analyzed together. At the

level of the population, updating activity was biased toward stronger firing in the within-hemifield condition, while latencies were faster on average for the across-hemifield sequences. This apparent dissociation between remapping signals in LIP and latency is intriguing, given the unusually short second-saccade latencies for across-hemifield sequences. The short latencies emerged with experience and indicate that the split-brain monkeys may have established a more automated strategy to generate the across-hemifield sequences. It would be useful to determine whether updating activity in other structures, such as the FEF or SC, might be more closely linked to second-saccade latency in the double-step task. Further investigation of these structures will be important to determine the compensatory pathways that contribute to double-step performance in the absence of the forebrain commissures.

In the intact monkey, there was a parallel between updating activity and behavior when we considered the overall population bias toward either within-hemifield or across-hemifield updating. This population analysis showed no relative differences between within-hemifield and across-hemifield conditions for any of the three measures – updating activity, saccade accuracy, or saccade latency. In our single neuron analysis, we did not observe strong evidence for a significant trial-by-trial correlation between updating activity and either accuracy or latency of the second saccade. This may be because performance was consistently good. In one of the seminal studies that uncovered a significant relationship between the activity of single neurons and behavior, an important feature was that the monkeys' performance was at threshold, with a number of successful as well as unsuccessful trials (Newsome et al. 1989). In the intact monkey, there was little variability in performance of the double-step task, which may have impeded detection of clear trial-by-trial correlations between updating activity and behavior.

It is important to note that, insofar as there is a correspondence between updating activity and double-step performance in the split-brain monkey, we cannot address the possibility of a *causal* relationship between these variables. For example, inaccurate double-step performance on the across-hemifield condition may be the result of reduced updating activity in area LIP. Alternatively, inaccurate performance may be due to disrupted activity in other structures, and the inaccurate 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 in the split-brain monkey between remapping in area LIP as a whole, and the overall performance of the double-step task.

In conclusion, these experiments have yielded three new findings about the dynamic nature of the circuitry for spatial updating in the primate brain. First, in the absence of direct cortico-cortical communication, animals are able to perform the double-step task well for targets whose representation has to be remapped across hemispheres, in addition to those whose representation remains within one hemisphere. Performance is more accurate for the within-hemifield than the across-hemifield condition, despite the split-brain monkeys' extensive experience with the task. Second, in parallel to the behavioral results, LIP population activity in the split-brain monkey is stronger for within-hemifield as compared to across-hemifield updating. Third, the difference in accuracy between within-hemifield and across-hemifield performance corresponds to differences in updating activity; this correspondence is detectable in single neurons in area LIP. This finding emphasizes that parietal cortex is an integral part of the network that updates spatial representations for the accurate guidance of eye movements. These experiments highlight the importance of direct cortico-cortical links for spatial updating, yet also

reveal considerable plasticity in the circuitry that constructs an internal representation of a stable visual world.

3.0 REPRESENTATION OF THE IPSILATERAL VISUAL FIELD BY NEURONS IN THE MACAQUE LATERAL INTRAPARIETAL CORTEX DEPENDS ON THE FOREBRAIN COMMISSURES

3.1 INTRODUCTION

Vision is an active process in which we move our eyes to explore the world around us. Eye movements introduce a complex problem for perception: they occur about three times per second, and with each eye movement a new image impinges on the retina. Even so, we perceive a stable visual world, enabling us to act. Neurons in lateral intraparietal cortex (LIP), frontal eye fields(FEF), extrastriate cortex, and the superior colliculus (SC) update spatial representations at the time of an eye movement (Mays and Sparks, 1980a; Goldberg and Bruce, 1990; Duhamel et al., 1992a; Walker et al., 1995; Nakamura and Colby, 2002). These areas transfer visual activity from neurons representing the salient location before the eye movement to neurons representing the salient location after the eye movement. It is hypothesized that updating in conjunction with every eye movement allows the formation of a stable perception.

Accurate spatial updating depends on neurons that receive visual information from the entire visual scene, even when the initial and final salient locations are in opposite visual fields. For example, a visual stimulus flashed 6º up and to the right of an initial fixation point is presumably represented by neurons in the left hemisphere. If an eye movement is made 12º to

the right, the location of the flashed stimulus will now be 6º up and to the left of fixation, represented by neurons in the right hemisphere. Neurons that remap in the right LIP must receive information about the visual stimulus that was original encoded by the left hemisphere. There is evidence that this is the case in the original LIP remapping study (Duhamel et al., 1992a). In this study, the task was configured so that a stimulus was flashed in the hemifield opposite the one represented by the neuron being recorded. The visual information was updated from one visual hemifield to the other, demonstrating that information is passed between hemispheres.

One potential route for the transfer of visual information across hemispheres is through the forebrain commissures, the fiber pathways that connect the cortical hemispheres. Berman and colleagues test this possibility by transecting the forebrain commissures (Berman et al., 2005). They found that behavior dependent on accurate spatial updating is impaired. Surprisingly, this impairment was not permanent and behavior recovered over time. Additionally, neurons in LIP continue to remap information across hemifields even in the absence of the forebrain commissures (Heiser et al., 2005). These studies indicate that the forebrain commissures are the primary pathway for the transfer of visual information across hemispheres but they are not the only possible pathway.

The finding that LIP neurons remap visual information from the opposite visual field even in the absence of the forebrain commissures implies that the opposite cortical hemisphere is not the only direct source of information (Heiser et al., 2005). One possibility is that information from both the ipsilateral and contralateral visual fields are represented in a single hemisphere. In other words, LIP neurons could have bilateral receptive fields. In intact monkeys, a small number of LIP neurons have been shown to have bilateral receptive fields (Andersen et al.,

1990b; Barash et al., 1991b; Platt and Glimcher, 1998; Ben Hamed et al., 2001). The aim of the present study was to determine whether there is any ipsilateral representation in LIP in the absence of the forebrain commissures.

The issue of the contribution of the forebrain commissures to construct ipsilateral RFs has been explained in inferotemporal cortex (IT). In area IT, neurons have large receptive fields, typically ranging from 10° by 10° to 30° by 30°, and they almost always include the fovea (Gross et al., 1969). Approximately one-third of the receptive fields extend out to 7° in both hemifields. The ipsilateral extent of the receptive field is dependent on interhemispheric connections. Ipsilateral representations are eliminated when the forebrain commissures are transected or when the contralateral striate cortex is removed (Rocha-Miranda et al., 1975). This means that the information about the ipsilateral visual field is coming from the contralateral visual cortex.

The goal of the current study was to determine if neurons in LIP retain bilateral representation even in the absence of the forebrain commissures. We addressed this problem by recording single LIP neurons in both split-brain and intact monkeys while they performed a receptive field mapping task. This task allowed us to measure the extent of the ipsilateral and contralateral representation of each neuron. Consistent with previous studies, we found a small number of neurons with bilateral receptive fields in the intact monkey. In contrast, we found no such neurons in the split brain animals. Similar to area IT, LIP neurons no longer represent the ipsilateral visual field. We conclude that bilateral representations in LIP following the forebrain commissures transection can not account for the observed across hemifield remapping.

3.2 METHODS

3.2.1 General Procedures

Four rhesus macaques (*Macca Mulatta,* 5-9 kg) were used in this study. The forebrain commisssures of monkey EM and CH were surgically transected at the beginning of a set of previous experiments (Berman et al., 2005; Heiser et al., 2005; Berman et al., 2007a). In the control animals FF and OP, the forebrain commissures remained intact. Animals were cared for and handled in accordance with NIH guidelines, and all experimental protocols were approved by the University of Pittsburgh Institutional Animal Care Use and Committee.

The commissurotomy is described in detail elsewhere (Vogels et al., 1994; Berman et al., 2005). Briefly, 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. The corpus callosum was transected along its full length using a small glass pipette with suction; the anterior commissures was fully transected. In the two weeks following the surgery, analgesics and antibiotics were administered daily.

All four monkeys underwent sterile surgery to implant an acrylic cap with an embedded head restraint bar, scleral search coils and a recording chamber. General anesthesia was induced with ketamine and was maintained with isoflurane. The acrylic cap was secured with embedded screws inserted into the skull. The recording chamber was placed over area the lateral bank of the intraparietal sulcus (area LIP, 5mm posterior and 12mm lateral in Horsley Clarke coordinates). We used MRI to guide and verify correct placement of the chambers.

3.2.2 Physiological Methods

During recording sessions, the monkey sat in a darkened room with its head fixed in a primate chair, facing a tangent screen. Visual stimuli were back-projected on the tangent screen using a LCD projector. Stimulus presentation was under the control of two computers running a C-based program, CORTEX, made available by Dr. Robert Desimone. Eye position was monitored using scleral search coils (Judge et al. 1980), with a sampling rate of 250 Hz.

Neural activity was recorded using tungsten microelectrodes (Frederick Haer, Bowdoinham, ME) inserted into cortex through stainless steel guide tubes that were stabilized in a nylon grid system (Crist Instruments). The neural signal was amplified and filtered with a band-pass of 500 Hz to 5 kHz. Individual neurons were isolated with an on-line spike-sorting system using a template-matching algorithm (Signal Processing Systems, Prospect, Australia) or with both on-line and off-line template matching and principle component analysis sorting (Plexon, Dallas, Tx).

3.2.3 Reconstruction of Recording Locations

We reconstructed the approximate recording locations within the lateral bank of the intraparietal sulcus with MRI images. For three out of the four monkeys, prior to the MRI scan, the nylon grid system used for neural recording was placed within the recording chamber. Two to four metal wires were inserted into the cortex through grid holes spaced throughout the chamber. The wires and the outline of the recording chamber were clearly visible in coronal magnetic resonance images. We used the wires and the outline of the chamber to determine the center of the LIP recording chamber. We used the center as a reference point to determine the

approximate recording locations. In the fourth monkey, the recording chamber was removed before the MRI scan. A depression left by the absence of the chamber was clearly visible on MRI scans. This depression was used to approximate the chamber location. The MRI scans were coronal sections 2mm thick.

3.2.4 Behavioral Paradigm

Single unit activity in LIP was recorded while the monkey performed a task designed to map the RF of the neuron rapidly. The trial began when the monkey fixated on a central point (FP) for 300 to 500ms. While the monkey fixated, stimuli were presented sequentially at 1 to 9 locations (Fig. 17A). When the fixation point was extinguished, the monkey had to make a saccade to the location of the most recently presented stimuli. Because the number of stimuli presented was unpredictable, the monkey was forced to attend to the location of each stimulus.

Each stimulus was presented for 50ms, with an interstimulus interval of 200ms. The stimuli were presented at 24 possible locations (Fig. 17B). If the monkey landed within ±2.5° of the target location he received a liquid reward.

The advantage of this RF mapping task was that multiple displays of visual stimuli in each trial yielded a large number of target locations and large number of trials for each location without the requirement of holding a single neuron for a long period of time. Data collection for a single neuron was complete when the stimulus was presented at least 12 times at each of the locations. In addition to decreasing the time for each session, the unpredictability of when the final target appeared in each trial forced the monkey to attend to each stimulus presentation, which is important for LIP. Neural responses are enhanced in LIP when the monkey is attending

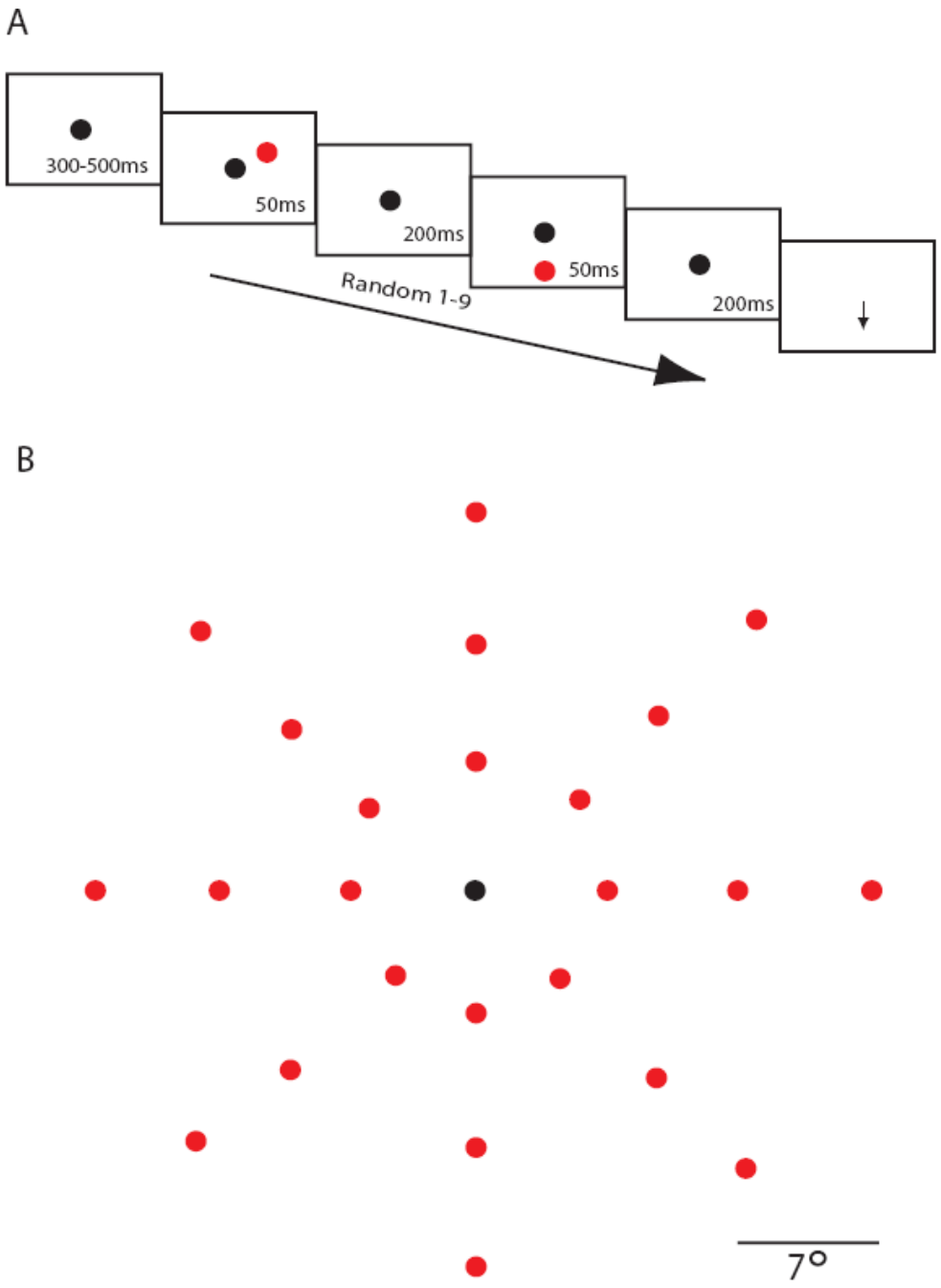


Figure 17. Receptive field mapping task.

A: Monkey begins each trial fixating a central location (black circle). While the monkey fixates, a random number (1-9) of visual stimuli (red circle) are presented for 50ms with a 200ms interstimulus interval. Once the fixation point is turned off the monkey is free to make an eye movement (arrow) to the last stimulus presented. B. The stimulus was placed at one of eight locations in three rings with amplitudes of 7º, 14º or 21º, for a total of 24 locations. Each red dot represents a possible target location.

to a stimulus (Bushnell et al., 1981). A neuron fires more when a peripheral stimulus is behaviorally relevant compared to when the monkey can passively fixate and ignore the stimulus. By requiring the monkey to attend to each stimulus we ensured that we were not underestimating the extent of the receptive field.

3.2.5 Data Analysis

3.2.5.1 Determining significant locations

We used a three step process to determine whether a neuron had a significant visual response to stimuli presented at a particular location. First, we determined the baseline activity of the cell. The baseline activity was defined as the average activity in a 100ms window starting 50ms before each stimulus appeared. This means that the number of baseline epochs in a trial varied depending on the number of stimuli presented. We used this method instead of a single baseline, measured only once at the beginning of the trial, to avoid a potential confound. This confound would occur if a stimulus evoked a burst of activity that gradually declined but did not reach the original single baseline before the next stimulus was flashed. If we were comparing visual activity only to the first pre-stimulus baseline, then the response to the second stimulus presented might appear to be significant, when in fact it is a lingering elevated response from the first stimulus. By using an epoch that occurred before the presentation of each stimulus we eliminated the possibility of a spurious result due to a lingering response. For each cell we used the same baseline measure. The stimulus was presented at least 12 times at each of the 24 locations. Each presentation had a baseline measurement. Therefore, the baseline measure contained at least 288 measurements.

Second, we determined the onset of neural activity (neural latency) for each location using a Poisson detection method (Maunsell and Gibson, 1992; Bisley et al., 2004). The first step was to compile the neural responses at each stimulus location into peristimulus time histograms (PSTH) with a 10ms binwidth. The next step was to find a Poisson distribution that best fit the baseline data. From the Poisson distribution a threshold was determined. The threshold was the level at which the spike count would be expected to lie 99% of the time. Therefore if a firing rate was greater than the threshold it had a probability of $p<.01$ that it was different from the fitted Poisson distribution of the baseline activity. Once the threshold was determined we went back the raw PSTH and searched in individual 10ms bins from 50ms to 200ms after stimulus onset. The latency was the beginning of the first of 3 consecutive bins that contained firing rates above the threshold.

Third, we determined if there was a significant visual response at a given location by comparing the visual epoch to the baseline population. The visual epoch was defined as the activity in 100ms starting at the neural latency. We tested for significant difference between the visual epoch and the baseline epoch using an ANOVA test with Bonferroni multicomparison correction ($p<.05$).

3.2.5.2 Creating contour plots

For each cell, a contour plot of actual data points and interpolated data points was constructed. To construct the contour plots, we need a firing rate for each location. In the previous analysis we used a visual epoch that started at the neural latency. However, not every location yields a visual response and so not every location has a latency measurement. To construct the contour plots, we chose a new epoch. For each actual data point, the firing rate was

equal to the mean firing rate across all trials from an epoch from 70 to 200ms after stimulus onset.

The interpolated data points are a weighted average of the four closest measured data points. The mean firing rate at the actual points was multiplied by the inverse of the distance to the interpolated point. This value was then summed and divided by the sum of the inverse of the distance to give a weighted average. The mean baseline firing rate was subtracted from both the known and interpolated points for the final plot.

From the contour plots, we determined the peak, the size RF, the width RF, and center of mass of the RF. The peak had the location that has the highest firing rate; if more than one location has the highest firing rate we took an average of those locations. The size of the RF was measured as the total number of locations that are greater than 75% of the peak. The width is the square root of the RF size. The center of mass is the sum of the locations of the RF divided by the sum of the firing rate at those locations.

3.3 RESULTS

The goal of these experiments was to determine if LIP neurons in split brain monkeys have ipsilateral representations. We recorded from 268 visually responsive LIP neurons in four monkeys while they performed a receptive field mapping task. For the two split brain animals, we recorded 52 neurons from monkey EM and 70 in monkey CH. For the intact animals, we recorded 25 neurons in monkey FF, and 121 in monkey OP.

3.3.1 LIP neurons only represent the contralateral visual field in split brain monkeys.

Our primary finding is that in the split brain monkey LIP neurons represent only the contralateral visual field. We measured the response of LIP neurons to a visual stimulus that was presented at 24 locations. An example cell from a split brain monkey is shown in Fig. 18A. Each histogram represents the response of the neuron to a stimulus presented at that spatial location. This neuron fired when a stimulus was present in the lower visual field, either on the midline, on in the contralateral field. To quantify the RF, we calculated the RF's width, peak and center of mass based on the contour plots of each neuron (Fig. 18B, see methods). For this example cell, the width of the RF was 9.27º. The peak activity was located at 1º to the right and 1ºdown. The center of mass was located at 3 º to the right and 8 º down. An example cell from an intact monkey is shown in Fig. 19. Similar to the split brain example cell, this neuron fired when the stimulus was presented in the lower visual field. This neuron was also active when the stimulus was presented in right visual field (the contralateral field). Its strongest activity was for stimuli presented in the left visual field (the ipsilateral field). The width of the RF was 15º. The peak activity was located 11 º to the left and 16 º down. The center of mass was located 9 º to the left and 16 º down.

In the intact monkeys, we found 25 neurons with bilateral receptive fields and 5 neurons with ipsilateral receptive fields. The bar graphs in Fig. 20 represent the number of neurons that have significant visual activity for locations separated into three categories: ipsilateral, contralateral and both hemifields. If the individual neuron had a significant response for a stimulus at least one location in the ipsilateral side of space it is included in the ipsilateral group. If the neuron had at least one significant response for a stimulus at a location in the contralateral

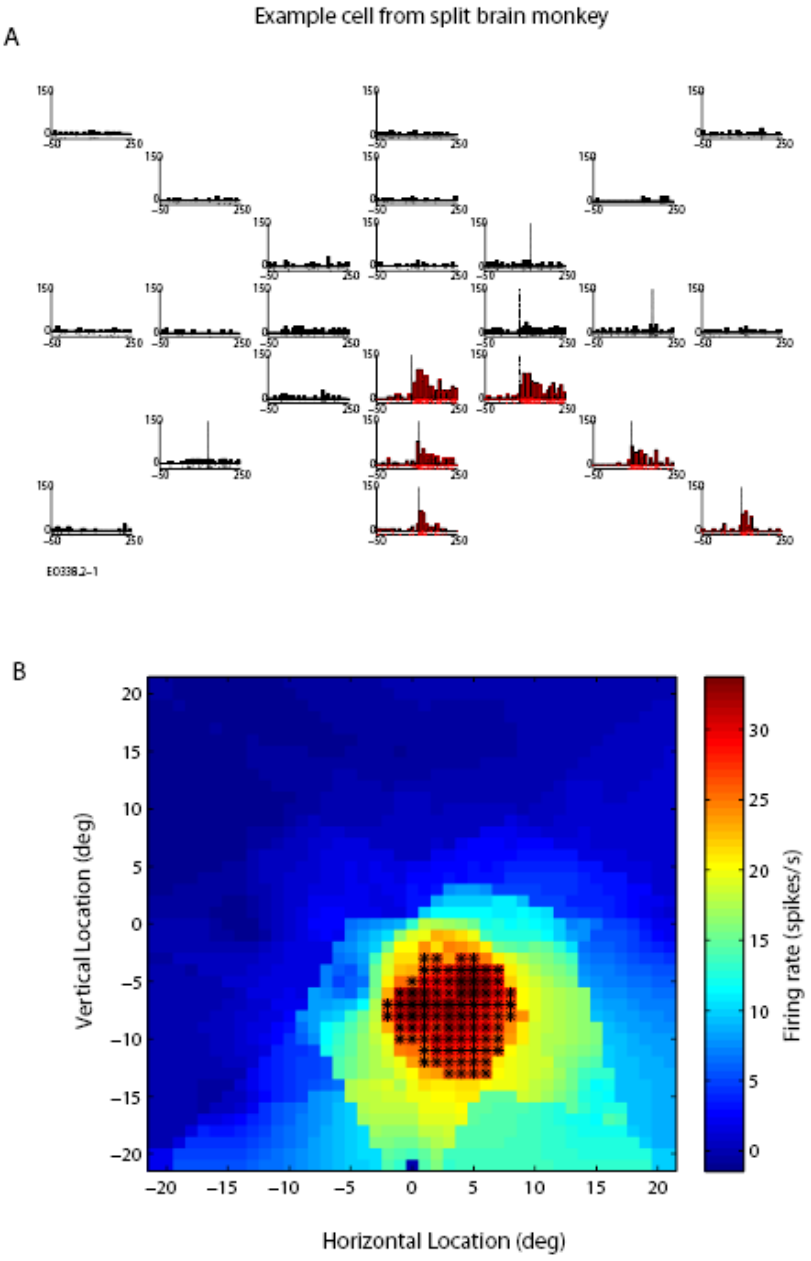


Figure 18. Example cell from split brain monkey.

A. Each histogram and rasterplot represents the activity of the same LIP neuron for one particular stimulus location. This cell was recorded from the left hemisphere. Histograms are red when the activity during the visual epoch is significantly greater than the baseline epoch (see methods). The data are aligned on stimulus onset. The vertical line represents the neural latency for that location. If a neural latency could not be determined, then no line is present. B. Contour plot of the same neuron as in A. The x-axis represents the horizontal location in real degrees. The y-axis represents the vertical location. The color represents the firing rate of the neuron. The black asterisks indicates that the firing rate at the location was at lest 75% of the peak firing rate. This neuron had a receptive that was down and slightly to the right (contralateral visual field).

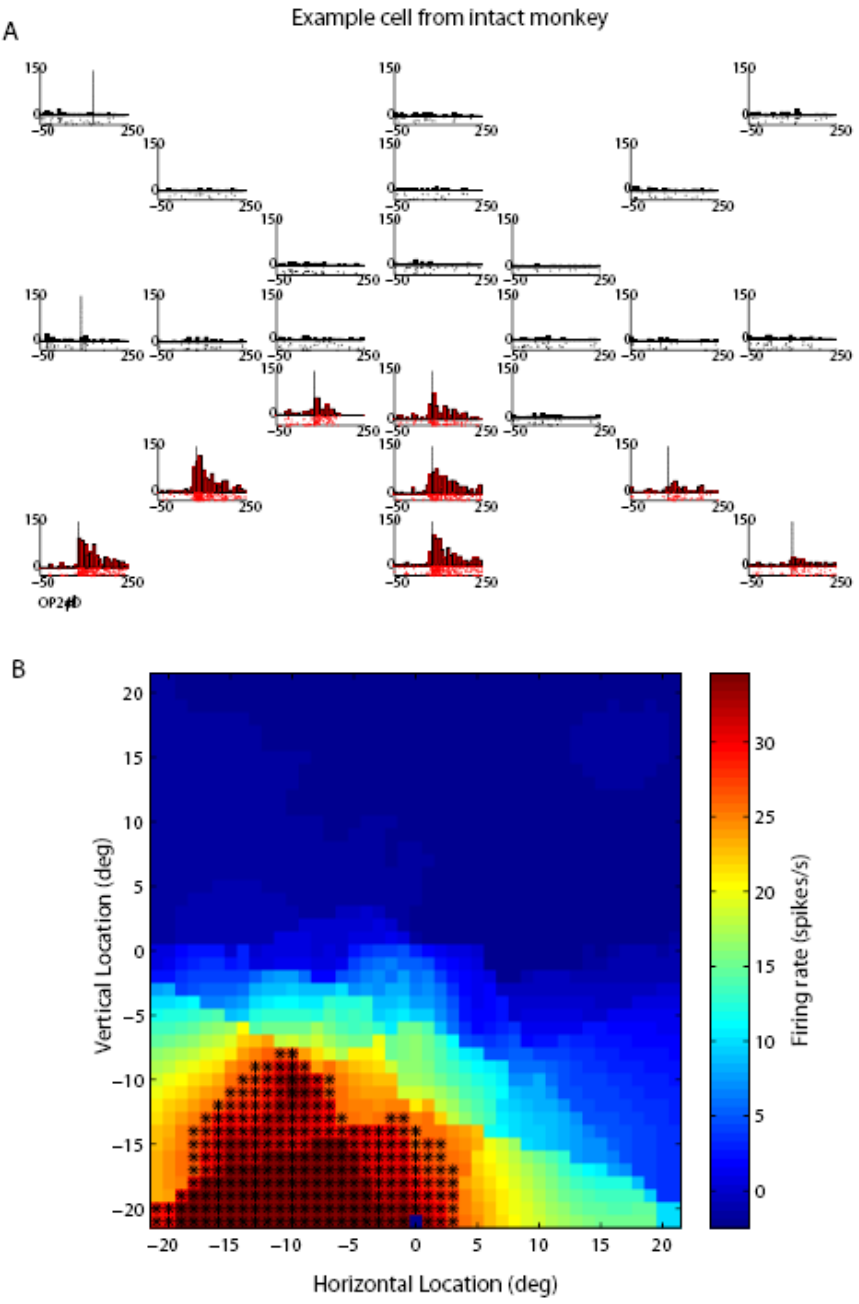


Figure 19. Example cell from an intact monkey.

A. The activity of an LIP neuron recorded from left hemisphere of an intact monkey. The conventions are the same as Fig. 18. B. Contour plot of the same neuron as in A. This neuron had a receptive that was down and to the left (ipsilateral visual field).

side of space it was included in the contralateral group. If there was a significant response to both the ipsilateral and contralateral side of space it was included in the both group. If the neuron only responded when the stimulus was presented at a midline location it was not included in the bar plot. Activity was completely absent for the ipsilateral hemifield in the split brain monkeys (Fig. 20A).

3.3.2 The spatial distribution of the LIP receptive fields are different for intact and split brain monkeys.

We calculated the spatial distribution of the RFs in two ways. First, we determined the location of the peak firing rate within the RF. Second, we determined the location of the center of mass of the activity inside the RF. The main focus of this study was to examine ipsilateral and contralateral representation; therefore, we focused on the horizontal coordinates of both measurements. The distribution of the horizontal coordinates of the peak firing rate for split brain and intact animals is show in Fig. 21. When we compared the distribution of the split-brain monkeys to that of the intact monkeys we found that the two populations were significantly different ($p=0.02$, Wicoxon rank-sum test). This difference was due to the small number of neurons in the intact animals that had a peak in the ipsilateral field. If those neurons were removed from the intact population, then there was no significant difference between split brain and intact animals ($p=.27$, Wicoxon rank-sum test).

We next compared the distributions for the horizontal coordinates of the center of mass (Fig. 22). We found comparable results to the peak firing rate. When we compared the distribution from the split-brain monkeys to that of the intact monkey we found a significant difference between the two populations ($p=.04$, Wicoxon rank-sum test). Once again, this

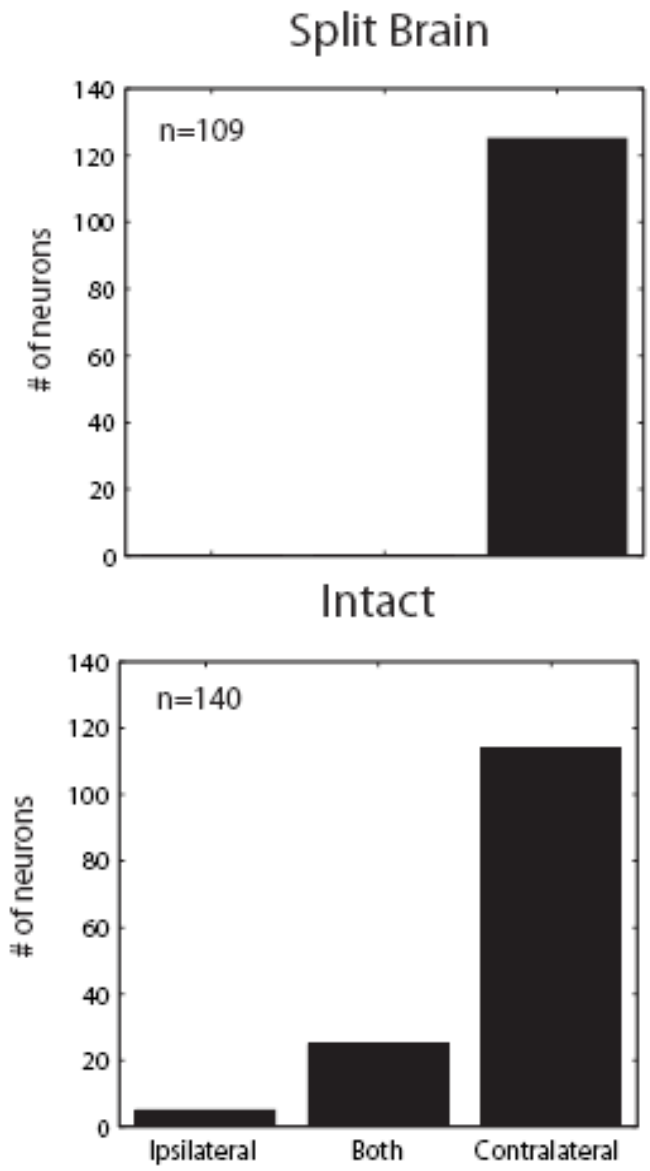


Figure 20. The number of neurons with ipsilateral, contralateral, or both representations

The bars represent the number of neurons with ipsilateral, contralateral, or both representations. If the neuron fires in response to a stimulus presented at least one location in the ipsilateral field, it is in the ipsilateral group. If the neuron fires in response to a stimulus presented at least one location in the contralateral field, it is in the contralateral group. If the neuron fires response to a stimulus when it is present in the ipsi- and contra-lateral field, it is in the both group. If the neuron only responds to cell on the midline it is not included. Each group is mutually exclusive. A. In the split brain monkey, there are no neurons that fire when the stimulus is in the ipsilateral field. B. In the intact monkey, a small number of cells are bilateral, and even fewer are ipsilateral only.

difference was due to the small number of neurons that had ipsilateral repesentations in the intact animal. If those neurons were removed, then there was no difference between split brain and intact animals (p=.25, Wicoxon rank-sum test).

In summary, the horizontal spatial distributions of LIP neurons, whether measured as peak activity or as the center of mass, are significantly different for intact and split brain animals. This difference was due to neurons with ipsilateral representations. This further suggests that ipsilateral representations in LIP depend on the forebrain commissures.

3.3.3 The widths of LIP receptive fields were not different for intact and split brain monkeys.

The overall size of the RF was defined as the portion of the contour map that exceeds seventy-five percent of the peak. The width is the square root of the RF size. We measured the RF width of each neuron. We compared the distribution of RF widths from the split brain monkey to that of the intact monkey. We found no significant difference between the two populations (p= .81, Wicoxon rank-sum test). Even though neurons in the split brain animal lose their ipsilateral representation, the overall sizes of the RFs are compatible between the split brain and intact monkeys.

3.3.4 The recording locations in LIP in the split brain monkeys overlap with the recording locations in the intact monkeys.

As discussed above, we found a small number of LIP neurons with ipsilateral representations in the intact monkeys, but none in the split brain monkeys. Before we attribute the loss

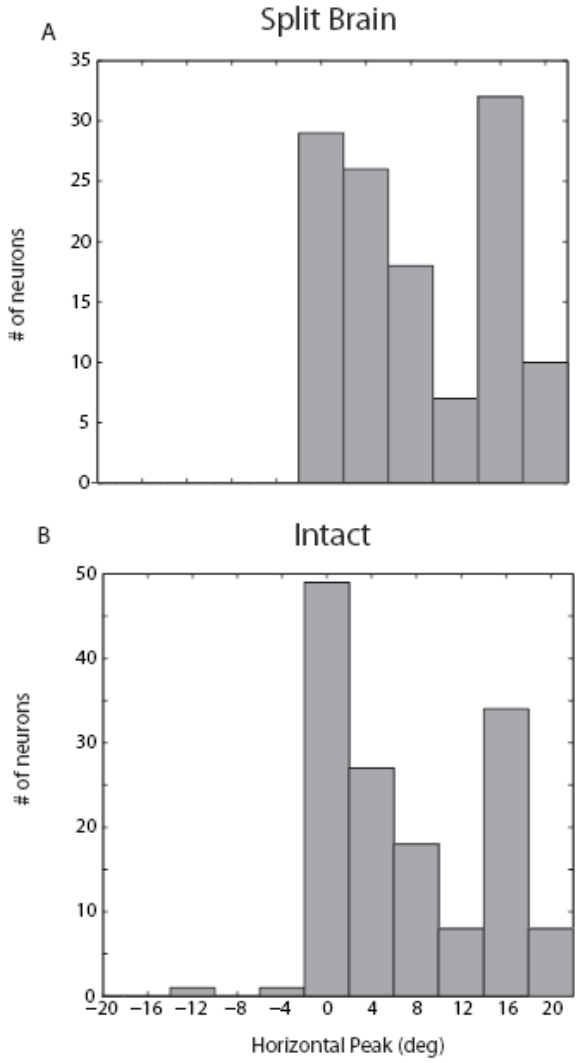


Figure 21. Distributions of the location of peak firing of LIP receptive fields in split brain and intact monkeys.

On the x-axis, the horizontal coordinates of spatial location of peak firing rate. Positive values represent contralateral space, negative values represent ipsilateral space. A. In the split brain monkey the location of peak firing varies from 0 to 20 degrees. B. In the intact monkey the location of peak firing varies from 12 degrees in the ipsilateral field to 20 degrees in the contralateral field. There is a significant difference between the split brain and intact populations.

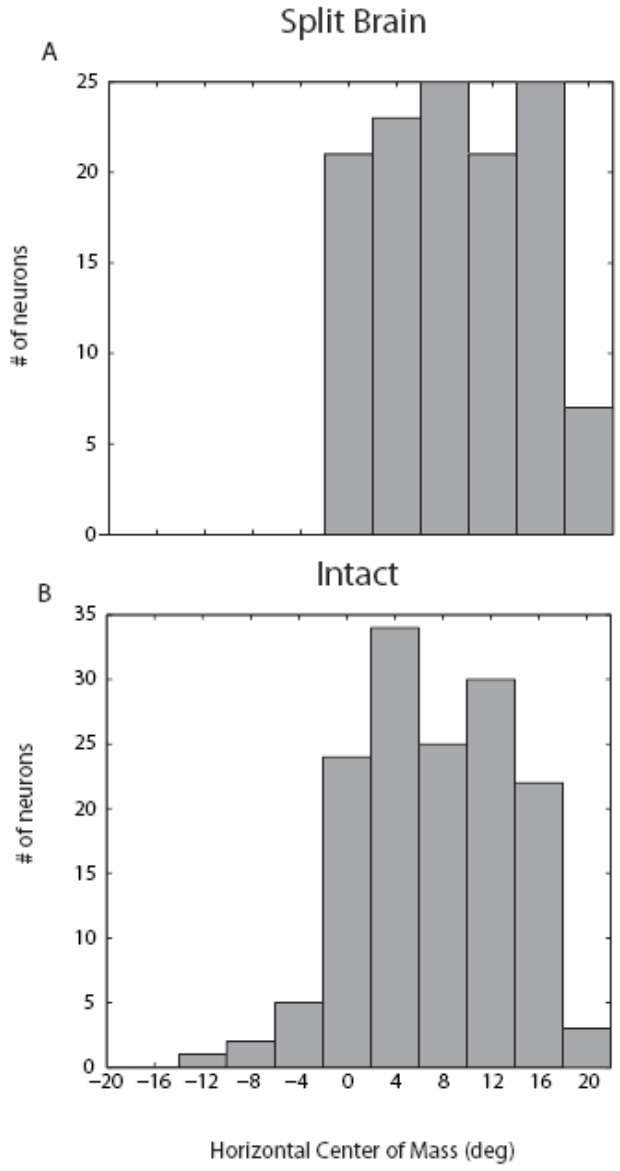


Figure 22. Distributions of the center of mass of LIP receptive fields in split brain and intact monkeys.

On the x-axis, the horizontal coordinates of spatial location of the center of mass. Positive values represent contralateral space, negative values represent ipsilateral space. A. In the split brain monkey the center of mass varies from 0 to 20 degrees. B. In the intact monkey the location of peak firing varies from 12 degrees in the ipsilateral field to 20 degrees in the contralateral field. There is a significant difference between the split brain and intact populations.

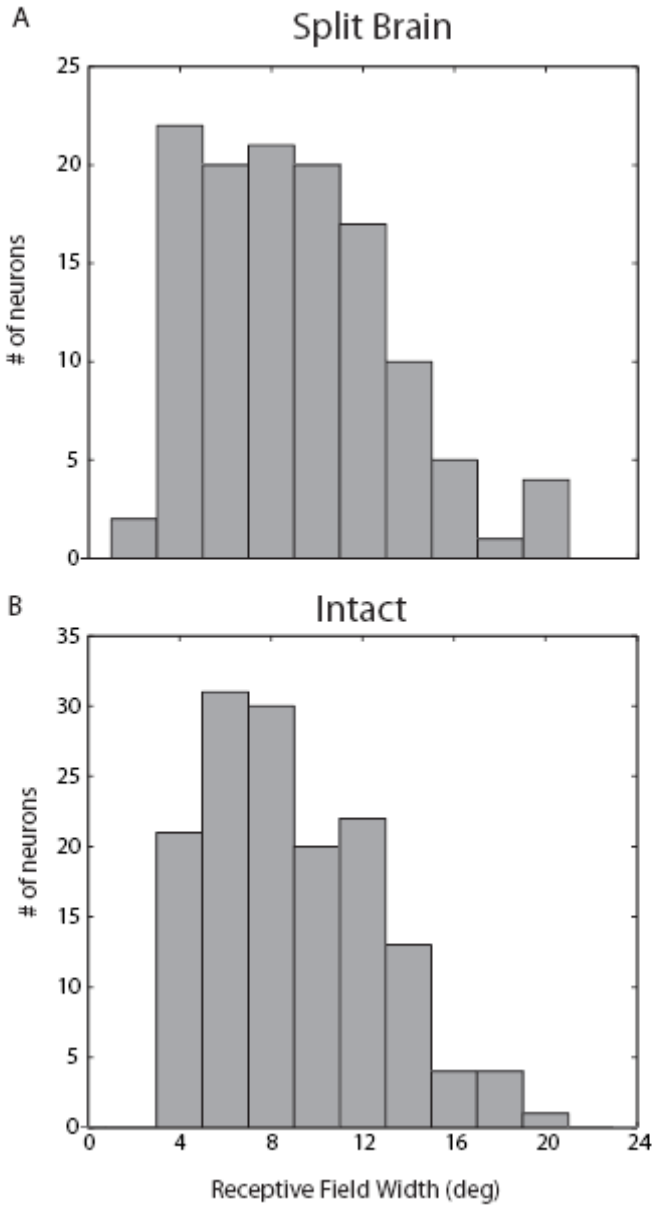


Figure 23. Distributions of LIP receptive field widths in split brain and intact monkeys.

A. In the split brain monkey and Intact monkeys (B), receptive field widths vary from a few degrees to as mush as twenty degrees. There is no significant difference between the two populations. Even in the absence of ipsilateral representations, split brain and intact monkeys have comparable RF sizes.

of ipsilateral representation to the absence of the forebrain commissures we first must address another potential explanation. It is possible that we recorded from different portions of the parietal cortex. If ipsilateral representations are restricted to a localized portion of LIP, and we missed this spot when recording from the split brain monkeys, it would appear that the LIP neurons in the split brain monkey had no ipsilateral representations when in fact they do.

We estimated the approximate recording location using MRI images and compared across monkeys. In Fig. 24, we matched the MRI images from split brain monkey EM to images from intact monkey OP. We recorded from the left hemisphere in both animals. We aligned the images based on anatomical landmarks. The recording sites from these two animals aligned (red arrows). We found neurons with ipsilateral representation at all the recording locations in the intact monkey OP. This suggests that ipsilateral representations are not restricted to a localized location in LIP, but instead are scattered throughout. Fig. 25 shows the MRI images for split brain monkey CH and intact monkey FF. We recorded from the right hemisphere in these two monkeys. We recorded from more posterior locations in split brain monkey CH compared to the other three monkeys. Between the two split brain monkeys, we covered a large posterior-to-anterior extent of LIP. Additionally, the recording sites in the split brain monkeys overlapped with the recording sites in the intact monkeys. These two pieces of evidence make it unlikely that LIP in split brain monkeys have ipsilateral representations that we missed during this experiment.

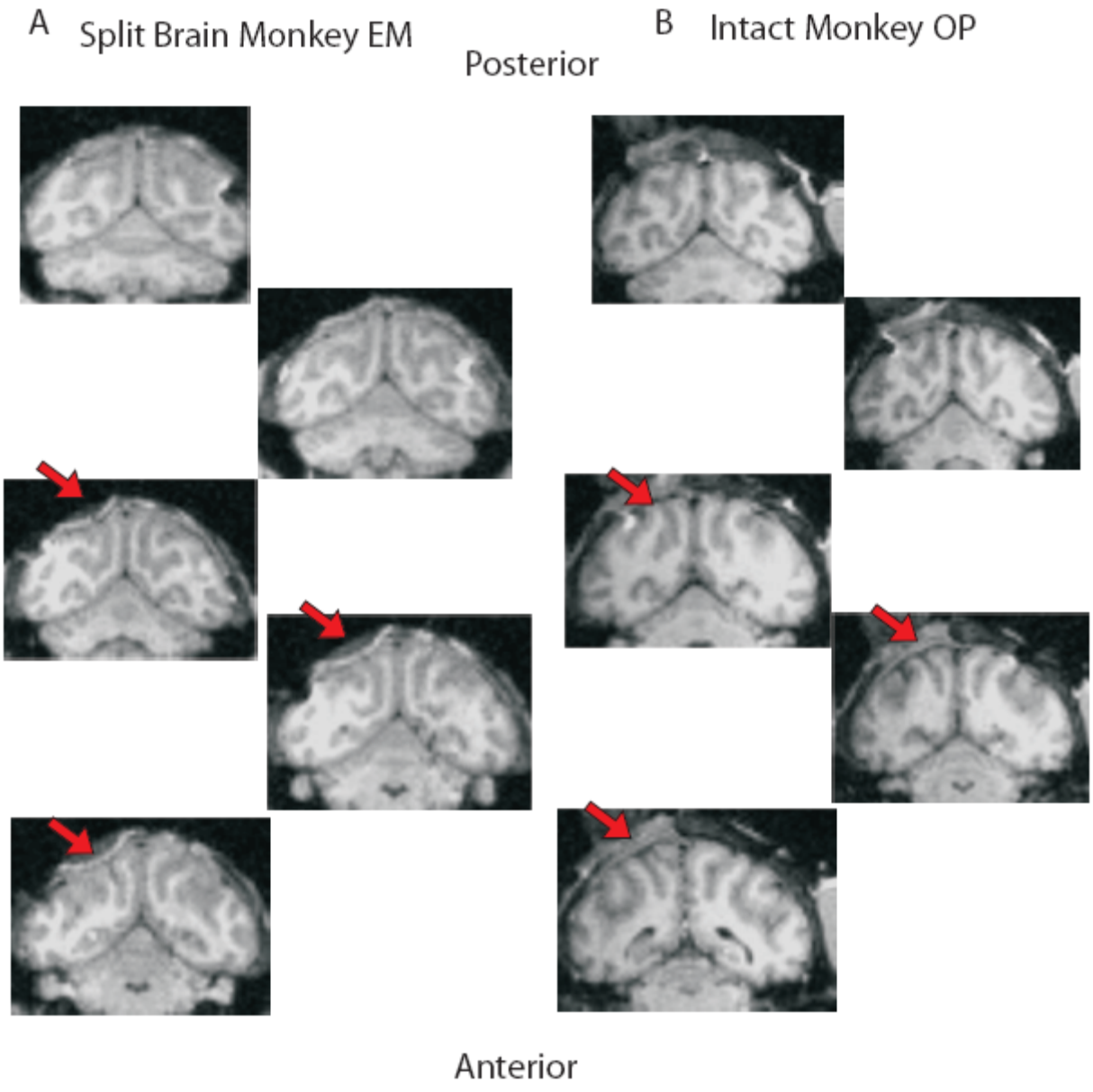


Figure 24. Coronal magnetic resonance images of monkeys EM and OP

The images are in order from top to bottom, from posterior to anterior. A. The images from split brain monkey EM. The recording chamber was over left parietal cortex. The chamber was removed before the MRI scan. The location of the chamber was estimated based on the depression the remained after the chamber was removed. B. The images from intact monkey OP. The recording chamber was over left parietal cortex. The red arrows indicate the estimated recording locations. Recordings in the split brain monkey were aligned with the recordings in the intact monkey.

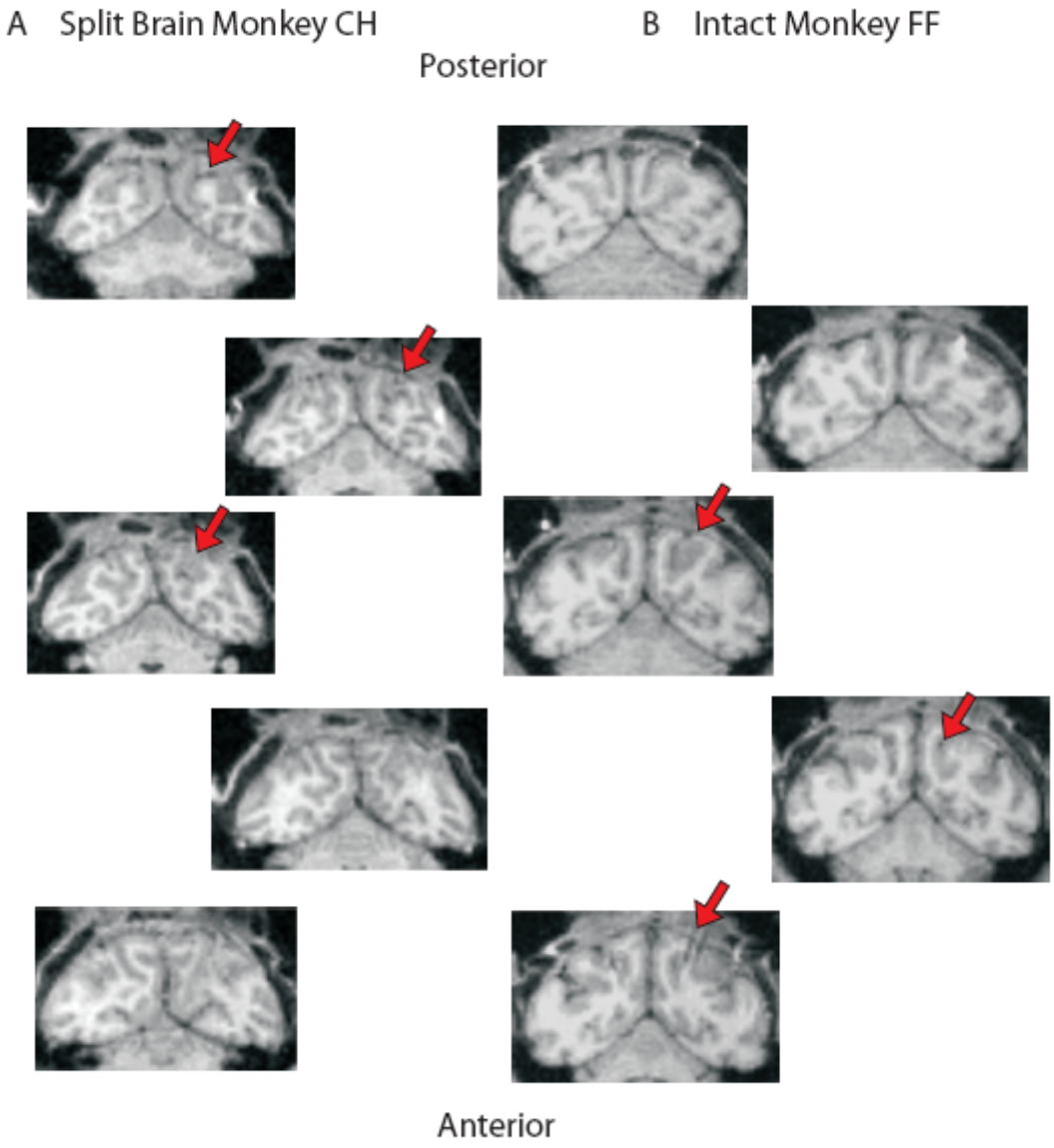


Figure 25. Coronal magnetic resonance images of monkeys CH and FF.

The conventions are the same as Fig. 24 A. The images from split brain monkey CH. The recording chamber was over right parietal cortex. B. The images from intact monkey FF. The recording chamber was over right parietal cortex. The red arrows indicate the estimated recording locations. Recording in the split brain monkey were more posterior, while the recordings in the intact animal was more anterior.

3.4 DISCUSSION

Our aim was to determine if neurons in the LIP retain bilateral receptive fields after the forebrain commissures have been transected. We addressed this aim by having both split-brain and intact monkeys perform a receptive field mapping task while we recorded from LIP neurons. We found that a small minority of LIP neurons in the intact animals encoded both the ipsilateral and contralateral visual fields. In contrast, LIP neurons in the split-brain animals only encoded the contralateral visual field. These results are significant because they eliminate the possibility that connections within LIP in one hemisphere can explain the intact across hemifield remapping in the split brain monkeys.

3.4.1 LIP neurons over represent the contralateral visual field in intact monkeys

We found that even in the intact monkeys the majority of the neurons fire only for visual stimuli in the contralateral visual field. This is consistent with previous studies. In one of the original papers that characterized the properties of cells in LIP, the lack of large bilateral receptive fields was used to distinguish LIP from a neighboring region, area 7a (Blatt et al., 1990). The first rigorous, quantitative analysis of LIP receptive fields was conducted by Ben Hamed and colleagues (2001). They found that the representation of LIP neurons extend to about 5 ° into the ipsilateral visual field (2001). These finding however are inconsistent with the results from Platt and Glimcher (1998). Platt and Glimcher found an equal representation for the ipsilateral and contralateral visual field. The major difference between the study conducted by Platt and

Glimcher and the rest of the studies is the visual epoch and the number of trials. They used a large visual epoch of 200ms. The goal of the Platt and Glimcher study was to use as many locations as possible. They had monkeys making eye movements to 441 locations. The consequence of having so many locations was they had very limited number of trials for each location. The differences between the studies make them difficult to compare. Our results are consistent with the finding of Ben Hamed and colleagues. Even in intact animals, it seems unlikely that connections within a single hemisphere contribute to across hemifield remapping. Only a minority of cells have bilateral receptive fields, but the majority of cells are capable of remapping.

3.4.2 LIP neurons only represent the contralateral visual field in split brain monkeys

Our results indicate that the forebrain commissures are necessary for ipsilateral representation in LIP. These results are consistent with anatomical studies that showed that ipsilateral projecting ganglion cells contribute to only a 1-degree strip around the vertical meridian (Stone et al., 1973). Our results are also consistent with two other split brain studies in monkeys. First, as we described in the introduction, ipsilateral representations by neurons in the inferotemporal cortex depend on the forebrain commissures (Rocha-Miranda et al., 1975). The forebrain commissures also play a role in the area V4 (Desimone et al., 1993). V4 neurons in an intact animal typically do not represent the ipsilateral visual field. However, the classically defined RFs are often surrounded by a large suppressive surround. This surround can extend beyond the vertical meridian into the ipsilateral field. When Desimone and collegues transected the corpus collosum, the suppressive surround was greatly reduced.

3.4.3 Alternative pathways

The V4 study, in addition to examining the role of the corpus callosum in ipsilateral representation, also provided another important result. While the suppressive surround was greatly reduced in the absence of the corpus callosum it was not completely eliminated. Similar to the remapping studies, the forebrain commissures may be the primary pathway, but alternative pathways can be utilized. Desimone and colleagues suggested that long range interactions within the retina may contribute to the suppressive surround observed in V4. While this may be a plausible explanation for the V4 result, it seems highly unlikely that connections within the retina can explain across hemifield remapping in the split brain monkeys.

One possible source of across hemifield remapping activity in LIP of the split brain monkeys is the superior colliculus (SC). SC neurons are capable of remapping and the SC has projections to LIP through thalamic structures (Walker et al., 1995; Clower et al., 2001).

It has been demonstrated that the SC is important for visual representation in at least one cortical area, the superior temporal polysensory area (STP) (Bruce et al., 1981). In the intact monkey, STP neurons have large bilateral receptive fields. Even when striate cortex is removed unilaterally, these neurons retain their representation of the contralateral space. It is only when the superior colliculus was also removed that activity in these neurons was abolished. The SC can provide visual information to cortical areas independent of the geniculostriate system. Further research needs to be conducted to determine if the SC is the source of across hemifield remapping.

4.0 SPATIAL UPDATING IN MONKEY SUPERIOR COLLICULUS IN THE ABSENCE OF THE FOREBRAIN COMMISSURES: DISSOCIATION BETWEEN SUPERFICIAL AND INTERMEDIATE LAYERS

4.1 ABSTRACT

One hypothesis of stable perception is that visual representations are spatially updated with each eye movement. The neural mechanism behind this hypothesis is the phenomenon of remapping. Remapping activity is thought to be the neural representation of a transfer of visual information from neurons representing a salient location before an eye movement to neurons that will represent the location after the eye movement. In previous studies, we demonstrated that the forebrain commissures may be the primary pathway for remapping from one hemifield to the other; they are not required (Berman et al., 2005; Heiser et al., 2005; Berman et al., 2007b). Remapping in area LIP occurs across hemifield even in split brain monkeys; this indicates that a subcortical structure contributes to remapping. The primary goal of this study was to characterize remapping activity in a subcortical structure, the superior colliculus, in intact and split brain monkeys. We recorded neurons in both the superficial and intermediate layers of the SC. We compared remapping activity in a condition that required across-hemifield remapping, to another condition that required within-hemifield remapping. We found that across hemifield remapping was reduced compared to within hemifield remapping in the intermediate layers of the SC in the

split brain monkeys. These results mirror our findings in area LIP. In contrast, we found no difference in across hemifield remapping in the superficial layers. The differences between the layers suggest different circuitry underlying remapping in the superficial and intermediate layers. Cortical activity contributes to the remapping in the intermediate layers, but not in the superficial layers.

4.2 INTRODUCTION

Every day we interpret and interact with our surroundings. The brain evolved so that we can process incoming sensory stimuli and use this information to control our actions. Yet each one of our actions can, in turn, influence incoming sensory information. For example, our eyes constantly move, allowing us to attend to different visual objects in our environment. With each eye movement, a single object activates an new set of visual neurons. If our perception relied solely on incoming visual information then the object would appear to jump with each eye movement. Despite these frequent eye movements, we perceive a stable scene, a phenomenon known as spatial constancy.

Helmholtz (1866) proposed that we perceive a stable scene because we know when we move our eyes. When an eye movement is made, a copy of the motor command is relayed to visual areas. The brain integrates internally generated information about the movement with the incoming sensory information to create a visual representation. In this way, the visual representation is spatially updated with each new movement.

Evidence from neurophysiological studies in monkeys supports the idea that the brain performs spatial updating. Neurons in lateral intraparietal cortex (LIP), frontal eye fields (FEF),

extrastriate cortex, and the superior colliculus (SC) update stimulus traces at the time of an eye movement (Mays and Sparks, 1980a; Goldberg and Bruce, 1990; Duhamel et al., 1992a; Walker et al., 1995; Nakamura and Colby, 2002). In these studies, single neurons were recorded in monkeys performing simple eye movement tasks. When the eye movement brought the neurons' receptive field (RF) onto a location where a visual stimulus had appeared, the neurons fired. Remarkably, these neurons fired even if the visual stimulus was turned off before the eye movement began. There was never a stimulus physically inside the RF. Neural activity was driven by a memory trace of the stimulus. The response of the neurons is termed remapping. It is thought that information is transferred from neurons representing the stimulus or a salient location before the eye movement to neurons representing the salient location after the eye movement.

Remapping depends on neurons being able to receive visual information from the entire visual scene, even when the initially salient location is in the opposite visual field. In the original experiments on remapping, stimuli were flashed at a location in the hemifield opposite the receptive field of the neuron being recorded (Duhamel et al., 1992a). Visual information was updated from one visual hemifield to the other, indicating that information was transferred between hemispheres. Heiser and Colby (2006) further addressed this issue by asking the question: was there a difference in the prevalence or magnitude of response when the stimulus representation was updated within a single hemifield compared to across hemifields? They found that for the population of LIP neurons there was no differences between within- and across-hemifield remapping.

An LIP neuron that has remapping activity can receive information representing multiple areas of visual space. But how is information transferred from one side of the brain to the other?

One possible pathway is through direct cortico-cortical connections. Specifically, when updating across-hemifields, information could be transferred through the forebrain commissures-- the corpus callosum and the anterior commissures. Berman and colleagues tested this possibility by transecting the forebrain commissures of two monkeys. They examined the effects of the removal of the forebrain commissures on performance in a behavioral task that required spatial updating, and on remapping activity in LIP (Berman et al., 2005; Heiser et al., 2005; Berman et al., 2007).

Berman et al. (2005) used the double-step task, which requires that spatial information be updated when the eyes move. Both humans and monkeys are able to perform the double step task accurately (Hallett and Lightstone, 1976; Mays and Sparks, 1980b; Gnadt and Andersen, 1988; Baizer and Bender, 1989; Goldberg and Bruce, 1990; Ray et al., 2004a; Medendorp et al., 2006). In this task, the monkey must make two consecutive eye movements. The two target locations are presented sequentially while the monkey maintains fixation at a starting location. To complete the task successfully, the monkey must remember the order and locations of the two saccade targets. Importantly, the memory of the second location must be adjusted so that it is relative to the endpoint of the first saccade. In other words, the representation of the second target must be updated after the first saccade is made.

Berman et al. compared two versions of the double-step task (2005). During the within version, the second target location remained within the same hemifield before and after the first saccade. In the across version, the second target location was in the opposite hemifield after the first saccade. They hypothesized that the forebrain commissures would not be necessary for remapping when the representation of the second target remained within a hemifield; therefore, performance would be correct on the within version of the task. In contrast, the forebrain

commissures would be necessary when the representation of the second target passed across hemifields; therefore, the monkeys would be unable to perform the across version of the task.

At first, the monkeys' performance confirmed their hypothesis. The monkeys were unable to perform the double-step task when the visual information had to be transferred across hemispheres. Surprisingly, recovery began almost at once. Both monkeys ultimately recovered to the point where they could correctly perform the task that required across-hemisphere remapping of visual information.

If the forebrain commissures are not necessary for behavior dependent on spatial updating, are they necessary for remapping in LIP? Heiser and colleagues (2005) addressed this question by recording in LIP neurons while the monkeys performed two versions of the single-step task. In the within version of the task, the representation of the flashed stimulus remained within a single hemifield (Fig. 26B). In the across version of the task, the representation of the flashed stimulus shifted across hemifields (Fig. 26A). Heiser and colleagues found that LIP as a population is capable of remapping both within and across conditions; however, the across signal is attenuated and occurs later than the within signal.

These studies in split brain monkeys demonstrate that the forebrain commissures may be the primary pathway of across-hemifield remapping but they are not the only pathway. The monkeys' recovery indicates that a subcortical pathway must also contribute to the transfer of remapping activity. One possible pathway is through connections between the two superior colliculi. While remapping has been demonstrated previously in the SC, it has not been shown in the split brain monkey (Walker et al. 1994). We first asked, do neurons in the SC remap in the absence of the forebrain commissures? We then asked, is across-hemifield remapping activity modified in the SC in the absence of the forebrain commissures?

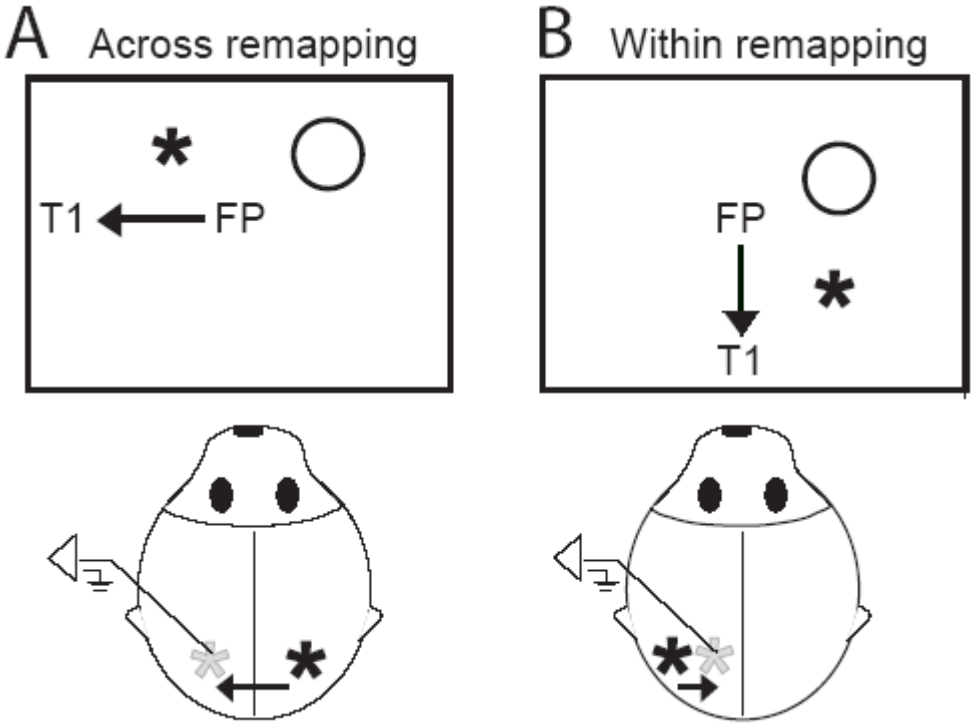


Figure 26. Spatial configurations for across and within remapping.

The exact configuration of the task is determined by the location of the receptive field. In this hypothetical example, the neuron is in the left hemisphere (gray asterisk) with a receptive field in the upper right visual field (circle). A. Across-hemifield condition. The stimulus is flashed in the left visual field and is represented by neurons in the right hemisphere (black asterisk). When the eyes move to the target (T1), the location where the stimulus had been presented is now in the right visual field. The memory of the stimulus is represented by neurons in the left hemisphere (gray asterisk). B. Within-in hemifield condition. The stimulus appears in the right visual field. It is represented by neurons in the left hemisphere (black asterisk). After the saccade to T1, the location where the stimulus had been presented is still in the left hemisphere. Modified from Heiser et al. 2005.

The superior colliculus is comprised of multiple layers, with different anatomical connections and response properties (Huerta and Harting, 1984). We were interested in whether the different layers play a different role in remapping. Neurons in the superficial layers receive projections directly from the retina, as well as other striate and extrastriate visual cortices (Schiller et al., 1974; Finlay et al., 1976; Wurtz and Albano, 1980; Fries, 1984; Huerta and Harting, 1984; Distler and Hoffmann, 2001; May, 2005). Neurons in the superficial layers are visually responsive (Goldberg and Wurtz, 1972). The deeper layers (intermediate and deep) receive projections from for a wide variety of brain areas including visual cortex, parietal cortex

and the frontal eye fields (Mohler and Wurtz, 1976; Fries, 1984; Huerta and Harting, 1984; May, 2005). The response properties of SC neurons in the intermediate layers are diverse (Wurtz and Goldberg, 1971, 1972; Mohler and Wurtz, 1976; Wurtz and Albano, 1980; Fries, 1984; Huerta and Harting, 1984; Dorris et al., 1997; May, 2005). Neurons in the intermediate layers could have a visual response to the onset of the stimulus, a motor response to the movement of the eye, or a combination of these signals. Additionally, activity in the SC could be important for covert and overt attention and target selection (Keller and McPeek, 2002; McPeek and Keller, 2002; Cavanaugh and Wurtz, 2004; Ignashchenkova et al., 2004; McPeek and Keller, 2004; Muller et al., 2005; Shen and Pare, 2007; Li and Basso, 2008; Port and Wurtz, 2009).

The goal of this study was to determine whether remapping activity is present in the superior colliculus in the split brain monkeys. We recorded from neurons in both superficial and intermediate SC layers. We found that across-hemifield remapping activity is present in both the superficial and intermediate layers of SC. The responses of neurons in the intermediate layers of SC strongly resemble neurons in area LIP; the amplitude of across-hemifield remapping is selectively reduced in split brain compared to intact animals. In contrast, the magnitude of remapping activity in the superficial layers of SC is equal for the within and across conditions in both split brain and intact animals. Remapping activity in the superficial layers differs from remapping in the intermediate layers of the SC in several other ways. We conclude that remapping is present in the SC in the split brain monkeys. This activity in the SC may be a source of the preserved remapping in area LIP in the split brain monkeys.

4.3 METHODS

4.3.1 General procedures.

Four rhesus macaques (*Macca Mulatta,* 5-9 kg) were used in this study. The forebrain commisssures of monkey EM and CH were surgically transected at the beginning of a set of previous experiments (Berman et al., 2005; Heiser et al., 2005; Berman et al., 2007b). In the control animals FF and OP, the forebrain commissures remained intact. Animals were cared for and handled in accordance with NIH guidelines, and all experimental protocols were approved by the University of Pittsburgh Institutional Animal Care Use and Committee.

The commissurotomy is described in detail elsewhere (Vogels et al., 1994; Berman et al., 2005). Briefly, the monkeys were prepared for surgery with dexamethasone, and anesthesia was induced with ketamine and maintained with isoflurane. Mannitol was administered throughout the surgery to minimize tissue swelling. The corpus callosum was transected along its full length using a small glass pipette with suction; the anterior commissure was fully transected. In the two weeks following the surgery, analgesics and antibiotics were administered daily.

All four monkeys underwent sterile surgery to implant an acrylic cap with an embedded head restraint bar, scleral search coils and a recording chamber. General anesthesia was induced with ketamine and was maintained with isoflurane. The acrylic cap was secured with embedded screws inserted into the skull. The recording chamber was positioned on the midline, angled posteriorly at approximately 40°. The SC was approximately 25-30mm below the surface of the brain. The SC was identified by a large burst of neuronal activity in response to visual stimuli after the electrode moved through a period of relatively no activity. This signaled the entry of the electrode into the surface of the SC. As the electrode moved from the superficial layers to

the intermediate layers, neurons fired not only for visual stimuli but also around the time of a saccade. We used MRI to guide and verify correct placement of the chambers.

4.3.2 Physiological methods.

During recording sessions, the monkey sat in a darkened room with its head fixed in a primate chair, facing a tangent screen. Visual stimuli were back-projected on the tangent screen using a LCD projector. Stimulus presentation was under the control of two computers running a C-based program, CORTEX, made available by Dr. Robert Desimone. Eye position was monitored using scleral search coils (Judge et al. 1980), with a sampling rate of 250 Hz.

Neural activity was recorded using tungsten microelectrodes (Frederick Haer, Bowdoinham, ME) inserted into SC through stainless steel guide tubes that were stabilized in a nylon grid system (Crist Instruments). The neural signal was amplified and filtered with a band-pass of 500 Hz to 5 kHz. Individual neurons were isolated with an on-line spike-sorting system using a template-matching algorithm (Signal Processing Systems, Prospect, Australia) or with both on-line and off-line template matching and principle component analysis (Plexon, Dallas, TX).

4.3.3 Behavioral Paradigms.

4.3.3.1 Single-step task.

The trial began with the monkey fixating a central fixation point for 300-500 ms. A visual stimulus appeared in the periphery at the same time as a target for a visually guided saccade. The visual stimulus was turned off after 50 ms, at the same time as the fixation point.

Fixation off was the cue to the monkey to make a saccade to the still lit target. The target was positioned so that the RF of the neuron landed on the screen location where the visual stimulus had been flashed. The monkey fixated the new target for 500-700 ms to receive a liquid reward.

4.3.3.2 Double-step task.

The double-step task was similar to the single-step task with one important difference. The monkey made a second saccade to a previously flashed stimulus. The monkey began by fixating a central point for 300-500 ms. The target for the first saccade (T1) was turned on and remained on. The second target (T2) appeared 100 ms later and remained on for 50 ms. The T2 was at the same spatial location as the flashed stimulus in the single-step task. The FP was turned off simultaneously with the disappearance of T2. This cued the monkey to make two saccades: a visually-guided saccade to T1 and then a second, memory guided saccade to T2. The T1 target was turned off at the completion of the first saccade. Once the monkey reached the T2 location, the T2 target reappeared to provide feedback on the correct target locations. The monkey maintained fixation at the T2 location for 300-500 ms and then received a liquid reward.

4.3.3.3 Stimulus only control task.

The stimulus only control task was used to ensure that the stimulus location used in the single-step task was outside the RF of the neuron. The monkey fixated for 300-500 ms, and then a visual stimulus was flashed for 50 ms in the same location as in the single-step task. In contrast to the single-step task, no saccade was made; the monkey fixated for an additional 1200-1500 ms before a reward was received. Only neurons that showed no significant activity (t-test, $p<0.05$) in the visual epoch (50-250 ms after stimulus onset) as compared to the baseline epoch (200-300 ms after start of fixation) were included for further analysis.

4.3.3.4 Saccade only control task.

The saccade only control task was used to determine the extent of activity observed in the single-step task that can be attributed to the generation of the saccade. The configuration and timing of the task differed from the single-step task in only one respect, the peripheral visual stimulus was not displayed. Many cells had significant activity during the saccade only control task. It is possible that the activity observed in the saccade only task was due to the eye movement made by the monkey. This possibility seems unlikely because the monkey made an eye movement to a target outside the receptive field of the neuron. Another possibility is that the activity was due to the remapping of the fixation point. Remapping of the fixation point would occur if the receptive field of the neuron lands on the screen location were the fixation point had been presented. To take this activity into account, we subtract the activity measured during the saccade only task from the activity measured in the single-step task.

4.3.3.5 Memory guided saccade task.

In the memory guided saccade task (MGS), the monkey began the trial by fixating for an initial period of 300-500 ms. Next, a stimulus was flashed inside the RF of the neuron for 50 ms. The monkey maintained fixation during the flash and for an additional 400-800 ms. Finally, the fixation point was turned off and the monkey made an eye movement to the remembered stimulus location. After the saccade, the visual stimulus reappeared and the monkey maintained fixation at the cued location for an additional 300-500 ms.

4.3.4 Experimental Design

For each neuron in the study we collected a complete data set that contained 11 types of trials. We started each session with the MGS task into the RF in order to classify the neuron. A neuron was classified as being in the superficial SC based on the recording location and the response of the cell. First, it was a superficial neuron only if it was recorded within 600 μm of the surface of the SC. Second, it was a superficial neuron if it had a visual response (50ms to 150ms after stimulus onset), and no response during a delay period (-300 to 0 from saccade onset), or around the time of the saccade (-30 to 30 from saccade onset). The remaining 10 trial types consisted of five tasks (stimulus control, saccade control, single-step, double-step, and MGS from T1 location to T2 location) and two conditions (within-hemifield and across-hemifield) for each task. We collected 12-20 trials of each trial type. The tasks were run in separate blocks, always in the same order: stimulus only control, saccade only control, single-step, double-step, T1 to T2 MGS. We collected data in this order because intertrial memory responses can persist after experience with a remapping task (Umeno and Goldberg, 2001b). In each block, the within and across conditions were randomly interleaved.

The exact geometry of the within-hemifield and across-hemifield conditions was tailored for each neuron, based on the location of the RF (Fig. 26). By definition, different spatial configurations were required for remapping stimulus traces within and across-hemifields. We held saccade amplitude constant and varied only the direction of the first saccade to achieve the within and across conditions. The second saccade always had the same direction and amplitude for the two conditions because it was described by the vector between central fixation and the neuron's RF. We used two standard configurations for most neurons. In the within-hemifield condition, a vertical saccade kept the representation of the second target within the same

hemifield both before and after the first saccade. In the across-hemifield condition, a horizontal ipsiversive saccade moved the representation of T2 from one hemifield to the other. For the remaining neurons, we used diagonal saccades for one or both conditions.

4.3.5 Data Analysis

4.3.5.1 Measuring remapping activity for single-step task.

A neuron was considered to have significant remapping activity if the activity during the single-step task was significantly greater than activity during the saccade control task (one-sided t-test $p>.05$). We measured activity in identical epochs for both tasks (0 to 300 ms from saccade onset). Remapping activity was defined as the activity in the single-step task that exceeded activity in the corresponding saccade control task. We used a simple subtraction to quantify the remapping response: Remapping = Single-step activity-Saccade control activity.

4.3.5.2 Measuring remapping activity for double-step task.

We measured remapping activity for the double-step task in an epoch beginning at the initiation of the first saccade (S1), and ending at the initiation of the second saccade (S2). This epoch was computed individually for each trial of the double-step task. We chose this epoch so that remapping was measured during a time-window that was identical from trial to trial with respect to the eye movements. If, for example, we had measured remapping solely in relation to the second saccade, the remapping epoch would include variable amounts of time before or after the first saccade. We therefore measured remapping in relation to both S1 and S2 to minimize the effects of variability in first saccade latencies. It is important to note that, although the epoch

is variable in its duration, the measure of firing rate (spikes per second) is inherently independent of epoch duration.

We computed the average firing rate in the saccade control task in an epoch that was identical to the average double-step remapping epoch for the individual neuron. We did this for all neurons, for both the within and across conditions, regardless of whether there was significant activity in the saccade control task. The average double-step remapping epoch was computed separately for within and across conditions because each condition required a different first saccade. This computation ensured that the saccade control epoch for each condition corresponded to the same time window as used for the double-step task. For example, if a neuron had an average across-hemifield remapping epoch of 190 ms (beginning at the start of the first saccade), then the across-hemifield saccade control epoch was also 190 ms, beginning at the start of the first saccade. We report remapping activity as the average firing rate in the double-step epoch minus the average firing rate in the corresponding epoch of the saccade control task. Throughout the paper, the phrase "double-step remapping activity" refers to this adjusted firing rate. If activity in the saccade control exceeded activity in the double-step task, updating activity takes on a negative value. Remapping activity in the double-step task was deemed significant when the firing rate in the epoch exceeded that in the corresponding saccade control epoch at a significance level of $p<.05$ (t-test).

4.3.5.3 Within-across index.

We computed a Within-Across Index to quantify the strength of remapping activity for the within condition compared to that in for the across condition.

WA Index = $\underline{(SSw\text{-}SACw) - (SSa\text{-}SACa)}$

$$(SSw+SACw) + (SSa+SACa)$$

The index normalized remapping activity from the single-step task to the total activity in the single-step and saccade control tasks. SSw and SSa represent the average activity in the single-step task in the within and across conditions, respectively. SACw and SACa represent the average activity in the corresponding saccade control conditions. The denominator of this formula accounted for the fact that the saccade-alone activity exceeds the single-step activity for at least one condition in some neurons. While the denominator was crucial to ensure that the index has a range of -1 to +1, it also introduced a problem. The problem arises because in the numerator, the saccade alone activity was subtracted from the single-step activity, while in the denominator the saccade alone activity was added to the single-step. A value of 1 or -1 only occurs if there is no activity during the saccade control tasks. This problem occurred only when there is absolutely no activity for both within and across condition in single-step task and in the saccade only task. In our data set, every neuron had some spontaneous firing; therefore there was never a case where the values were 0. Positive index values indicate stronger remapping for the within condition, and negative values indicate stronger remapping for the across conditions.

A second potential problem could arise if there were fundamental differences between saccade only activity for within and across conditions. If this were the case, then the WA index would reflect differences in saccade only activity, not just differences in remapping activity. We found no differences in average firing rate for within and across conditions during the saccade only task. This finding was true for both superficial and intermediate layers of the SC in the split brain and intact monkeys (Wilcoxon matched paired test, Superficial split brain: $p=.62$, Superficial intact: $p=.76$, Intermediate split brain: $p=.69$, Intermediate intact: $p=.30$). Given

that there are no fundamental differences between activity during the within and across saccade only conditions, the WA index reflects only differences for within and across remapping.

4.3.5.4 Measuring neural latency for single-step task.

We defined the neural latency of remapping activity as the time when the response in the single-step task first became significantly different from the response in the saccade control task. We searched for the beginning of activity in an epoch from 150 ms before to 250 ms after the onset of the saccade. We took a 20 ms bin of activity at corresponding time intervals in the single step and saccade only tasks. We compared the activity in the corresponding bins using a one-sided t-test ($p < .05$). We then shifted the bin 5 ms forward and repeated the procedure. We defined the neural latency as the middle of the first of 3 consecutive bins that were significantly different between the two tasks.

4.3.5.5 Trial-by-trial analysis.

Our assessment of the relationship between neurons and behavior included an analysis of the trial-by-trial correlation between updating activity in single neurons and double-step saccade performance. As stated above, one of the challenges in measuring updating activity is that we must remove the contributions of saccade-alone activity. When we consider individual trials, there is no obvious way to match individual saccade-alone trials to individual double-step trials for this subtraction. We used the following method to remove the contributions of saccade-alone firing from double-step activity on single trials. For a given neuron, we computed the double-step firing rate for each trial as described above, measuring the spikes per second in the epoch from the beginning of the first saccade to the beginning of the second saccade. From each

individual-trial double-step firing rate, we then subtracted the average saccade-alone firing rate for that condition (within or across). The average saccade-alone firing rate was computed using the epoch corresponding to the average double-step epoch for that neuron and condition. This method allowed us to remove the contributions of saccade-alone activity while maintaining information about updating activity on individual trials. We assessed the relationship between updating activity and behavior (accuracy or latency) by performing a Pearson's correlation analysis.

4.4 RESULTS

Our primary finding is that individual neurons in the superior colliculus are capable of remapping visual information both within and across-hemifields in the split brain monkey. We found remapping in both the superficial and intermediate layers of the SC. We compared our results to those we had previously obtained in cortical area LIP (Heiser et al., 2005; Heiser and Colby, 2006; Berman et al., 2007b). In most respects remapping in the intermediate layers of the SC was comparable to that in area LIP while remapping in the superficial layers of the SC differed.

We measured the strength of the remapping signal and the time of remapping. We assessed how physiological remapping is related to behavior by measuring performance in a double-step task that requires remapping. Finally, we examined how experience with certain target configurations affected performance and neural response. For each analysis we will compare results from intermediate layers of the SC to results from area LIP and then to results from the superficial layers of the SC.

We recorded from 246 SC neurons in two split-brain monkeys. Neurons were excluded from further analysis if they had a significant response when the stimulus was presented outside the RF in the stimulus control task. 176 SC neurons had no significant response in either the within or across stimulus-only control conditions. We also recorded 173 SC neurons in two intact animals. Of these, 120 SC neurons had no significant response in either the within or across stimulus control conditions and were included in further analysis. We compare results from intermediate SC and superficial SC to data previously collected from LIP (Heiser et al., 2005; Heiser and Colby, 2006; Berman et al., 2007b). In some cases we modified our previous analysis methods. In those instances, the LIP data were reanalyzed using the same method that we used on the SC data.

4.4.1 SC neurons remap stimulus traces across-hemifields in the split brain monkeys

Our primary finding is that individual neurons in the SC are capable of remapping visual information both within and across-hemifields after the forebrain commissures are severed. An example neuron is shown in Figure 2. This cell was recorded from the intermediate layers of the SC. The cell had a strong visual response to a stimulus that was presented inside the RF (Fig. 27K), as well as delay period and saccade related activity (Fig 2L). In the within condition of the single-step task, the neuron fired at the time of the saccade and activity continued for several hundred milliseconds (Fig. 27C). Two control conditions showed that this activity was not due to either the stimulus or the saccade alone. First, there was no response in the stimulus only control,

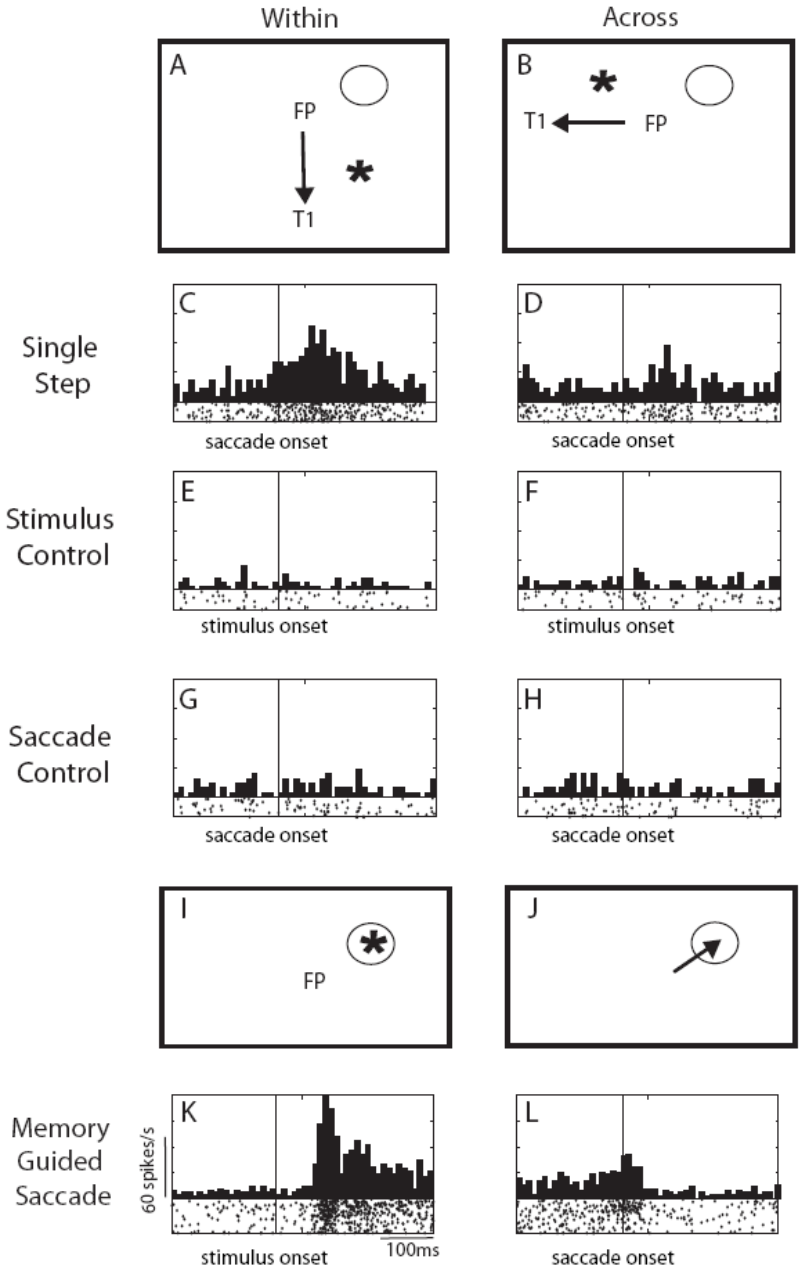


Figure 27. Intermediate layers cell.

Spatial configuration for the single-step task (A and B). The monkey makes an eye movement (the arrow) from the original fixation location (FP) to the target (T1). The receptive field (RF) of the neuron is represented by the circle. Before the eye movement is initiated a stimulus is flashed outside the RF of the neuron (asterisk). During the within condition, the stimulus is flashed in the same hemifield as the RF of the neuron (A). The monkey makes a vertical saccade, shifting the RF to the location where the stimulus had been presented. During the across condition, the stimulus is flashed in the opposite hemifield as the RF of the neuron (B). The monkey makes a horizontal saccade to shift the RF to the stimulus location. In both configurations the stimulus is turned off before the onset of the saccade. Histograms represent the average firing rate of the neuron; rasters represent the time of an individual action potential for each trial. The vertical lines represent either the onset of the stimulus (E, F, G, L) or the onset of the saccade (C, D, G, H, L). The firing of the neuron increases during the single-step task for both the within (C) and across (D) conditions. The firing of the neuron does not increase for the stimulus control condition (E and F) or the saccade control conditions (G and H). The configuration during the memory guided saccade task (I and J). While the monkey fixates the stimulus is presented inside the RF of the neuron. Once the FP is turned off the monkey makes an eye movement to the remembered location of the stimulus. The neuron has a strong visual response and a continued response during the delay period (K). The neuron has an increase of activity around the time of the saccade (L).

in which the visual stimulus was presented outside the RF and no eye movement was made (Fig 2E). Second there was no significant response in the saccade only control, in which the saccade was made without the peripheral stimulus being presented (Fig. 27G). The critical question was whether this same neuron would also respond when information had to be transferred across hemifields. This cell was still active in the across condition of the single-step task (Fig. 27D). This activity indicates that the memory trace of the stimulus was remapped in conjunction with the saccade (Fig. 27D). There was no significant activity in either of the control conditions (Fig. 27F and H). In the absence of the forebrain commissures, this SC neuron remapped visual information both within and across-hemifields.

In the superficial layers of the SC, we also found neurons with remapping activity during both the within and across conditions of the single-step task. Fig. 28 shows a cell recorded from the superficial layers of the SC. The cell fired strongly to a stimulus presented in the RF (Fig. 28K). It had no response for a saccade made into the RF (Fig. 28L). During the within condition of the single-step task, the cell fired long after the saccade (Fig. 28C). The cell had a similar pattern of firing during the across condition (Fig. 28D). This response was not due to the stimulus or the saccade alone; firing did not increase significantly above baseline for the stimulus and control conditions. In the superficial layers, as in the intermediate layers, neurons can remap across hemifields even in the absence of the forebrain commissures.

4.4.2 More neurons in the intermediate layers remap for within compared to across-hemifields.

How does the percentage of cells that remap compare for within and across conditions in the intermediate layers of the SC of the split brain monkey? We found that 48% (57/118) of cells in

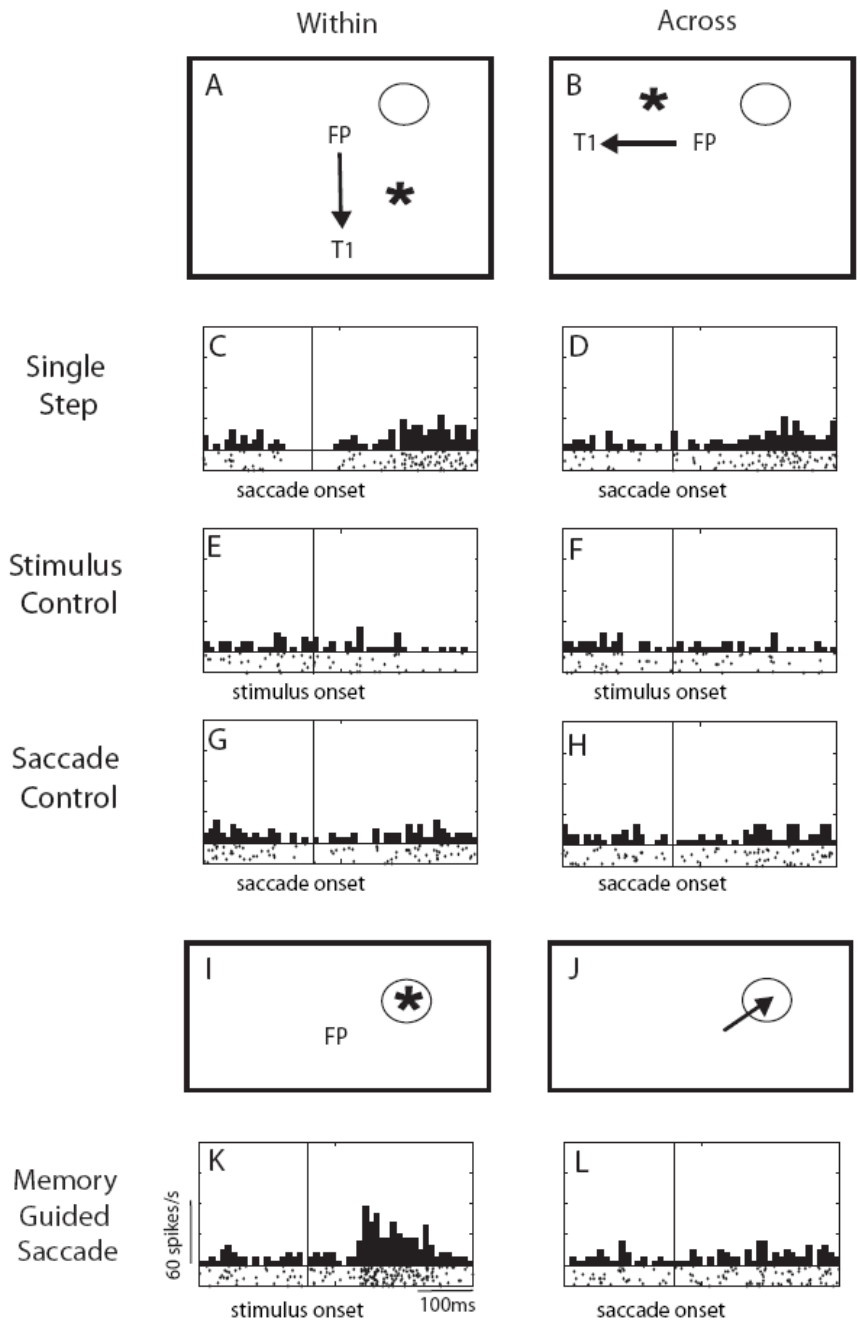


Figure 28. Superficial layers cell.

Example of a superficial layers SC neuron that remaps both within and across hemispheres in the split brain monkey. Spatial configuration for the single-step task (A and B). This neuron has significant remapping activity during the single-step task for both the within (C) and across (D) conditions. The firing of the neuron is not significantly different from baseline for the stimulus control condition (E and F) or the saccade control conditions (G and H). The configuration during the memory guided saccade task (I and J). The neuron has a strong visual response (K) but no delay period or saccade related activity (L). Conventions the same as Fig 2.

the intermediate layers had significant remapping activity in at least one of the remapping conditions (Fig. 29C). Of these cells, most had significant activity either in both conditions (42%, 22/57) or in the within condition only (39%, 22/57). Fewer cells had significant activity in only the across-hemifield remapping condition (19%, 11/57). In the intact animal, just over 50% (38/75) of cells remap in at least one of the conditions for the intact monkey. Similar proportions of cells had significant remapping activity in the within only (31.5%, 12/38), across only (31.5%, 12/38), and both conditions (36%, 14/38: Fig.4D). The distributions of the proportion of neurons with remapping activity are significantly different for split brain compared to intact animals (chi_square test,χ^2=7.09,df=2, p<.05). We conclude that the reduced prevalence of across-hemifield only remapping in the intermediate layers of the SC resulted from the removal of the forebrain commissures.

We compared the results from the intermediate layers of the SC to our previous results in area LIP (Heiser et al., 2005; Heiser and Colby, 2006). In area LIP, we found a substantial reduction in across-hemifield only remapping in area LIP in the split-brain monkeys. Of the neurons that had significant remapping activity, only 6% had remapping activity during the across only condition (Fig. 29E). The distributions of LIP neurons with remapping activity are significantly different for the split brain and intact monkeys (chi-square test, χ^2=26.192, df=2, p<.001). However, the findings in LIP and intermediate SC are not identical. The distributions of neurons with remapping activity were significantly different between the two regions (Fig. 29C and E chi-square test, χ^2=19.865, df=2, p<.001). While both regions showed a decrease in the number of neurons with remapping activity in the across only condition, the decrease was much more pronounced in area LIP.

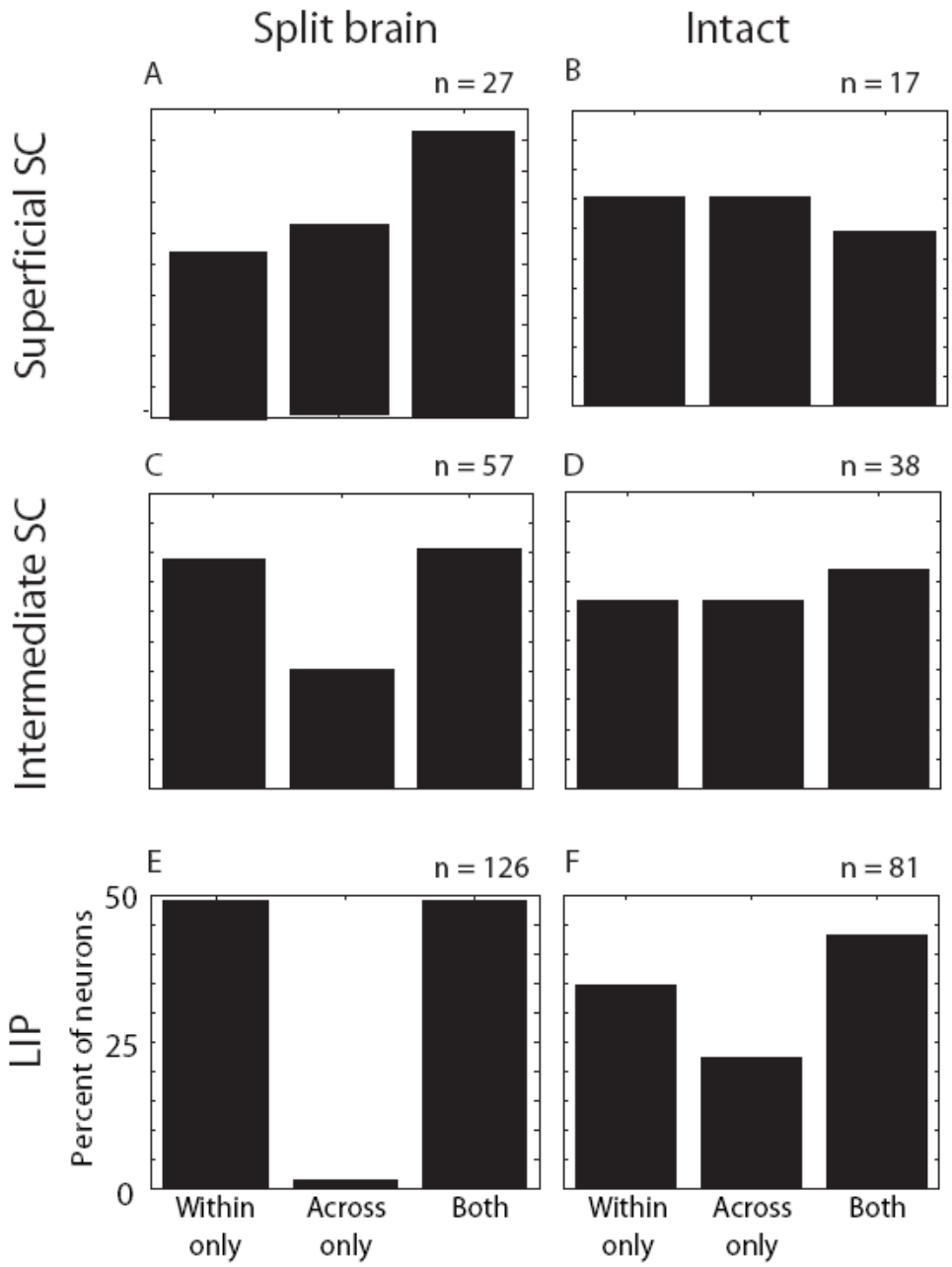


Figure 29. Proportion of neurons with significant remapping.

In the superficial layers of the SC in the split-brain monkey (A) and the intact monkey (B), an equivalent proportion of neurons show significant remapping for within, across, and both conditions. In the intermediate layers of the SC in the split brain monkey, there is a lower proportion of neurons that show significant remapping for the across conditions compared to the within and both conditions (C). In the intermediate layers of the intact monkey, an equivalent proportion of neurons show significant remapping for within, across and both conditions (D). In LIP of the split brain monkey there is a striking decrease in the proportion of neurons that remap for the across condition only (E). This decrease is not observed in the intact monkey (F).

Neurons in superficial layers of the SC showed a different pattern of results than either the intermediate layers of the SC or area LIP. We found that 37% (27/73) of neurons remap in the superficial layers in the split brain monkeys. Of those that remap, fewer than half had significant remapping activity in the within only (26%, 7/27), across only (30%, 8/27), and both (44%, 12/27) conditions (Fig. 29A). The results from the split brain monkey were comparable to those in the intact monkey. Overall 38% of the neurons (17/45) remapped. Of those, 35% (6/17) remapped in the within only, 35% (6/17) in the across only, and 30% (5/17) both conditions (Fig. 29B). The findings in the superficial SC are significantly different from both the LIP and intermediate SC (superficial vs. intermediate= chi-square test, χ^2=8.97, df=2, p=.01; superficial vs. LIP = chi-square test, χ^2=47.95, df=2, p<.001). The absence of the forebrain commissures does not influence the proportion of cells that remap across hemifields in the superficial layers of the SC.

4.4.3 Strength of across-hemifield remapping is attenuated in the intermediate layers of the SC in split brain monkeys.

How does the magnitude of the remapped response compare for within and across conditions in the intermediate layers of the SC of the split brain monkey? We found that the magnitude of across-hemifield was remapping reduced compared to within-hemifield (Wilcoxon matched-pairs test, p=0.02; Fig. 30C). We restricted this and all other analyses to cells that had significant remapping for at least one of the conditions. In the intact monkey, there was no difference in magnitude for within and across-hemifield remapping in the intermediate layers (Wilcoxon matched-pairs test, p>0.05; Fig. 30D). The present results in intermediate SC are similar to our previous results in LIP.

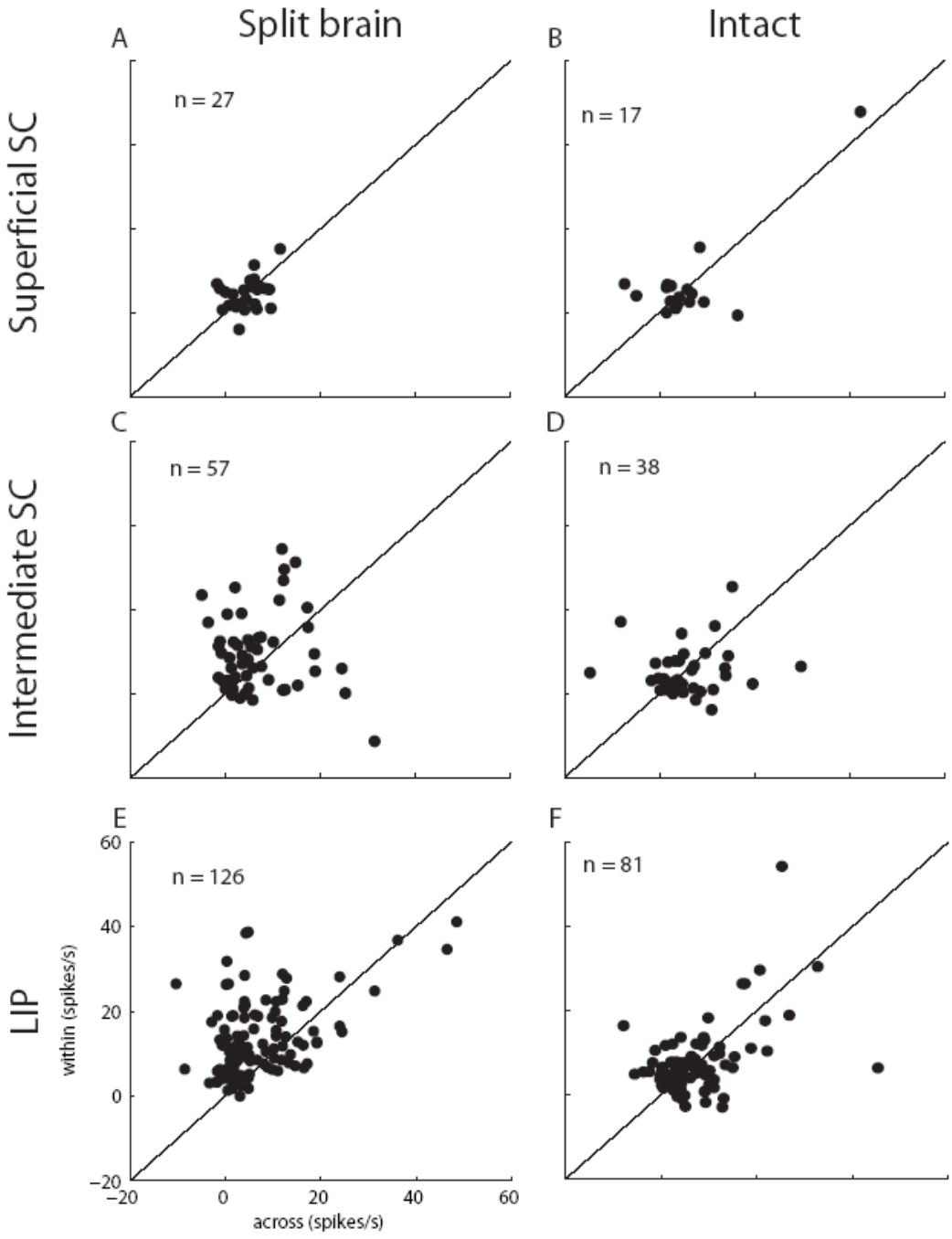


Figure 30. Magnitude of response for within and across remapping.

Each point represents data from a single neuron. Magnitude of remapping activity is calculated as the difference between activity in the single-step task and saccade control task. If the activity in the saccade control task is greater than the activity in the single-step task then the magnitude of remapping will be negative. In the superficial layers of the split brain monkey, there is no difference in magnitude of within and across-hemifeld remapping (A). In the intermediate layers of SC and in area LIP of the split brain monkey more points are above the unity line, activity is significantly greater for within than for across-hemifeld remapping (C and E). In the intact monkey in all three brain areas, there was no difference in magnitude of within and across-hemifeld remapping (B, D, F).

In order to match our SC population, we selected for analysis only LIP neurons that had significant remapping in at least one condition. In LIP, we found that the magnitude of across-hemifield remapping was significantly reduced compared to within-hemifield remapping in the split brain monkey (Wilcoxon matched-pairs test, $p<.001$; Fig. 30E).

The reduced magnitude of remapped responses for across conditions was found only in the intermediate layers of the SC and area LIP. In the superficial layers, there was no difference in magnitude for within and across-hemifield remapping in either the split brain or the intact animals (split brain: Wilcoxon matched-pairs test, $p>0.05$; Fig. 30A, intact: Wilcoxon matched-pairs test, $p>0.05$; Fig. 30B). Activity in the superficial layers was not modified in the absence of the forebrain commissures.

To quantify the strength of remapping, we computed a Within-Across remapping index (WA index, see Methods). With this index, we can assess how robustly neurons remap stimulus traces across hemifields versus within a single hemifield. The WA index normalizes remapping activity measured in a 300 ms epoch from the start of the saccade in the single-step task to the total activity in the single-step and saccade only control task during the same epoch for each cell. This calculation provides a single value that is independent of the overall firing rate of the cell. Positive index values indicate that activity was stronger for within-hemifield compared with across-hemifield remapping, whereas negative values indicate that activity was stronger for across-hemifield remapping. A value of zero indicates no difference in the magnitude of remapping between within and across-hemifields.

We found stronger remapping for within-hemifield trials in the intermediate layers of the SC. The distribution of WA index values from the intermediate layers of the SC of the split brain monkeys was significantly skewed toward positive values (sign test, $p=0.02$; Fig. 6C),

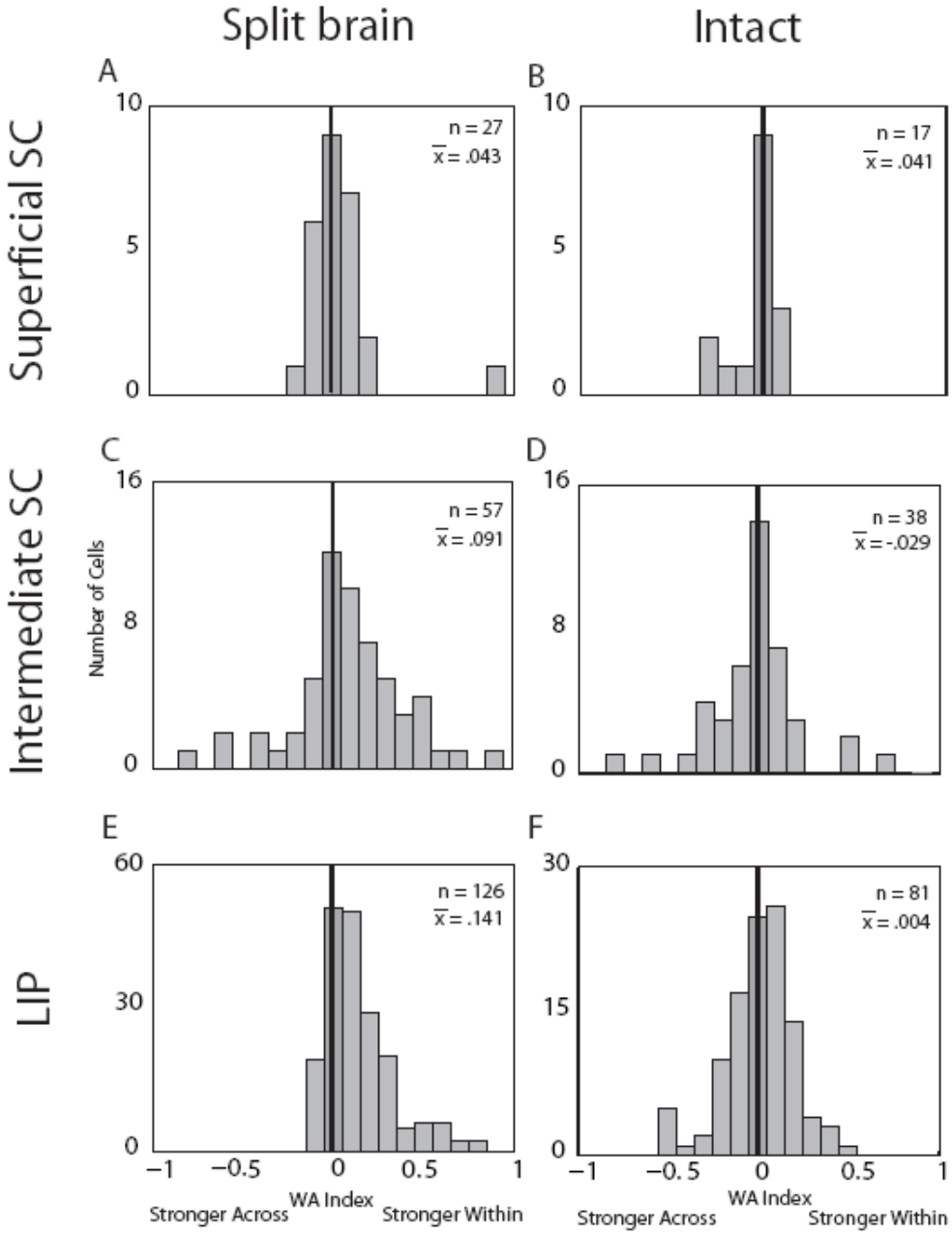


Figure 31. Within-across remapping index.

The WA index distribution for the superficial layers of the SC is not significantly different from 0 for both the split-brain (A) and intact monkeys (B). In the intermediate layers of the SC of the split-brain monkey, the distribution is positively skewed towards the positive (C). Neurons have greater magnitude for the within condition compared to the across condition. In the intermediate layers of the SC of the intact monkey, the distribution is not significantly different from 0 (D). In LIP of the intact monkey, the distribution is positively skewed towards the positive (E). In LIP in the intact monkey, the distribution is not significantly different from 0 (F).

indicating stronger remapping for the within-hemifield condition. We did not find a significant shift in the distribution for the intermediate layers of the SC in the intact animal (sign test, p=.51; Fig. 31D). When we compared the split brain animals to the intact animals, we found a significant difference between the two populations (Wilcoxon rank sum, p=.02). These results demonstrate that the magnitude of across-hemifield remapping was reduced in the intermediate layers of the SC in the absence of the forebrain commissures.

These results mirror the findings from area LIP in split brain and intact monkeys. In the split brain monkeys we found that the distribution of WA index values was significantly skewed toward positive values (sign test, p<.0001; Fig. 31E). This result was not observed in the intact animal; there was no shift in the distribution (sign test, p=.58; Fig. 31F). If we directly compare WA index values from the intermediate layers of the SC and area LIP, there was no significant difference between the distributions (Wilcoxon rank sum, p=.15). In the absence of the forebrain commissures, the across-hemifield remapping signal is reduced in both the intermediate layers of the SC and in area LIP.

We found a different pattern of WA index values in the superficial layers of the SC of the split brain animal compared to the distributions in the intermediate layers of the SC and in LIP. In the superficial layers, we found no significant shift in the WA index distributions for either the split brain or the intact monkey (sign test, p>0.05, Fig. 31A). These results reveal a distinction between remapping activity observed in the superficial layers of the SC compared to area LIP (Wilcoxon rank sum, p<.001). There is no reduction in across-hemifield remapping in the superficial layers, while there is in the intermediate layers and area LIP.

The results on the strength of remapping are summarized in Table 1. In our previous study, we found that split-brain monkeys were impaired on the double-step task, a behavioral

task that depends on accurate spatial updating (Berman et al. 2005). This behavioral impairment corresponded to a reduction in neural activity. Across-hemifield remapping activity was reduced compared to within-hemifield remapping in area LIP. In the current study, we found that the intermediate layers of the SC resembled area LIP; across-hemifield remapping was reduced compared to within-hemifield remapping. In contrast, there was no reduction of across-hemifield remapping in the superficial layers of the SC.

Table 1. Across-hemifield remapping compared to within-hemifield remapping

	Split-Brain	**Intact**
Behavior	Impaired, then recovers	same
Magnitude of response		
Superficial SC	same	same
Intermediate SC	Reduced	same
LIP	Reduced	same
Latency of response		
Superficial SC	same	same
Intermediate SC	Delayed	same
LIP	Delayed	same

4.4.4 Neurons in the intermediate layers of the SC remap later for across compared to within-hemifield.

Remapping within a hemifield is thought to be accomplished by circuits on one side of the brain. Remapping across-hemifields presumably requires additional circuitry to transfer information from one side of the brain to the other. This could result in longer average latencies for remapped responses. This leads to the question, how does the timing of remapped responses compare for within and across conditions in the split-brain monkey? We addressed this question in two ways, first by analyzing the entire population and then by analyzing individual neurons in

the SC and area LIP. The first analysis focused on signals present in the population as a whole. We asked whether neural latencies are comparable for within and across conditions. We performed an analysis that included all neurons that had a latency in either the within or across condition. This was an unmatched analysis because we did not directly compare the within and across latency for each single neuron but instead compared the combined latencies for all neurons.

In the intermediate layers of SC of the split brain animals (Fig. 32E and G), we found that the response was earlier when remapping took place within a hemifield (mean=20 ms, relative to saccade onset) compared to remapping across-hemifields (mean=42 ms); however this difference was not significant (Wilcoxon rank sum test, $p>0.05$). No difference was found between neural latency for within and across remapping in the intact animals. The average latency for within was 30 ms, and for across was 35 ms. These results indicate that in the forebrain commissures provide a pathway for fast transfer of remapping activity across-hemifields even for activity in the SC.

These findings match the results found in LIP of the split brain and intact monkeys. In LIP of the split brain monkeys, the average neural latency for within-hemifield remapping was 38 ms, while the neural latency for across-hemifield remapping was 65 ms. These two distributions were significantly different from each other (Wilcoxon rank sum test, $p<.05$). We did not find a difference in the distributions of within (34 ms) and across (42 ms) neural latency for LIP in the intact animals (Wilcoxon rank sum test, $p>.05$).

In contrast to the latency results for intermediate SC and area LIP there was no significant difference between within and across-hemifield remapping in superficial SC in the split brain monkey (within mean = 67 ms vs. across mean=80). The absence of the forebrain

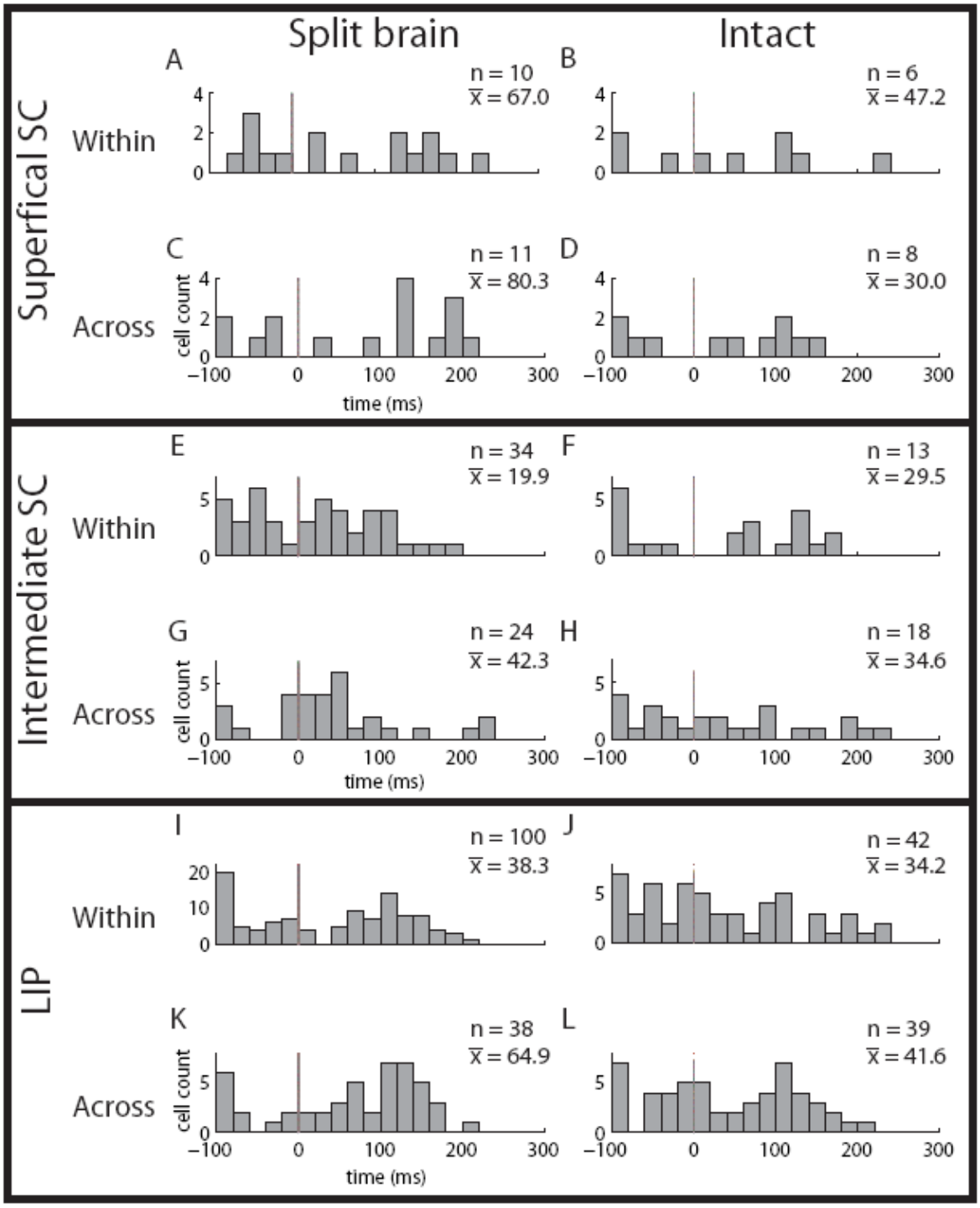


Figure 32. Neural latency for within and across remapping.

Comparision of latency of remapping within and across-hemifields. Latency is defined relative to saccade onset (vertical line). In the superficial layers of the SC in the split brain monkey the remapping occurs at the about the same time for within (A) and across (C) conditions. In the intact monkey, there is no difference in latency for within (B) and across (D) conditions. In the intermediate layers of the SC in the split brain monkey, remapping in the within condition (E) occurs around the same time as in the across condition (G). In area LIP in the split brain monkey, remapping in the within condition (I) occurs earlier than remapping in the across condition (K).

commissures does not affect the latency of response for the superficial layers of the SC. This result is consistent with the idea that there are different sources of remapping activity for the superficial layers compared to the intermediate layers and LIP.

A second analysis directly compared neural latency for within and across remapping in individual neurons (Fig. 33). By definition, this analysis included only neurons for which valid latencies could be determined in both conditions. Points that fall along the unity line represent neurons with remapping activity that began at the same time for the within and across conditions. For the intermediate layers of the SC in the split-brain monkeys most points fall below the line, indicating that remapping across-hemifields is delayed relative to the within-hemifield remapping (Fig. 33A Wilcoxon signed rank test, $p=0.03$). In contrast, in the intermediate layers of the SC in the intact animal, the points are equally distributed around the unity line: there was no significant difference between the neural latency for within compared to across remapping (Fig. 33B, Wilcoxon signed rank test, $p=0.06$). We found a similar trend in LIP. In the split-brain monkeys, the majority of points lie below the unity line (Fig.8C, Wilcoxon signed rank test, $p<0.05$). In the intact monkeys, the points are equally distributed above and below the line (Fig. 33D, Wilcoxon signed rank test, $p>0.05$). The number of cells that had remapping activity for both within and across-hemifield in the superficial layers of the SC was too small to complete the second analysis.

We conclude that in the intact animal there is no difference in the timing of remapping when information remains within or must be transferred across-hemifields. This result is true for both the SC and area LIP in the intact animal. In the absence of the forebrain commissures, however, the remapped response is delayed when information must be transferred across-

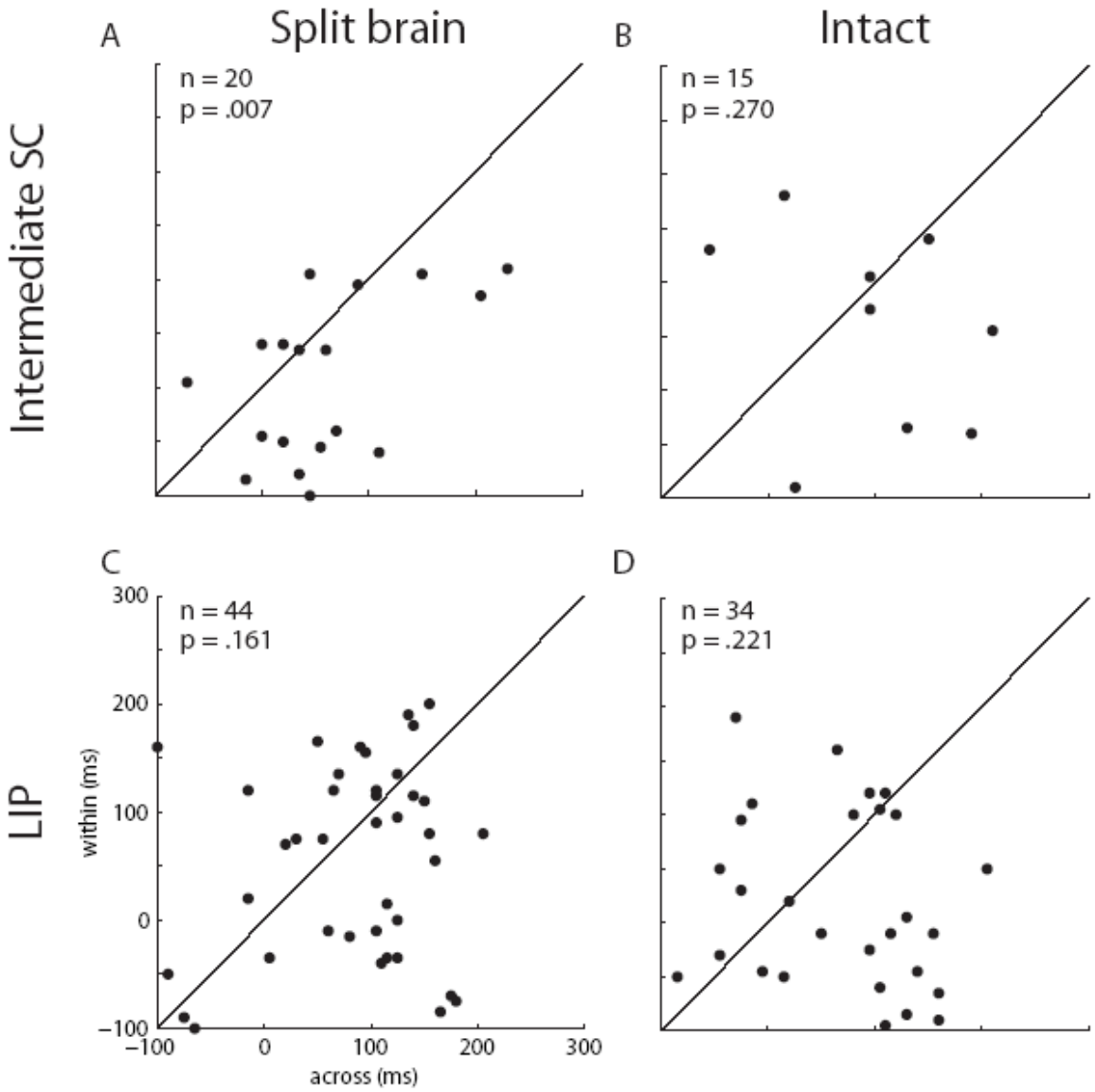


Figure 33. Neural latency for within and across remapping.

Each point represents data from a single neuron. In the intermediate layers of the split brain monkey, there is a difference in neural latency for within and across-hemifield remapping (A). Remapping activity occurs later during the across condtions. In LIP, neural latencies occur later during the across conditions (C). There is no difference in neural latency in the intermediate layers and in LIP for the intact animal (B and D).

hemifields. This is the case for both LIP and the intermediate layers of the SC. These results are summarized in Table 1.

4.4.5 The earliest across-hemifield remapping signals are absent in the intermediate layers of the SC of the split brain monkeys.

We observed considerable variability in the latency of remapping in all brain regions in both intact and split brain animals. This is consistent with previous studies, in which a wide range of latencies were observed (Duhamel et al. 1992a; Goldberg and Bruce 1990; Heiser and Colby, 2006; Nakamura and Colby 2002; Umeno and Goldberg 1997; Walker et al. 1995). Remapping is considered predictive if the response in the single-step task relative to the beginning of the saccade occurs earlier than the visual latency observed in the memory-guided saccade task. These predictive signals provide an updated representation well before reafferent visual signals are available. For some predictive neurons, the response in the single-step task begins before the onset of the saccade. For these neurons, the location of the RF shifts even before the eyes begin to move. Neurons with *presaccadic* latencies are a subset of those with *predictive* latencies.

We asked whether neurons in the intermediate layers of the SC in the split-brain monkey exhibit predictive remapping. Specifically, we tested whether the proportions of predictive and presaccadic latencies would be similar for the within and across conditions. We addressed this issue by analyzing the entire population of neurons for which a latency could be determined. We observed a similar proportion of predictive responses for within- and across-hemifield remapping in the split-brain monkey (Fig. 34C gray bar, within 64%, across 57%). In contrast, in the intact monkey; we found more neurons with across-hemifield predictive remapping than neurons with within-hemifield predictive remapping (Fig. 34D gray bar, within 18%, across 47%).

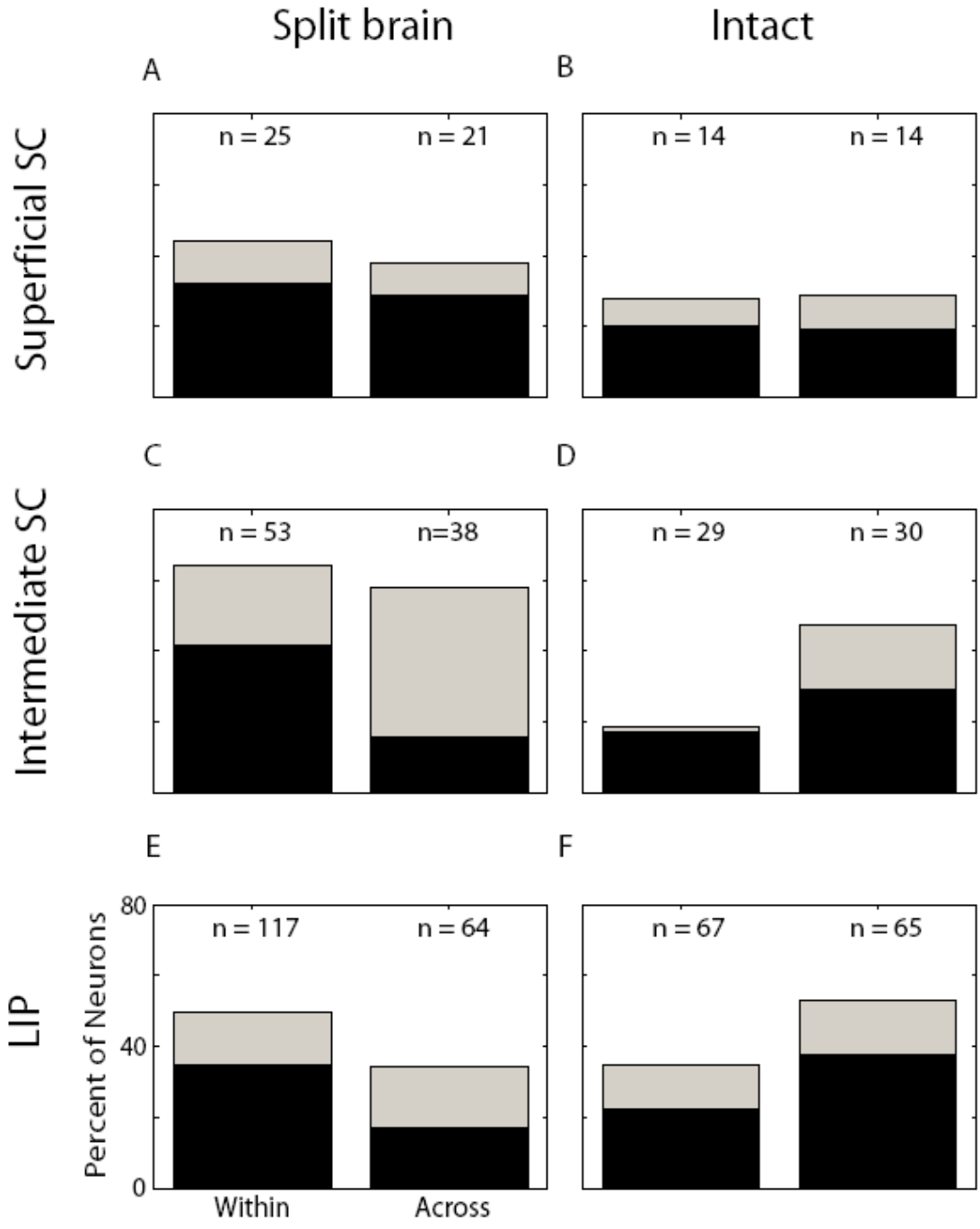


Figure 34. Proportion of neurons with significant predictive and presaccadic remapping for within and across-hemifield conditions.

In the superficial layers of the SC in the split brain monkey (A) and the intact monkey (B), an equivalent proportion of neurons show significant predicitive (gray bar) and presaccadic (black bar) remapping for within and across conditions. In the intermediate layers of the SC in the split brain monkey (C), and in area LIP (E) there is a lower proportion of neurons that show significant predictive and presaccadic remapping for the across condition compared to the within condition (C). In the intermediate layers of the intact monkey (D) and in area LIP (F) more neurons show significant predictive and presaccadic remapping for within compared to across conditions.

What about the occurrence of neurons with *presaccadic* latencies? Is there any difference in the number of neurons that respond to the remapped stimulus traces before the saccade begins? In contrast to our findings on the overall number of predictive neurons, we found that presaccadic responses were more common for within-hemifield remapping in the intermediate layers of the SC in the split-brain monkey (Fig 9C black bar, within 41%, across 15%). In contrast, in the intact monkey, presaccadic latencies occurred within greater frequency for the across condition than within condition (Fig. 34D black bar, within 17%, across 30%).

The results for predictive remapping in the intermediate layers of the SC in the split brain monkey are similar to those previously observed in area LIP (Heiser et al. 2005). In area LIP of the split brain, there were more neurons that had predictive responses for within compared to across-hemifield remapping; 50% predictively remapped for within and 35% for across. For the intact monkey, we found the opposite result, 35% predictively remapped for within and 53% for across.

The pattern of results for presaccadic remapping in area LIP was similar to that in the intermediate layers of the SC (Hesier et al. 2005). Fewer neurons remapped presaccadicly across-hemifields within. 35% of LIP neurons in the split brain monkey had presaccadic within-hemifield remapping, while only 17% had presaccadic across-hemifield remapping. In area LIP of the intact monkey the results were reversed, with presaccadic remapping for within (22%) and across (38%) hemifield conditions.

Results in the superficial layers of the SC are unlike the results observed in the intermediate layers and LIP. In the superficial layers of the SC in the split brain and intact monkeys, there were equivalent proportions of neurons that had predictive responses for within and across-hemifield remapping. For the split brain monkeys, 44% of neurons predicatively

remap within-hemifield and 38% for across. In the intact monkey, 28% predictively remapped for within and 29% for across. In sum, in the superficial layers of the SC we found no relative difference between within and across-hemifield predictive remapping in both the split brain and intact animals.

What about presaccadic remapping? In the superficial layers of the SC in the split brain monkey, we found an equivalent number of neurons with presaccadic remapping for within-hemifield (32%) and across-hemifield (28%). Likewise in the intact animals we found equal proportions with presaccadic remapping for within-hemifield (20%) and to across-hemifield (19%). The results observed in the superficial layers of the SC cannot be due to the absence of the forebrain commissures. The different pattern of results for presaccadic remapping in the superficial layers compared to intermediate layers of the SC suggests the idea that the source of remapping is different for these layers.

4.4.6 The time course of across-hemifield remapping is altered in the intermediate layers of the split-brain monkeys.

We analyzed the time course of signals during within and across-hemifield remapping. We did so by calculating the WA index over time for the population of neurons that showed significant remapping for both within and across conditions (Fig. 35). The WA index is a single value at each time point for each neuron. It quantifies the difference between the magnitude of remapping for within-hemifield compared to across-hemifield conditions. The WA index was computed for each neuron in a 50 ms epoch that was successively shifted by 10 ms. We averaged the WA index values for all neurons in each group and determined the point at which the values first

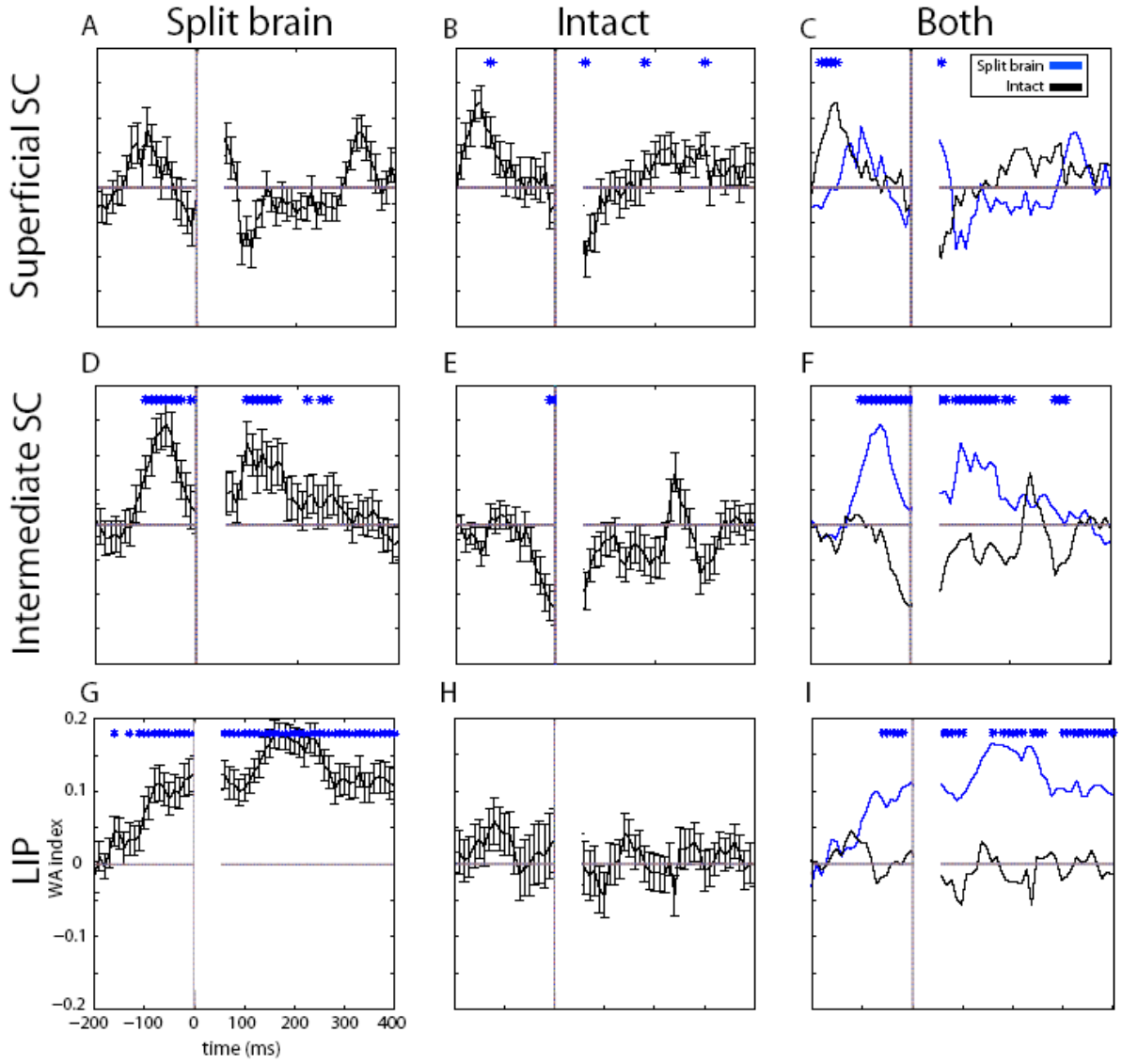


Figure 35. Time course of WA index.

Each panel shows the Within-Across Index computed as a function of time. Positive values indicate that remapping is stronger for the within compared to the across conditions. Values near zero indicates that remapping is equal for the two conditions. The index is computed in 50 ms epoch that is shifted by 10 ms. Error bars represent SE. There is blue astricks if the data point is significantly different from zero (A, B, D, E, G, H) or if the data point is significantly different between the split brain and intact monkey (C, F, I). There is no difference in magnitude for within and across remapping in the superficial layers in the split brain monkey at all time points (A). The index becomes positive for the intact monkey in the superficial layers very early and at a few data points after the saccade (B). The WA index is significant different for the split brain and intact monkeys mainly at the earliest time points. For the intermediate layers (D) and LIP (G), the Index becomes positive only for split brain monkeys. The index remains near zero for the intact monkey for both the intermediate layers (E) and LIP (H). Data from split brain (blue lines) and intact animals (black lines) are plotted together (C, F, I).

began to diverge significantly from zero. This divergence was the time at which signals associated with within- and across-hemifield remapping first began to differ.

The WA index is a ratio. When the firing rate is extremely low only a few spikes can make a large difference. Around the time of the saccade, the remapped signal in the SC decreases significantly. Remapping activity declines drastically because the monkey is making an eye movement to a target outside of the neurons receptive field. This instability in the WA index due to a suppression of activity makes the measurement unreliable around the time of the saccade. To get around this unreliability, we omitted the WA index values in an epoch 50 ms after the saccade.

In the absence of the forebrain commissures, the WA index for the intermediate layers of the SC first significantly differed from zero before the onset of the saccade. The data show that, well before the initiation of the saccade, there is a difference in the neural signal associated with updating stimulus traces for within as compared to across-hemifield conditions (Fig. 35D, F). This difference persists for hundreds of milliseconds after the saccade is completed. In contrast, in the intact animal, the WA index remains near zero throughout the duration of the analysis epoch (Fig. 35E).

Our previous studies revealed a similar result in area LIP. We found a difference in the time course of within compared to across-hemifield remapping in the split brain monkeys (Fig. 35G, I). For area LIP in the split brain monkey, the WA index first reached significance 150 ms before the onset of the saccade. The index reached its maximum 190 ms after saccade onset.

The time course of the WA index in the superficial layers of the SC differed from the time course for the intermediate layers and area LIP. For the superficial layers in the split brain animal the WA index was never significantly different from zero (Fig. 35A). There was no

difference in magnitude between within and across-hemfield remapping at any time point. The WA index for the intact animal was significant before the saccade and at a few time points after the saccade (Fig. 35B). When we directly compare split brain monkeys to intact monkeys, we found that the WA index differed mainly before the saccade (Fig. 35C). Unlike the results observed in the intermediate layers, the difference in magnitude between the within and across conditions was not due to the absence of the forebrain commissures. We observed the difference only in the intact monkey. The difference in results between the intermediate and superficial layers further supports the idea that the source of remapping is different between layers.

4.4.7 Performance on the double-step task.

In our previous study, the split brain monkeys' performance on the across-hemifield version of the double-step task was initially impaired (Berman et al., 2005). With experience on a standard sequence of targets, the monkeys' performance markedly improved. Nonetheless there was still a difference in accuracy for within compared to across sequences 4 years post surgery. In the present study, we asked if we could still, at almost 6 years, detect a difference in performance on within and across conditions of the double-step task in the split brain monkeys. We quantified the accuracy of the monkey's performance on the double-step task by computing the distance error of the second saccade. For each trial we measured the distance between the second target location and where the saccade actually landed. We included only trials in which the eye accurately reached the first target. We computed the distance error for all recording sessions and found that on average the error of the second saccade was significantly greater for the across than for the within conditions (Fig. 36A). Even with the experience gained both during the original behavioral tests and during subsequent LIP recording sessions, the split-brain monkeys were still

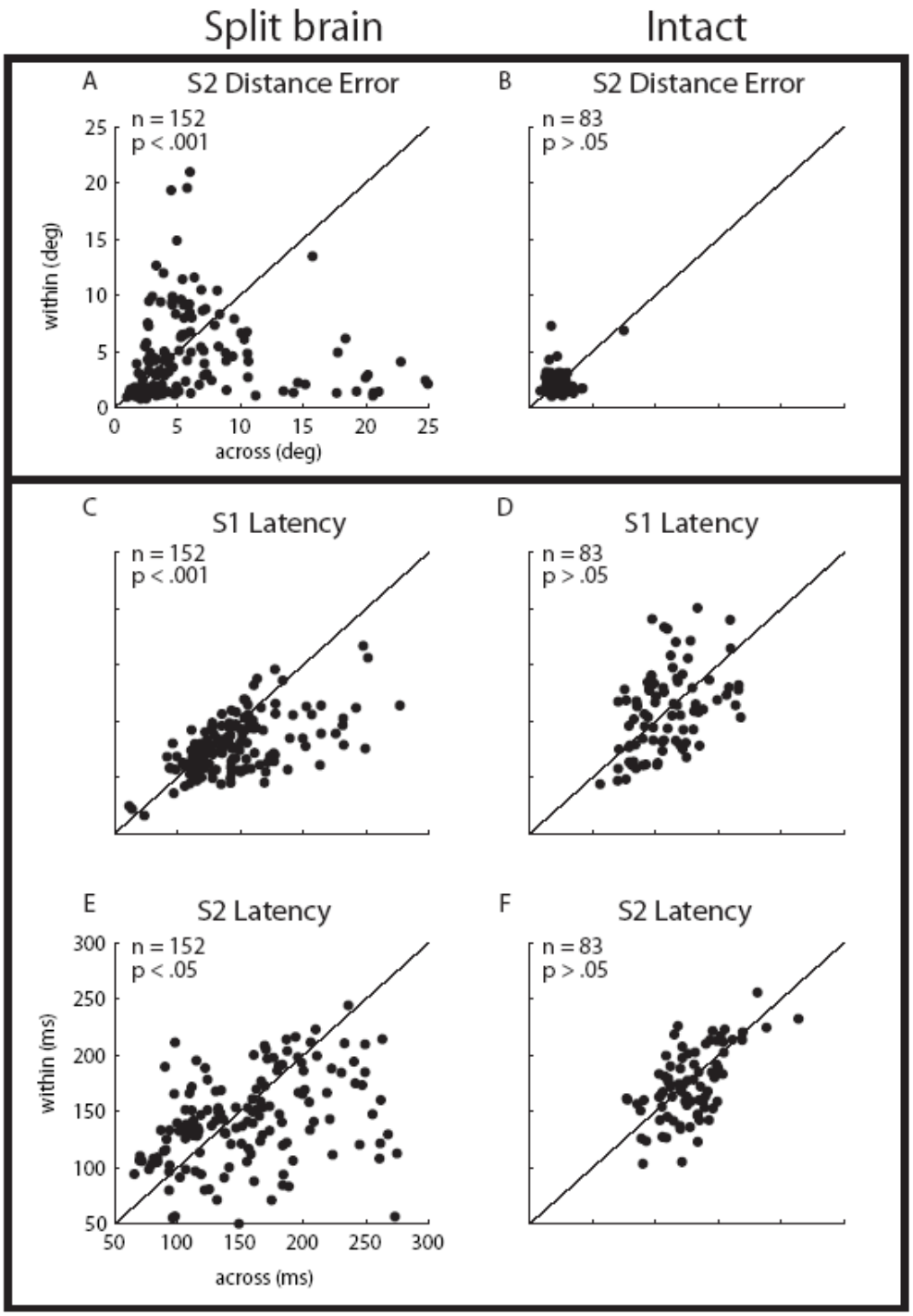


Figure 36. Distance error and latency of double-step performance during SC recordings.

Panels in the left column represent data from two split brain monkeys, panels in the right column represent data from an intact monkey. Each point represents the average behavior during one recording session for the within condition compared to the across condition. In the split brain monkey, the monkey have more error (A) and longer first (C) and second (E) saccades for the across condition. (B, D, F) There is no difference for the intact monkey.

impaired on across-hemifield sequences of the double-step task. We found no significant difference between distance error in within and across conditions in the intact monkey (Fig. 36B).

We also quantified the performance of the monkeys by measuring the saccade latencies of the first and second saccades. We asked whether there was a difference in saccade latencies for the within and across conditions of the double-step task. We found that the split-brain monkeys had slower first and second saccades for the across-hemifield condition compared to the within-hemifield condition (Fig. 36C and E). For the first saccade, the average latency was 121 ms ±25 (SD) for the within conditions compared to 141 ms ± 52 (SD) for the across. For the second saccade, the average latency was 139 ms ± 46 for the within conditions compared to 141 ± 52 for the across conditions. In addition to making more errors, the split-brain animals took longer to complete the across-hemifield condition of the double-step task. We found no difference in either the first or second saccade latencies for the intact monkey.

We compared the results of the saccade latency analysis from the SC recording sessions to the results of the same analysis from the LIP recording sessions. We expected that after 4 years performance would stabilize but this was not the case. During the LIP recording sessions, on average, the split brain monkeys were faster for the second saccade for the across condition than for the within condition during the LIP sessions (Berman et al. 2007). Berman et al. considered the possibility that the faster saccades resulted in more errors in performance but in fact the monkeys were both faster and more accurate. The authors speculated that as the monkeys gained experience on a given sequence they developed a more automatic strategy: the monkeys relied less on the visual stimulus, and relied more on a remembered motor sequence. The reason we see a different result in the SC recording sessions could be because the split-brain

monkeys abandon the automatic strategy. This could occur because, during the SC recording, the location of the RF varied more from day to day. Therefore, the sequences the monkeys performed varied more day to day. Due to the variability in sequences, the monkeys could not easily develop an automatic strategy.

In summary, we found a difference in the performance on the double-step task for the within and across conditions in the split brain monkeys during SC recording sessions. We found that the monkeys were faster and more accurate for within-hemifield sequences compared to across-hemifields sequences of the double-step task. Even after years of recovery, the absence of the forebrain commissures still influences the behavior of the monkey.

4.4.8 Remapping activity in the intermediate layers of the SC is related to the behavior on the double-step task.

Is the magnitude of remapping activity in the intermediate layers of SC related to accuracy of performance on the double-step task? We know from the preceding analyses that there are differences between the relationship between remapping activity and performance for within and across conditions in the split brain monkey (Fig. 31 and Fig. 36). We asked if a relationship between activity and behavior could be detected on a single trial. We wanted to know whether, on a given trial, performance was more accurate when remapping activity was stronger. We addressed this by calculating the Pearson's correlation coefficient (r) for the relationship between the distance error and the remapping activity for each neuron. If remapping activity for the population of intermediate SC neurons were related to performance, then the distribution of r values would be shifted away from zero.

We did the trial-by-trial analysis in two ways. We first computed the r value using a combination of trials from both the within and across conditions. The combined trial-by-trial analysis measured differences in neural activity and behavior that could be observed in a single neuron between within and across conditions. In the second analysis, we computed the r value separately for the within and across conditions. This separated trial-by-trial analysis allowed us to detect a relationship between activity and behavior that is not simply due to overall differences between within and across remapping.

In the following sections we compare neuronal activity to the accuracy of the second saccade during the double-step task. We perform two trial-by-trial analyses for the intermediate layers of the SC, area LIP and the superficial layers of the SC. As a control, we compare neuronal activity to accuracy during a memory guided saccade task. Finally, we use the same analyses to compare neuronal activity in relation to the saccade latency.

4.4.9 Correlation between double-step neuronal activity and behavioral accuracy for all trials.

In our first analysis of the relation between behavioral performance and neuronal activity we combined trials from within and across conditions of the double-step task. We found that there was a trend for the distribution of r values to be shifted negatively in the intermediate layers of the SC in the split brain monkey. The shift, however, was not significant (Fig. 37A, mean r=-.12, p=.06, sign test). A negative shift means that there was on average a negative correlation between neural activity on a given trial and the distance error on that trial. When the firing rate was higher, the distance error was lower. In other words, with higher firing rate, the monkey was more accurate. In the intact animal, we found no shift in the distribution of r values (Fig.

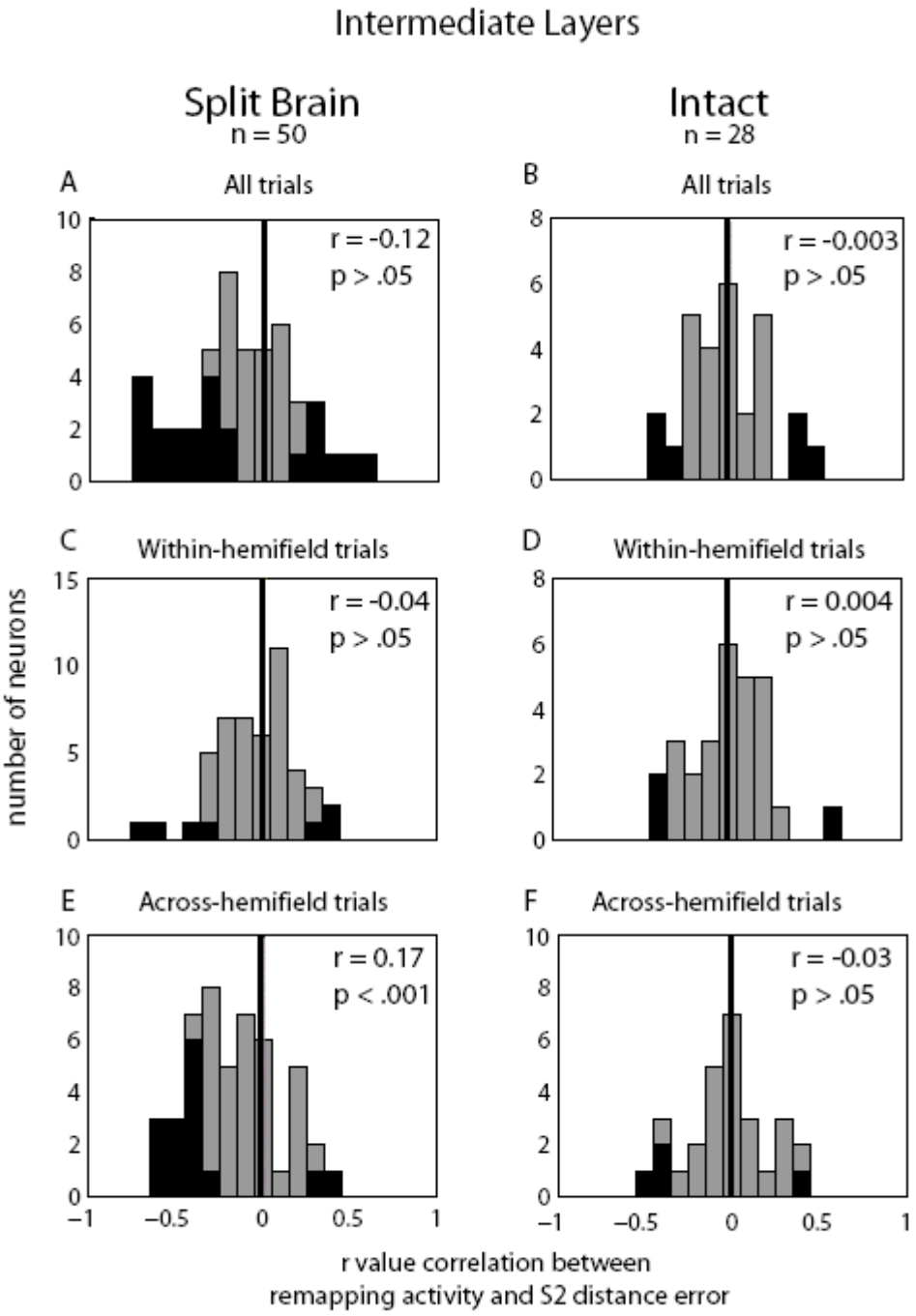


Figure 37. Trial-by-trial analysis for intermediate layers: relationship between remapping activity and S2 distance error.

Panels show the distribution of r values for the trial-by-trial correlation between remapping activity from the intermediate layers of the SC and the error of the second saccade. Left column: data from the split-brain monkeys. Right column: data from the intact monkey. Top row: data for all trials. Middle row: within-hemifield trial only. Bottom row: Across-hemifield trials only. Vertical line indicates zero. Negative values indicate that with greater remapping activity there is less error.

37B, mean r=-.003, p=.58, sign test). An equal number of cells had positive and negative r values.

The trend observed in the intermediate layers of the SC was more pronounced in previous results obtained from LIP (Berman et al. 2007). We re-analyzed a subset of the LIP data; we included only LIP neurons that had significant remapping in at least one of the remapping conditions. In area LIP, the distribution of WA index values was significantly shifted from zero (Fig. 38A, mean r=-.10, p<.01, sign test). Across the population, 30% of the neurons had a significant correlation between remapping activity and error rate (Fig. 38A, shaded in black). For the majority of these neurons the correlation was negative (31/39). This finding demonstrates that there is a small but significant relationship between firing rate in LIP and the performance of the monkey on the double-step task. However, this result could also reflect differences between the within and across conditions already observed. If there were a true relationship between activity in area LIP and performance, then we would expect to see this relationship independent of the conditional differences (within vs. across trials). We therefore carried out a second analysis where differences between conditions would not be a factor.

4.4.10 Correlation between double-step neuronal activity and behavioral accuracy separated for within and across trials.

In the second analysis, we separated the within and across trials. We calculated a separate correlation coefficient for each trial type. If there were a true relationship between firing rate and performance, then we should have observed a significant shift in the r distributions for each condition. We found no significant relationship between remapping activity in LIP and accuracy of the performance when the conditions were analyzed separately (within, Fig. 38C, mean r=-.01,

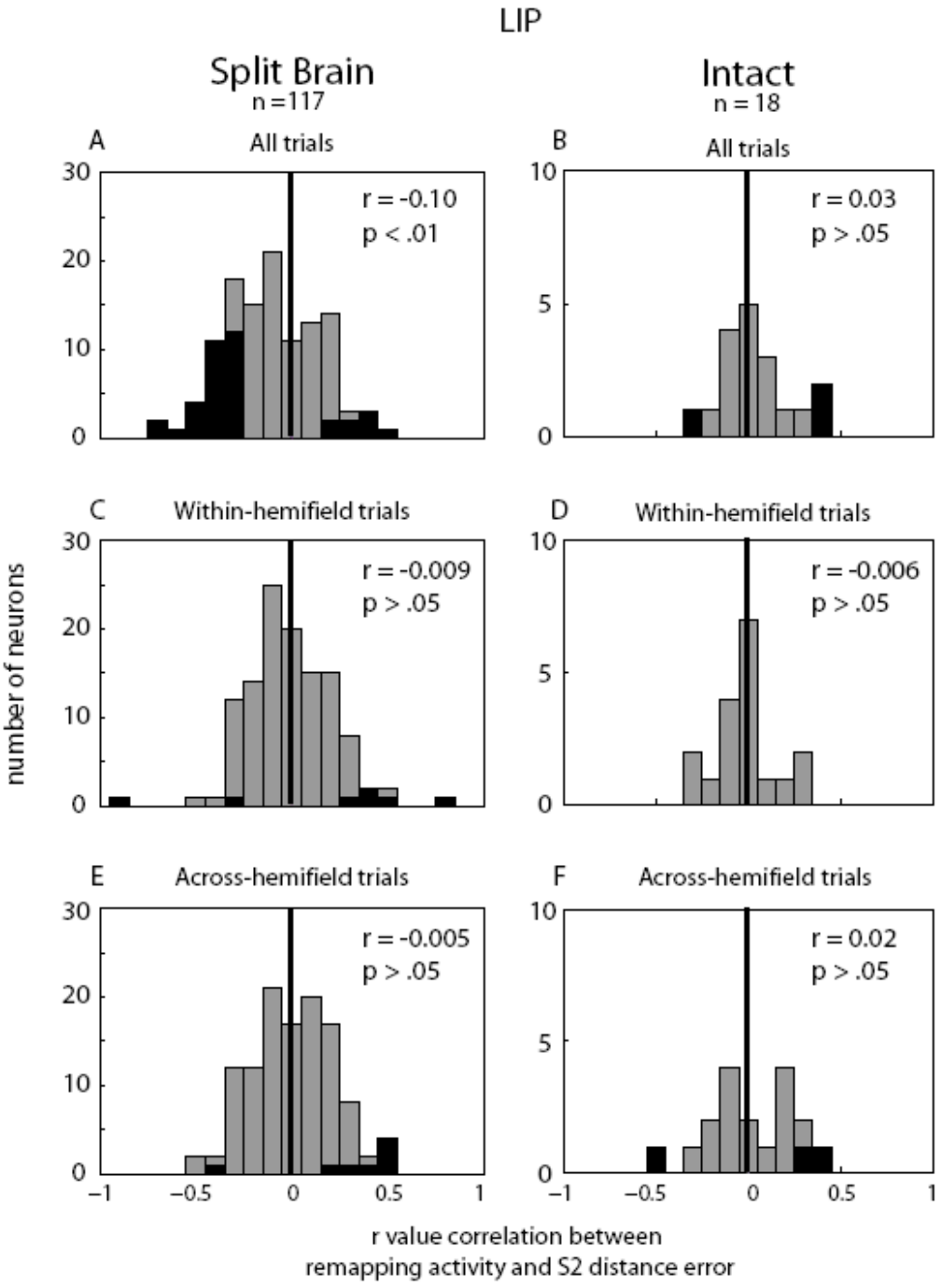


Figure 38. Trial-by-trial analysis for LIP: relationship between remapping activity and S2 distance error.

Panels show the distribution of r values for the trial-by-trial correlation between remapping activity from the LIP and the error of the second saccade. Left column: data from the split-brain monkeys. Right column: data from the intact monkey. Top row: data for all trials. Middle row: within-hemifield trial only. Bottom row: Across-hemifield trials only. Vertical line indicates zero. Negative values indicate that with greater remapping activity there is less error.

p=.60; across, Fig. 38E, mean r= 0.006, p=.85, sign test). In other words, once the conditional differences were removed, there was no relationship. We also found no relationship between firing rate and performance on a trial-by-trial basis in the intact animal. This was true for both the combined and separated data sets. When the within and across conditions were combined, the distribution was not significantly different from zero (Fig. 38B, mean r=.04, p>.05, sign test). One reason for the absence of a significant result in the intact monkey could be due to a lack of variability in accuracy. When the monkey is performing the task correctly there is very little variability in the performance. It is only with greater variability, as is the case for the split brain monkey's performance, that a relationship can be detected.

We analyzed the intermediate layers of the SC separately for the within and across conditions. While we found no relationship between firing rate and accuracy for the within trials, we did find a relationship for the across trials. The r distribution for the across trials was significantly shifted towards the negative (Fig. 37E, mean r=-.17, p<.0001, sign test). On a trial-by-trial basis, if the firing rate was higher, the monkey was more accurate. This relationship was not present in the intact monkey (Fig. 37F, mean r=-.03, p=.57, sign test). In sum, when the forebrain commissures are transected, a higher firing rate in the intermediate layers of the SC tends to correlate with improved performance.

4.4.11 Correlation between memory guided saccade neuronal activity and behavioral accuracy.

Before we can accept that there is a relationship between remapping activity in the SC and the behavior of the monkey, we must first consider an alternative explanation. The SC is known for its role in saccadic eye movements. Most SC neurons fire when a saccade is made into the

receptive field. The second saccade of the double-step task is, by design, always into the receptive field of the neuron. It is thus possible that some of the activity measured in the double-step task is due to the eye movement, and not due to remapping. In order to test this possibility we added a new control task in which the monkey made a memory guided saccade into the receptive field (see Methods). Orbital position effects were an additional concern. It is known that the position of the eye in the orbit can modulate the neuronal activity in many brain areas, including the SC (Van Opstal et al., 1995; Campos et al., 2006). To eliminate potential orbital position effects, we matched the memory guide saccade task configuration to the double-step configuration. During this memory guided saccade task, the monkey initially fixated at the double-step T1 location. The stimulus was flashed at the double-step T2 location. In both the double-step task and the memory guided saccade task, the monkey thus made a saccade from the T1 location to the remembered T2 location. We measured neural activity and distance error.

We looked for a correlation between distance error and memory guided saccade activity for each neuron recorded in the split brain monkeys. We found no relationship between firing rate and the performance of the monkey. This lack of correlation was found both when the within and across trials were combined (Fig. 39A, mean r= .04, p=.19, sign test) and when they were separated (within, Fig. 39C, mean r=-.04, p=.06; across, Fig. 39E, mean r=.05, p=.47, sign test). The results from this control task tell us that the relationship we did observe between remapping activity and performance on the across condition of the double-step task cannot be due to saccade activity alone. If it were due to the eye movement alone, we would have seen a correlation between performance and firing rate in the memory guided saccade task. The finding that there is no correlation between activity and distance error during the memory guided saccade

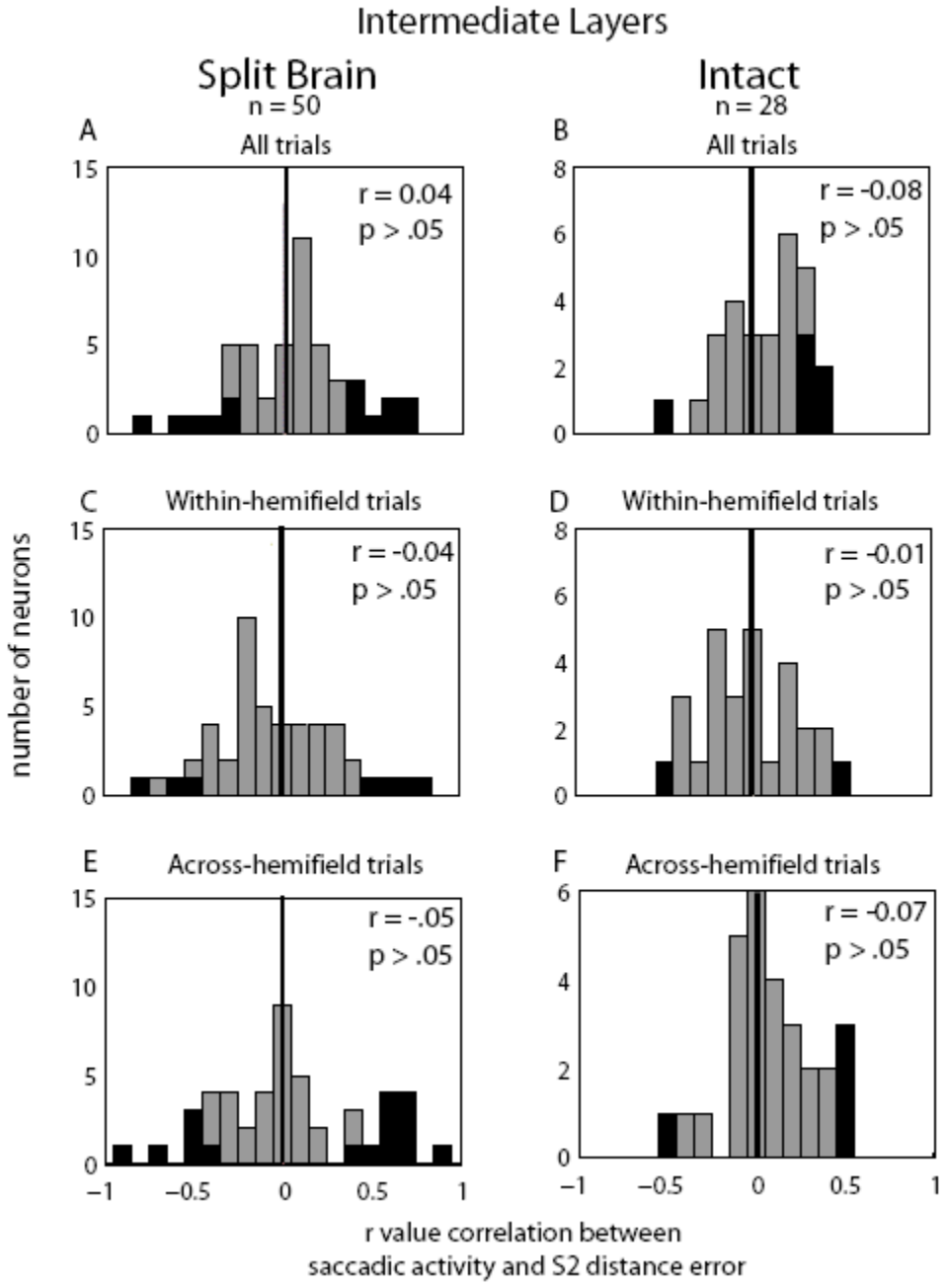


Figure 39. Trial-by-trial analysis for intermediate layers: relationship between saccadic activity and S2 distance error.

Panels show the distribution of r values for the trial-by-trial correlation between activity measured during the memory guide saccade task from T1 to T2 and the error of the second saccade. Recording were conducted in the intermediate layers of the SC. Left column: data from the split-brain monkeys. Right column: data from the intact monkey. Top row: data for all trials. Middle row: within-hemifield trial only. Bottom row: Across-hemifield trials only. Vertical line indicates zero. Negative values indicate that with greater saccade activity there is less error.

task supports the idea that when the primary pathway between the hemispheres is disrupted, the SC plays a role in behavior on the double-step task.

In the superficial layers of the SC, we found no difference in the magnitude of response for within and across conditions. We thus expected to find no relationship between neural activity and behavior on a trial-by-trial basis. Our expectations were confirmed when the trials for within and across conditions were combined. We found that the distribution of r values was not significantly shifted from zero for the split brain monkey (Fig. 40A, mean r=.-11, p=.34, sign test). When we separated the analysis for within and across conditions, we found that there was a significant shift for the within conditions but not for across (Fig. 40C and E within: mean r=-17, p=.04; across: mean r= -.13, p=.18, sign test). We also found a significant relationship between neural activity and behavior for the within only conditions for the MGS analysis (Fig. 41C, mean r=.12, p=.04). This relationship was in the opposite directions as the relationship between neural activity and behavior for the double-step task. We found no significant shift for intact monkey for both the combined and separated analysis (Fig. 40B, D, F and 16B, D, F).

4.4.12 Correlation between double-step neuronal activity and saccade latency.

We used a second behavioral measure, latency of the second saccade, to examine the relationship between remapping activity and performance. We calculated the relationship in two ways. First, we combined trials from both the within and across conditions. In the second analysis, we separated trials by condition. In the intermediate layers of the SC of the split brain monkey, we found a significant relationship only when the across trials were analyzed separately (Fig. 42E mean r=0.07,p=0.01, sign test). The population was significantly shifted toward the positive; when the firing rate was higher, the latencies were longer. In the intact monkey, we found a

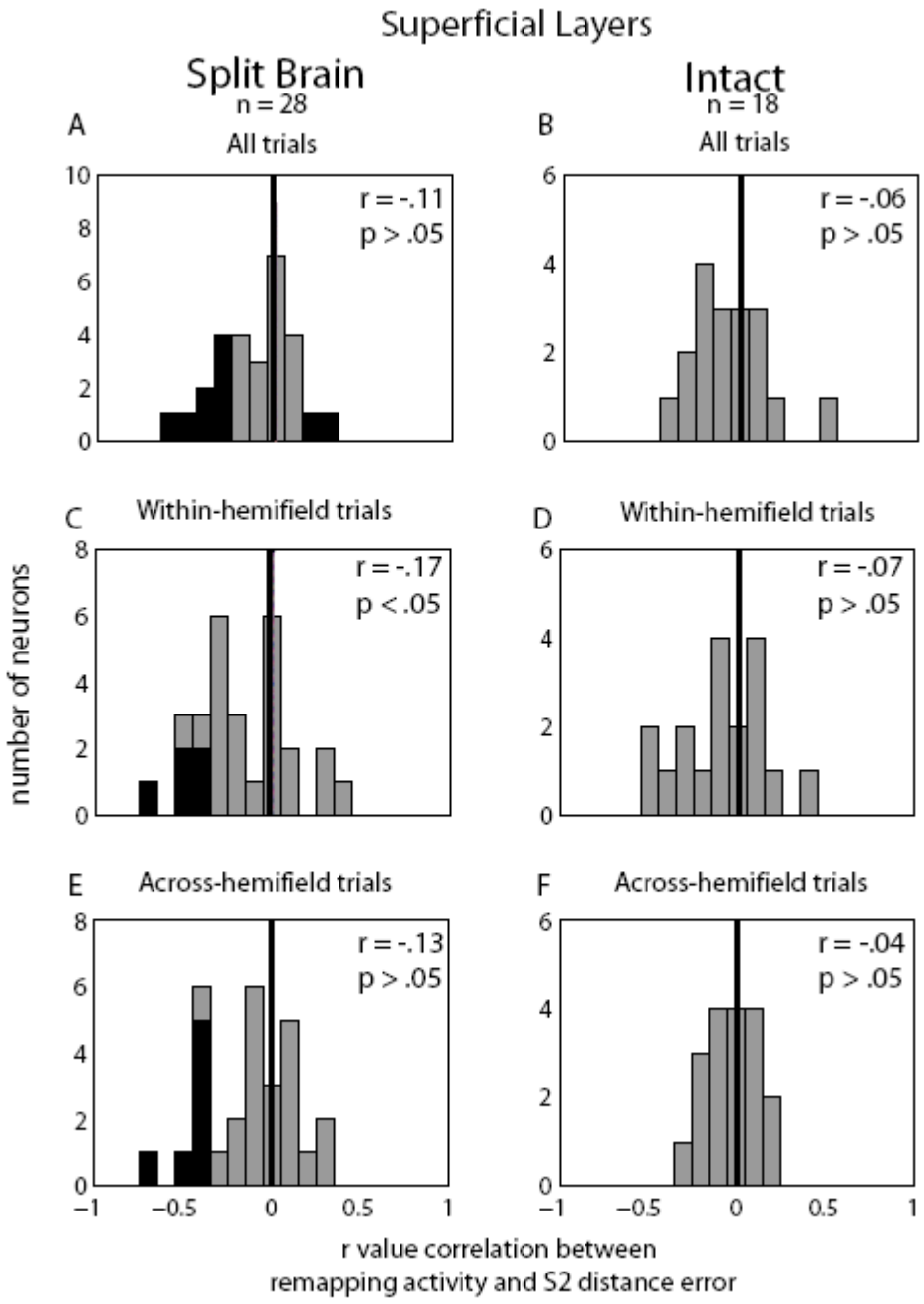


Figure 40. Trial-by-trial analysis for superficial layers: relationship between remapping activity and S2 distance error.

Panels show the distribution of r values for the trial-by-trial correlation between remapping activity from the superficial layers of the SC and the error of the second saccade. Left column: data from the split-brain monkeys. Right column: data from the intact monkey. Top row: data for all trials. Middle row: within-hemifield trial only. Bottom row: Across-hemifield trials only. Vertical line indicates zero. Negative values indicate that with greater remapping activity there is less error.

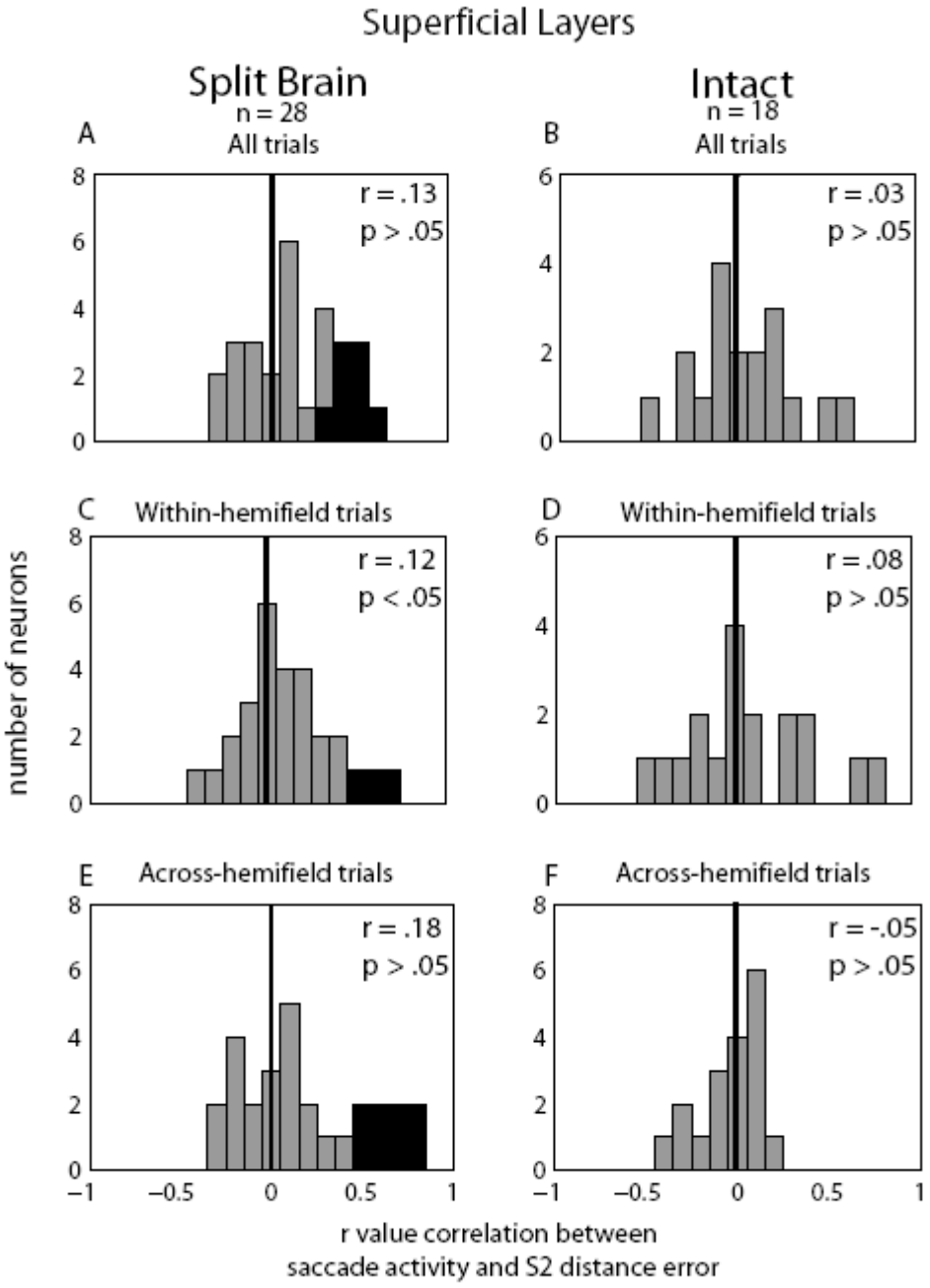


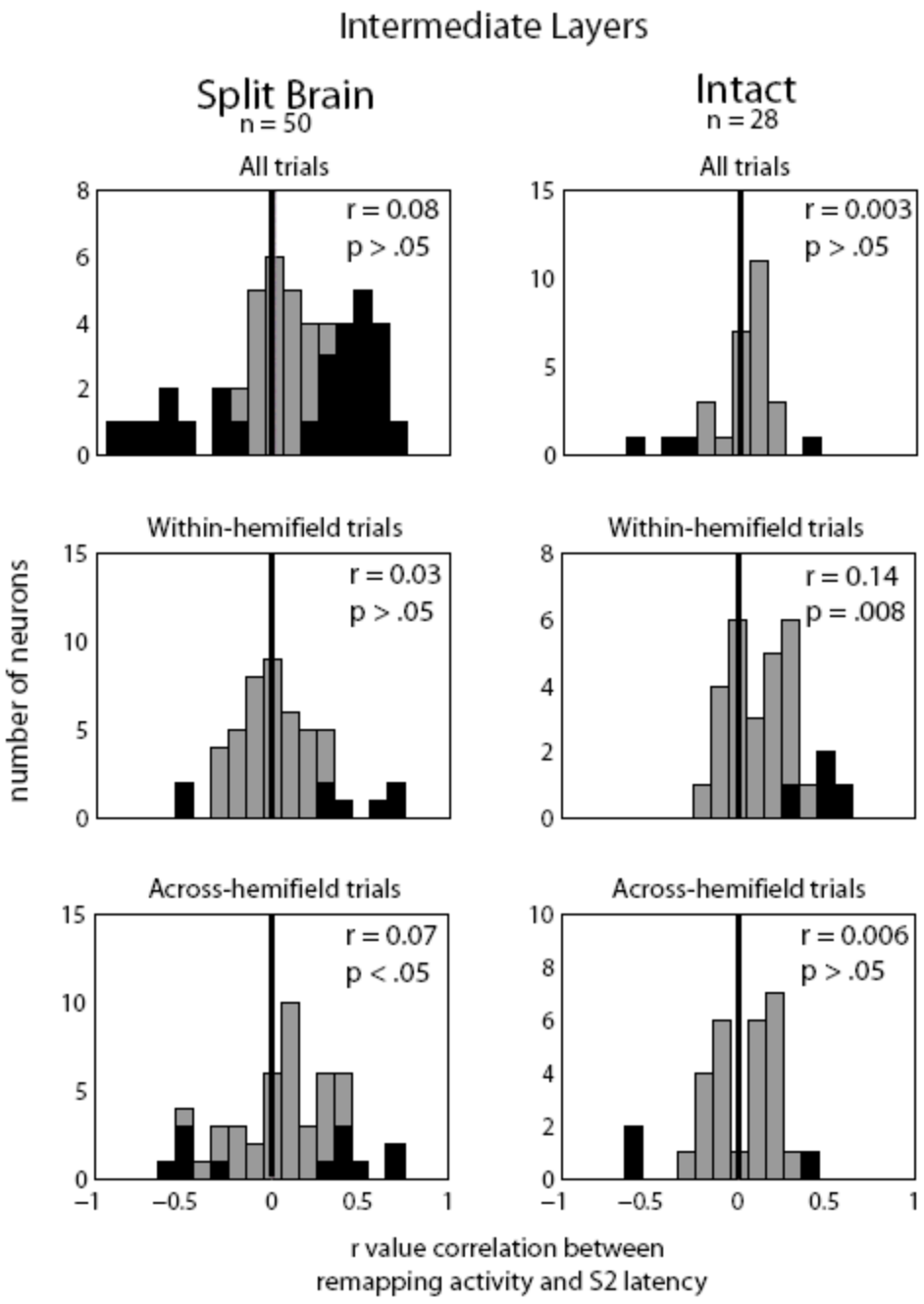
Figure 41. Trial-by-trial analysis for superficial layers: relationship between saccade activity and S2 distance error.

Panels show the distribution of r values for the trial-by-trial correlation between activity measured during the memory guide saccade task from T1 to T2 and the error of the second saccade. Recording were conducted in the superficial layers of the SC. Left column: data from the split-brain monkeys. Right column: data from the intact monkey. Top row: data for all trials. Middle row: within-hemifield trial only. Bottom row: Across-hemifield trials only. Vertical line indicates zero. Negative values indicate that with greater saccade activity there is less error.

significant relationship only when the within trials were analyzed separately (Fig. 42D mean r=.14, p=.008). We also found a significant difference between neural activity and saccade latency in the memory guided saccade task for the within only conditions (Fig. 43D, mean r=-0.12, p=.008). Once again this relationship for the memory guided saccade task was in the opposite direction as the relationship for the double-step task.

In area LIP, we found that there was a relationship only when the trials were combined for the within and across conditions (Fig. 44A mean r=0.07, p<.001, sign test). The positive relationship indicates that second saccade latencies were longer when there was more neural activity. When the trials were separated by condition, no relationship was present (within: Fig. 44C, mean r=0.02, p>.05; across: Fig. 44E, mean r=0.05, p>0.05, sign test). There was also no relationship between remapping activity and saccade latency for the intact monkey (Fig. 44B, D, F).

In the superficial layers of the SC we found that there was a significant relationship between remapping activity and saccade latency when the trials were combined for within and across and when the trials were separated. When the trials were combined, the relationship was shifted towards the positive; with higher firing rate, there were longer saccade latencies (Fig. 45A, mean r=0.18, p<0.001, sign test). When the trials were separated, there were significant positive relationships for both within and across conditions (within: Fig. 45C, mean r=0.17, p<0.01; across: Fig. 45E, mean r=0.21, p<0.001, sign test). We found no relationship between remapping activity in the superficial layers of the SC and saccade latency for the intact monkey (Fig. 45 B, D, F). We also found no relationship for activity recorded from neurons in the superficial layers of the SC during the MGS task and saccade latency. This is true for both the split brain and intact monkeys (Fig. 21). Therefore the relationship observed between remapping



Fiugre 42. Trial-by-trial analysis for intermediate layers: relationship between remapping activity and S2 latency.

Panels show the distribution of r values for the trial-by-trial correlation between remapping activity from the intermediate layers of the SC and the latency of the second saccade. Left column: data from the split-brain monkeys. Right column: data from the intact monkey. Top row: data for all trials. Middle row: within-hemifield trial only. Bottom row: Across-hemifield trials only. Vertical line indicates zero. Negative values indicate that with greater remapping activity there are faster saccades.

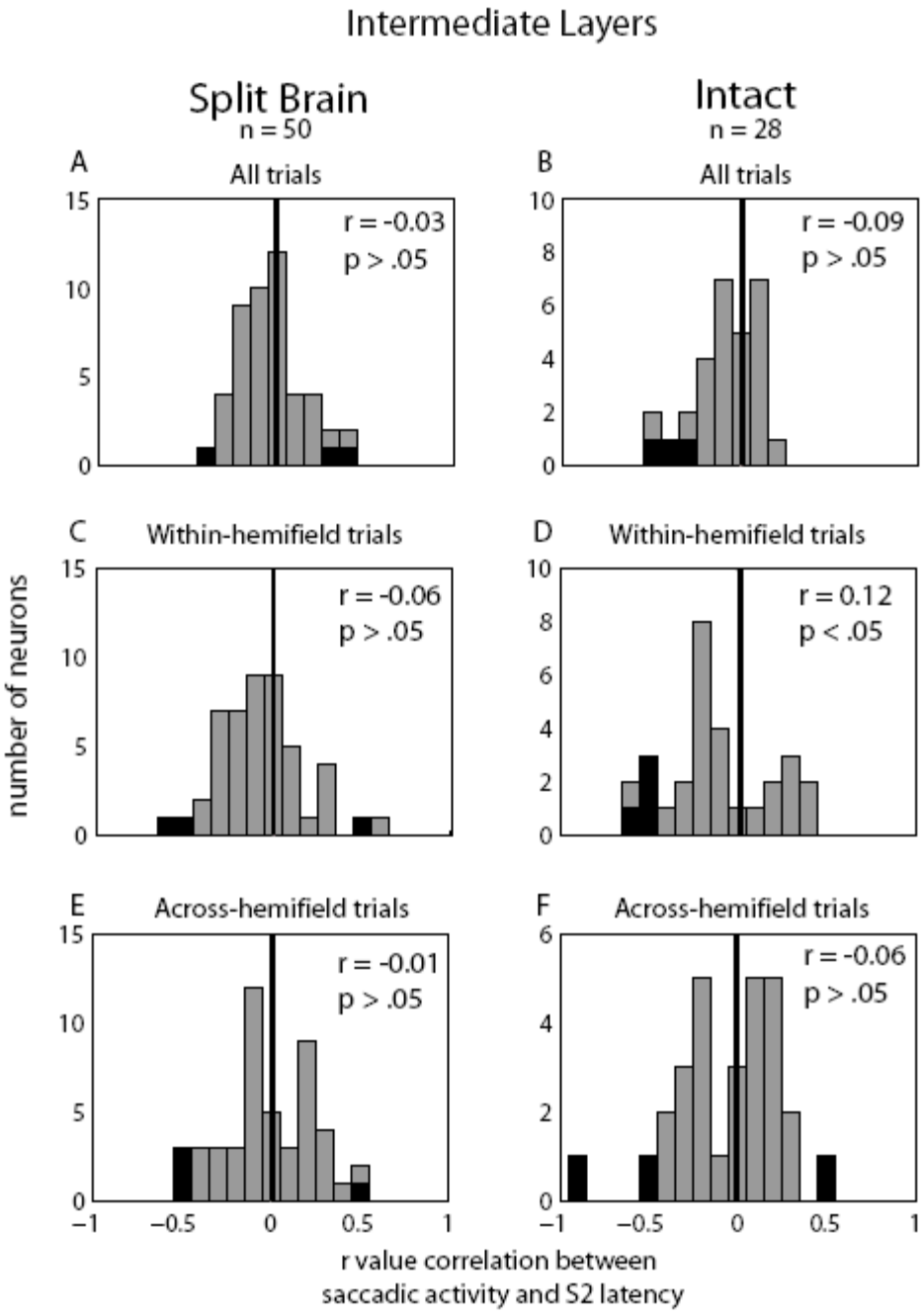


Figure 43. Trial-by-trial analysis for intermediate layers: relationship between saccadic activity and S2 latency.

Panels show the distribution of r values for the trial-by-trial correlation between saccadic activity from the intermediate layers of the SC and the latency of the second saccade. Left column: data from the split-brain monkeys. Right column: data from the intact monkey. Top row: data for all trials. Middle row: within-hemifield trial only. Bottom row: Across-hemifield trials only. Vertical line indicates zero. Negative values indicate that with greater saccadic activity there are faster saccades.

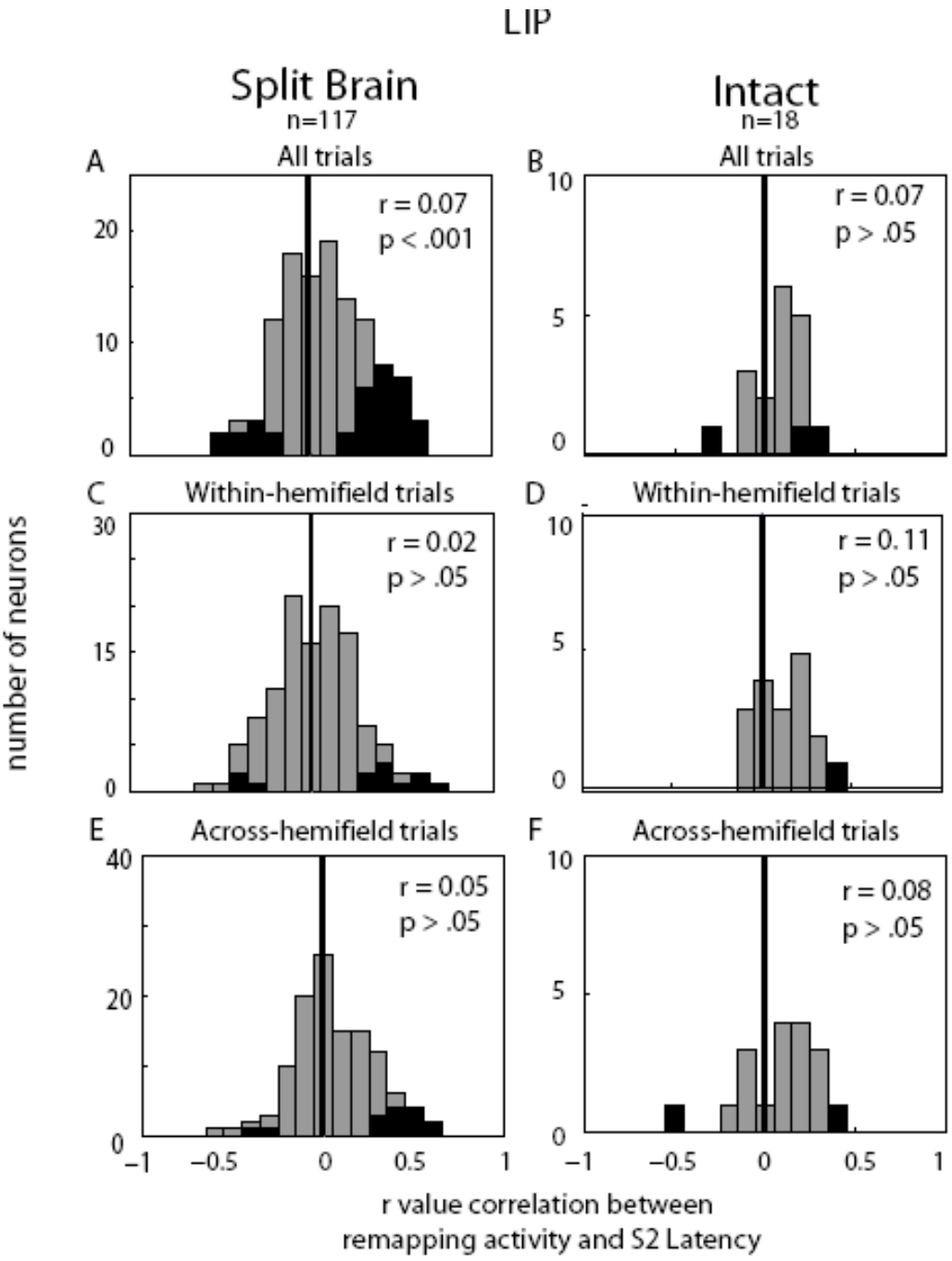


Figure 44. Trial-by-trial analysis for LIP: relationship between remapping activity and S2 latency.

Panels show the distribution of r values for the trial-by-trial correlation between remapping activity from LIP and the latency second saccade. Left column: data from the split-brain monkeys. Right column: data from the intact monkey. Top row: data for all trials. Middle row: within-hemifield trial only. Bottom row: Across-hemifield trials only. Vertical line indicates zero. Negative values indicate that with greater remapping activity there are faster saccades.

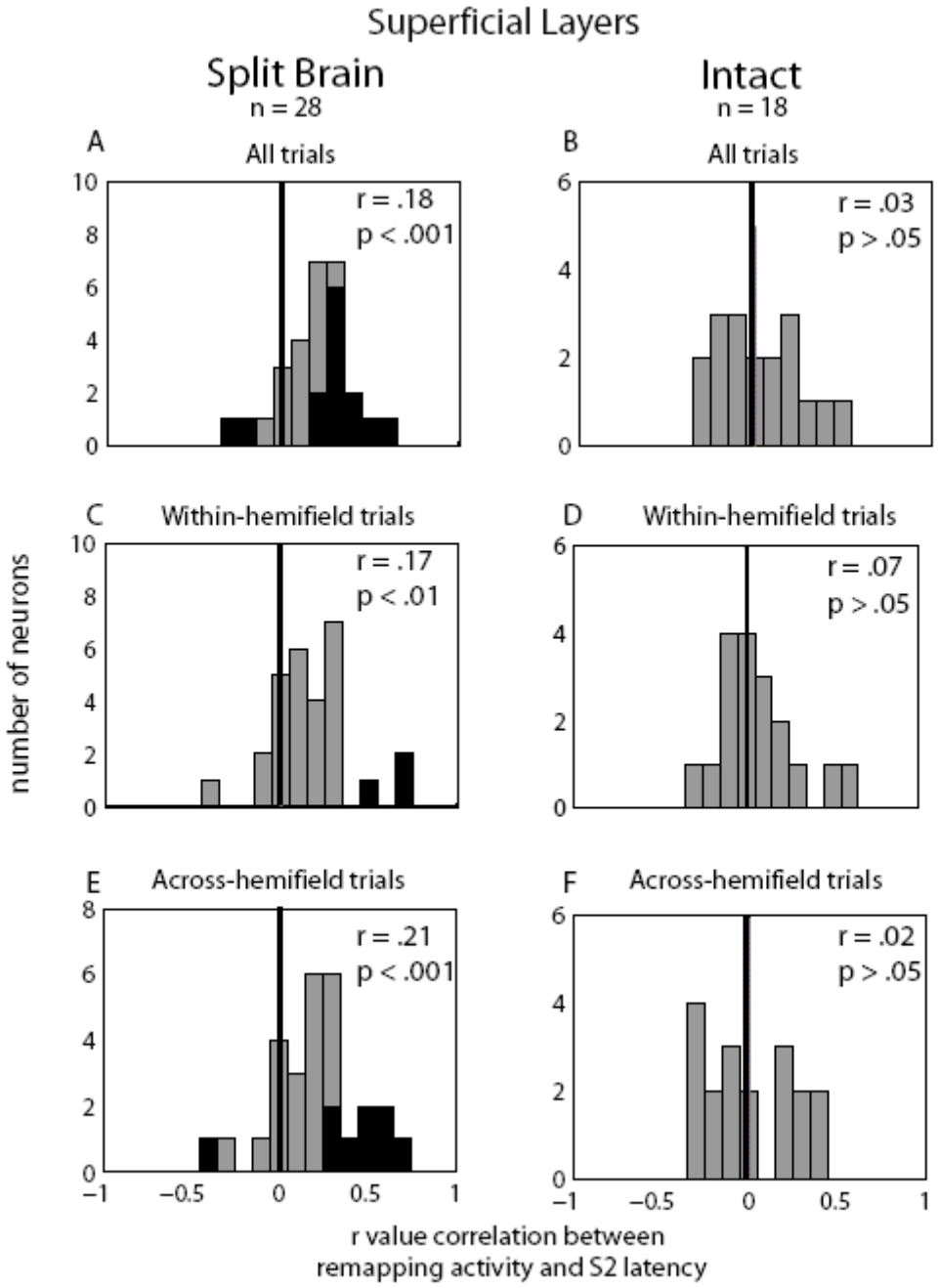


Figure 45. Trial-by-trial analysis for superficial layers: relationship between remapping activity and S2 latency.

Panels show the distribution of r values for the trial-by-trial correlation between remapping activity from the superficial layers of the SC and the error of the second saccade. Left column: data from the split-brain monkeys. Right column: data from the intact monkey. Top row: data for all trials. Middle row: within-hemifield trial only. Bottom row: Across-hemifield trials only. Vertical line indicates zero. Negative values indicate that with greater remapping activity there are faster saccades.

activity and saccade latency in the split brain monkey cannot be due saccade related activity alone.

The results from the trial-by-trial analyses are summarized in Table 2. For area LIP, we found a relationship between remapping activity and performance on the double-step task only when within and across trials were combined. This was the case for two measures of performance: accuracy and latency of the second saccade. There was no relationship when the conditions were analyzed separately. For the intermediate layers of the SC, we found a relationship for both measures of performance and remapping activity only when the across trials were analyzed separately. Finally, for the superficial layers of the SC, we found a relationship between saccade latency and remapping activity when the within and across trials were combined, as well as when they were separated.

Table 2. Trial by trial correlation between of behavior and neuronal activity

	Split-Brain	Intact
Distance error compared to remapping activity		
Superficial SC	Negative correlation: within trials only	None
Intermediate SC	Negative correlation: across trials only	None
LIP	Negative correlation: combined trials only	None
Distance error compared to MGS activity		
Superficial SC	Positive correlation: within trials only	None
Intermediate SC	None	None
LIP	None	None
Second saccade latency compared to remapping activity		
Superficial SC	Positive correlation: combined and separated trials	None
Intermediate SC	Positive correlation: across trials only	Positive correlation: within trials only
LIP	Positive correlation: combined trials only	None
Second saccade latency compared to MGS activity		
Superficial SC	None	None
Intermediate SC	None	Negative correlation: within trials only
LIP	None	None

4.5 DISCUSSION

To maintain visual stability, visual information must be updated with every eye movement. The neural circuits that underlie spatial updating remain unknown (Berman and Colby, 2009). In previous studies, we investigated the mechanism for updating visual information from one visual field to the other (Berman et al., 2005; Heiser et al., 2005; Berman et al., 2007b). We transected the forebrain commissures and expected to find that remapping would be abolished when memory traces had to be remapped across the vertical meridian. Instead we found that neurons in area LIP are capable of remapping memory traces across hemifields even in the absence of the forebrain commissures. In the current study, we asked whether there was remapping in a subcortical structure, the SC, in the split brain monkeys.

We have five main findings. First, neurons in the superficial and intermediate layers of the SC are capable of remapping visual information both when it remains within and when it is transferred across hemifields. Second, remapping differed in the intermediate and superficial layers. In the intermediate layers of the split brain monkey, remapping across hemifields was reduced compared to remapping within a hemifield. In contrast, in the superficial layers of the split brain monkey, magnitude of remapping was similar for within and across-hemifields. Third, in the double step task, the split brain monkeys were more inaccurate and had longer saccade latencies in the across-hemifield. Fourth, the accuracy of performance in the double-step task was correlated with the activity of neurons in the intermediate layers of the SC in the across-hemifield trials. In the superficial layers, accuracy was correlated with activity for within-hemifield trials during the double-step task and the memory guided saccade task. Fifth, the latency of the second saccade was correlated with activity of neurons intermediate layers of the SC in the across-hemifield trials. In the superficial layers, activity was correlated with the

latency of the second saccade for both within and across trials. We conclude that remapping is present in the SC in the split brain monkey. Activity in the SC may be the source of the preserved remapping in area LIP in the split brain animals.

4.5.1 Previous studies on remapping in SC

Two previous studies have shown that neurons in the SC are capable of remapping. The phenomenon was first described by Mays and Sparks (1980). They found "quasi-visual cells" that fired during the double-step task, even when there was no visual stimulus inside the RF of the neuron. The activity of these quasi-visual cells matches the remapping activity we observe in the single-step and double-step tasks. While the exact depth of these neurons was not reported, it was stated that the cells were located either just above or at the level at which neurons with saccade related activity were found. These cells may have been located in both the superficial and intermediate layers of the SC. Remapping in the SC in single-step task was first shown by Walker et al. (1995). They found remapping in both the superficial and intermediate layers. In contrast to the present results they did not observe predictive remapping in the superficial layers. Our present study additionally demonstrated that this remapping activity was present even in the absence of the forebrain commissures.

4.5.2 Neural circuits for remapping observed in the intermediate layers of the SC: corticotectal and tectocortical pathways

We found that in the split brain monkey, remapping activity in the intermediate layers of the SC resembles remapping activity in area LIP. For both brain regions, across-hemifield remapping is

attenuated compared to within-hemifield remapping. Across-hemifield remapping is also delayed compared to within-hemifield remapping. It could have been the case that amplitude and latency of remapping were unaffected by the transection of the forebrain commissures. The fact that we found reductions in across-hemifield remapping in SC implies that the remapped signal in the intermediate layers reflects cortical inputs. LIP has direct projections to the intermediate layers of the SC (Pare and Wurtz, 1997; Leichnetz, 2001; Pare and Wurtz, 2001; Ferraina et al., 2002; Lynch and Tian, 2005). Based on these anatomical connections and the similarity in remapping activity it is possible that remapping activity is passed from LIP to the intermediate layers of the SC.

The reverse relationship may also exist. Activity in the SC could influence activity in cortex through a multisynaptic pathway. The SC does not project directly to any cortical area; the thalamus relays information from the SC to cortex. LIP has reciprocal connections with the pulvinar (Benevento and Rezak, 1976; Leichnetz, 2001). Clower and colleagues (2001) found that the majority of the disynaptic connections to LIP through thalamic areas originate in the ipsilateral superficial layers of the SC. However, approximately 15% of cells labeled from the LIP injection were found in the intermediate layers. Some of the cells that project from the intermediate layers of the SC to area LIP could potential provide a remapping signal.

In addition to the pathway from the SC to the pulvinar to area LIP, the SC projects to several other thalamic nuclei. The intermediate layers project to the central lateral nucleus and medial dorsal nucleus (Huerta and Harting, 1984; May, 2005). These thalamic areas project to other cortical areas, which in turn project to area LIP. For example the medial dorsal (MD) nucleus project to area FEF, which in turn projects to area LIP (Petrides and Pandya, 1984; Andersen et al., 1990a; Schall et al., 1995b; Stanton et al., 1995; Bullier et al., 1996; Chafee and

Goldman-Rakic, 1998, 2000; Sommer and Wurtz, 2000, 2004a). While multiple signals are passed from the SC through MD to the FEF, Sommer and Wurtz (2004) concluded that presaccadic activity was particularly important. The authors further concluded that the presaccadic activity from the SC is an ideal candidate for a corollary discharge signal. Corollary discharge, a copy of the motor command to move the eyes, is the signal that is presumed to initiate the updating of visual representations. While a corollary discharge signal is important for remapping, it is not in itself a remapping signal. In addition to presaccadic activity, Sommer and Wurtz (2004), also demonstrated that visual, delay period and motor signals were also transferred to FEF from the SC. While they did not directly test for a remapped signal, it is possible that remapping activity is transferred from the SC through MD to the FEF. From the FEF, activity could be passed to LIP.

If activity is transferred from the SC to the cortex, then it seems reasonable to assume that at least some neurons in the intermediate layers of the SC are capable of remapping independent of the cortex. These neurons would then either be able to remap information between the two colliculi, or there could be another subcortical source of remapping.

4.5.3 Connections between the two colliculi.

Each colliculus represents the contralateral visual field in a retinotopically organized map (Cynader and Berman, 1972). For a neuron to show remapping activity during the across condition it must receive information from the ipsilateral visual field. It could be that information passes from one colliculus to the other through the intertectal commissure (Edwards, 1977; Yamasaki et al., 1984; Behan and Kime, 1996b; Olivier et al., 1998; Olivier et al., 2000; Tardif and Clarke, 2002). Early studies of the intertectal commissures focused on reciprocal

inhibitory connections between the two colliculi (Edwards, 1977). Physiological studies demonstrated that as activity increased in one colliculus, activity in the other colliculus decreased (Munoz and Istvan, 1998).

Anatomical studies have confirmed the presence of inhibitory connections but also revealed the presence of excitatory connections (Behan and Kime, 1996a, b; Olivier et al., 1998; Olivier et al., 2000). Tectotectal neurons are a morphologically heterogenous population, with a similar distribution of GABAergic and glutaminergic cell types (Moschovakis et al., 1988; Lee et al., 2001; Lee and Hall, 2006). Tectotectal neurons are present throughout the mediolateral and rostrocaudal extent of the SC (Olivier et al., 1998). Most tectotectal cells are located in the intermediate layers. Only about 15% of the tectotectal cells were located in the superficial layers of the colliculi, while most tectotectal cells were located in the more intermediate layers (Olivier et al., 1998). These tectotectal connections presumably allow communication between the two colliculi. This communication can occur for both the superficial and intermediate layers. The presence of these connections leaves open the possibility that the intertectal commissure is a pathway for remapping activity.

4.5.4 Other pathways for subcortical remapping.

The results from the original split brain study in LIP implicated the involvement of a sub-cortical pathway. In the current study, we examined the possibility that the superior colliculus was part of the subcortical pathway. There are other potential pathways. The intertectal commissure contains fibers that connect the two colliculi as well as other subcortical structures (Antonetty and Webster, 1975; Edwards, 1975, 1977; Jayaraman et al., 1977; Wallace et al., 1989, 1990). For example, many studies have demonstrated that the projections from the substantia nigra par

reticulate (SNr) to the SC are important for visual orienting and saccadic eye movements (Hikosaka and Wurtz, 1983b, a; Wallace et al., 1989, 1990; Basso et al., 2005; Basso and Liu, 2007; Liu and Basso, 2008). While it is thought that the main role of the SNr is to provide an inhibitory signal to the SC, the potential role of the SNr in remapping has not been explored.

A second potential subcortical pathway involves the cerebellum. Visual information is transferred from cortical visual areas and the SC to the pontine nuclei (Baker et al., 1976; Glickstein et al., 1980; Mower et al., 1980). The pontine nuclei project to the cerebellum (Mower et al., 1980). The cerebellum then projects back to the deeper layers of the superior colliculus (Huerta and Harting, 1984). The role of the cerebellum in remapping has yet to be examined. Visual information may be transferred within the cerebellum. The remapped signal could then be transferred to the SC and/or to cortical areas.

4.5.5 Neural circuits for remapping observed in the superficial layers of the SC: corticotectal and tectocortical pathways

In the superficial layers of the SC, remapping in the split brains was the same as in the intact animals. For both sets of animals, the magnitude and latency of the remapped response were similar for the within-hemifield and across-hemifield conditions. The results from the superficial layers contrast with those from the intermediate layers and area LIP results. We conclude that the circuitry underlying remapping in the superficial layers is different from circuitry that produces remapping in the intermediate layers.

While our results indicate that the circuitry for remapping in the superficial layers is different from the intermediate layers, we cannot claim that no cortical area influences the activity in the superficial layers. The superficial layers receive projections from striate and

prestriate visual cortex, as well as the FEF (Schiller et al., 1974; Finlay et al., 1976; Wurtz and Albano, 1980; Fries, 1984; Huerta and Harting, 1984; Distler and Hoffmann, 2001; May, 2005). We have data from only one cortical area, area LIP, to compare to the results from the SC. Potentially other cortical areas influence the SC, and that these cortical areas exhibit no difference between within and across-hemifield remapping in the split brain animals.

If neurons in superficial layers do remap independent of the cortex, then they must either pass information between the two colliculi, or there must be another sub-cortical source of remapping. As discussed above, the two colliculi are connected by the intertectal commissure. Through this pathway, visual information could be transferred across hemifields. However, these intertectal connections would not suffice for remapping to occur in the superficial layers. Remapping also requires information about the saccade, in other words, a corollary discharge signal. The superficial layers are purely visual; the neurons do not encode saccades. The intermediate layers, however, do have saccade related activity. It is possible that a corollary discharge signal is passed from the intermediate layers to the superficial layers.

4.5.6 Connections between intermediate and superficial layers

Connections from intermediate layers to superficial layers have been demonstrated in rats, cats and humans (Yamasaki et al., 1984; Isa, 2002; Tardif et al., 2005). One proposed function of these connections is a pathway for suppression of activity around the time of a saccade (Lee et al., 2007). The activity of many superficial cells is suppressed during saccades (Goldberg and Wurtz, 1972; Robinson and Wurtz, 1976). Studies in rat slices indentified inhibitory cells that project from the intermediate layers to superficial layers (Lee et al., 2007). These experiments were done in GAD67-GFP knockin mice. In other words, the experiment was restricted to

inhibitory cells alone. It remains unknown if there are excitatory connections from the intermediate to superficial layers, and what role those connections could play. The projections from the intermediate layers to the superficial layers may provide a corollary discharge signal.

4.5.7 Remapping activity and the behavior of the monkey

Many brain areas have neurons capable of remapping (Berman and Colby, 2009). How these areas interact to contribute to behavior remains unknown. We addressed this question by recording from neurons in area LIP and the SC while split brain and intact monkeys performed the double-step task. Previous studies have found a relationship between neural activity in the SC and performance in the double-step task (Lunenburger et al., 2003; Reyes-Puerta et al., 2009). Lunenburger and colleagues found a difference between SC neurons that are active during fixation, and SC neurons active during saccades. For the saccadic neurons, the neural latency was related to the time of the second saccade in the double-step task. The activity in the fixation neurons was unrelated to the time of the second saccade. Activity in fixation neurons were influenced by the predictability of the double-step task (Reyes-Puerta et al., 2009). In the current study, we did not record from fixation related neurons. We restricted our analysis to neurons with remapping activity.

We found that for the intermediate layers, there was a positive correlation between remapping activity and performance only for the across conditions. There are two possible explanations for a significant response only for the across trials. First, the monkeys' performance on the across conditions was less accurate. From trial to trial, there was more variability in saccade end points. Because there was greater variability, a relationship could be more easily detected. Second, it is possible that when the primary pathway that connects the two

cortical hemispheres is removed, activity in a sub-cortical structure becomes more important for the behavior of the monkey. It may be that accurate performance depends on precise integration of remapping signals from many brain areas. This integration process is undoubtedly affected when the forebrain commissures are transected. In order for the monkey to behavior accurately, the brain may have to recalculate the integration process, relying more on information from the SC.

In the superficial layers of the SC we found a significant relationship between remapping activity and latency of the second saccade. When the neurons fired more, the saccade latency was shorter. This relationship held when the within and across conditions were combined and when the conditions were separated. This increase of activity with shorter saccades suggests that activity builds to a threshold before a saccade is initiated. When activity reaches the threshold sooner, the saccade occurs sooner. What is remarkable about the relationship between activity of superficial layers and saccade latency is that neurons in the superficial layers of the SC are thought to be purely visual (Wurtz and Mohler, 1976). This correlation between neuronal activity and saccade latency in superficial layers of the SC of the split brain monkeys is further evidence that when the forebrain commissures are transected, remapping activity in the SC becomes more important for behavior.

We conclude that there is across-hemifield remapping in the intermediate and superficial layers of the SC in the split brain monkey. This SC activity may be a source of the across-hemifield remapping in area LIP in the split brain monkey. The remapping activity in that the intermediate layers of the SC is influenced by the remapping activity received from cortex. In contrast, the superficial layers of the SC appear to remap independent of area LIP. Either the remapping activity originates within the superficial layers of the SC or the information comes

from another subcortical source. This study also suggests that when information in cortical areas is impaired, the control over the behavior of the monkey is modified. Remapping activity from the SC appears to contribute more to the control of behavior in the absence of the forebrain commissures.

5.0 GENERAL DISCUSSION

The purpose of these experiments was to examine different mechanism of spatial updating in monkeys when the forebrain commissures have been transected. We had three specific aims. In the first aim, we asked if there was a relationship between neural activity in LIP and the behavior of the monkey. We addressed this question by recording from LIP neurons while the monkeys performed a task that depends on accurate spatial updating, the double-step task. We found that across the population, there was a small but significant relationship between the activity in LIP and the behavior of the split brain monkey. This result showed that information about the opposite visual field still reaches LIP, and this activity contributes to the overall behavior of the monkey. One possible explanation for the observed across-hemifield remapping is that information from both the ipsilateral and contralateral visual fields are represented in a single hemisphere. In normal animals, a small population of LIP neurons has bilateral receptive fields. This led to the question asked in the second aim.

Do LIP neurons in split brain monkeys have bilateral receptive fields? We recorded from LIP neurons in both intact and split brain monkeys while they performed a receptive field mapping task. We found no neurons in the split brain monkeys with ipsilateral representations. We concluded that there must be a subcortical source for the across-hemifield remapping observed in the split brain monkeys.

In the final aim, we examined remapping activity in the superficial and intermediate layers of the SC in intact and split brain monkeys. We found that activity in the intermediate layers of the SC in split brain monkey was different from remapping activity in the intact monkey. The activity in the intermediate layers of the SC resembled the observed activity in the LIP of the split brain monkeys. This finding suggests that remapping activity is passed from LIP to the intermediate layers of the SC. In contrast, remapping activity in the superficial layers of the SC did not differ between the intact and split brain monkeys. This suggests that the source of remapping is different for the intermediate and superficial layers of the SC. It may be that the superficial layer neurons are the source of the across-hemifield remapping in LIP observed in the split brain monkeys.

5.1 CIRCUITRY OF REMAPPING

Remapping activity has been measured in multiple areas, yet how these areas interact and their roles in remapping remain unknown. There must be at least two pathways that contribute to remapping. One pathway that provides a motor signal and a second pathway that provides a visual signal. It is only in an area where these signals converge that remapping can originate.

5.1.1 Pathways for motor information required for remapping

One potential source of a motor signal for remapping is a corollary discharge signal. Corollary discharge is a copy of motor command that moves the eye. Based on monkey physiology studies, the frontal eye fields (FEF) is part of a pathway that carries a corollary discharge signal

(Sommer and Wurtz, 2002, 2004a, b, 2006). Sommer and Wurtz demonstrated that a corollary discharge signal is transmitted from the intermediate layers of the SC to FEF through the medial dorsal thalamus (MD)(Fig. 46).

Multiple signals are passed to the FEF from the SC via the thalamus. Sommer and Wurtz concluded that presaccadic activity was particularly important (2004a). The majority of the neurons in the pathway contained presaccadic information, and the signal is unchanged throughout the pathway. The importance of the presaccadic activity is even more pronounced when compared to the other signals. Visual signals from the SC arrive at the FEF after signal from extrastriate visual cortex, limiting their influence. Activity during a memory delay period is drastically decreased in the MD neurons compared to the SC neurons, sending only a small amount of information to the FEF. Based on the signals sent to FEF, Sommer and Wurtz concluded that the activity from the SC is an ideal candidate for a corollary discharge signal.

To test their conclusion, Sommer and Wurtz interfered with SC-MD-FEF pathway hoping to affect the corollary discharge signal (2004b; 2006). Sommer and Wurtz shut down the pathway by inactivating MD using muscimol, a $GABA_A$ agonist. The authors found both saccade accuracy and precision deficits in the second saccade of the double-step task due to inactivation of the MD. This behavioral finding demonstrates that SC-MD-FEF pathway provides a signal required for accurate spatial updating. Does this pathway also play a role in remapping activity in FEF? Yes, inactivation of MD results in a decrease of on average 50% of the remapping activity in FEF neurons. The behavioral and physiology studies indicate that a corollary discharge signal is sent to the cortex from the SC and this signal is necessary for accurate spatial updating and remapping activity.

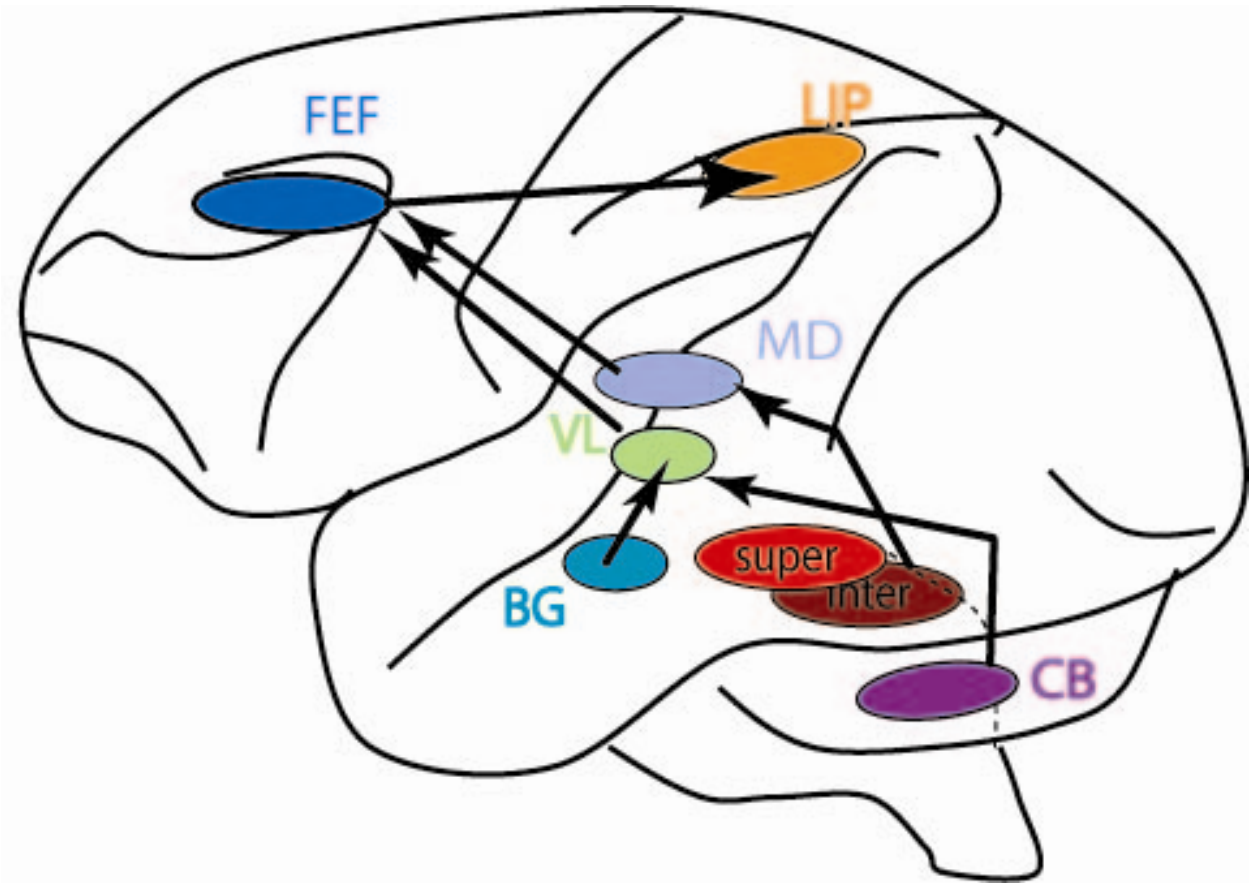


Figure 46. Possible pathways for motor signals required for remapping.

Lateral view of a macaque brain. Arrow represents possible projections that carry a corollary discharge signal. BG, Basal Ganglia. CB, cerebellum. FEF, frontal eye fields. LIP, lateral intraparietal cortex. MD, medial dorsal thalamus, Super, superficial layers of the superior colliculus. Inter, intermediate layers of the superior colliculus. VL, ventral lateral thalamus.

The corollary discharge signal could be transferred from area FEF to other cortical areas. LIP and FEF are two highly interconnected areas. Important for corollary discharge are the connections from FEF to LIP. There is some evidence for segregation of FEF signals to LIP (Stanton et al., 1995). Areas of the FEF with large saccades project mainly to the superficial part of LIP. While the area with smaller saccades project to the deeper lateral wall of the intraparietal suclus. However, there appears to be no relationship between the saccade amplitudes of the projecting FEF neurons and the receptive field size and location of the LIP neurons (Bruce et al., 1985; Stanton et al., 1995) This fits with the concept that FEF is sending corollary discharge signals. The LIP would need information about all saccade amplitudes, not just amplitudes that match their RF. Heiser and Colby found that while not all single neuron have remapping activity for all saccade directions, the majority of the neuron do have activity for more than one direction (2006). The neuron must receive information about multiple saccades.

The SC and FEF primarily encode saccade made into the contralateral visual field (Wurtz and Goldberg, 1971, 1972; Sparks and Mays, 1980; Bruce and Goldberg, 1985; Bruce et al., 1985; Schall, 1991; Schall et al., 1995a). Neurons in LIP are capable of remapping for multiple saccade direction, even when the saccade direction is ipsilateral (Heiser and Colby, 2006). Are the forebrain commissures necessary for the transfer of corollary discharge signals during remapping? Berman and colleagues addressed this question by testing split brain monkeys on two conditions of the double-step task (Colby et al., 2005). The corollary discharge signal either remained within one hemifield, or had to be transferred across hemispheres. For both conditions, the transfer of visual information remained within one hemifield. The authors expected that the monkey would be inaccurate during the corollary discharge across-hemifield condition, parallel to the finding for the visual across-hemifield condition. However, they found that the monkeys

were able to perform both when the corollary discharge signal remained within and was transferred across hemifields. The lack of impairment suggests that the forebrain commissures are not the primary pathway for the transmission of the corollary discharge signal.

The finding from the split brain monkey study is consistent with human split brain studies and recent monkey physiology studies (Holtzman, 1984; Hughes et al., 1992; Crapse and Sommer, 2009). Split brain humans are capable of generating ipsilateral and contralateral eye movement by either hemisphere. Additionally, hemispherectomy patients are capable of making eye movements in both directions (Sharpe et al., 1979). One possible explanation for the representation of ipsilateral saccade is a transfer of information from subcortical structure. Crapse and Sommer found that there are cross connections from the SC to FEF. A neuron in FEF that receives connections from the opposite SC has ipsilateral receptive fields. This provides a pathway independent of the forebrain commissures. The combination of human split brain studies and monkey physiology studies suggest that information about saccades is represented in both hemispheres.

The SC-MD-FEF is an important pathway for remapping; it provides information about the upcoming eye movement. However, it may not be the only pathway that provides motor information. The deficits observed by Sommer and Wurtz were only partial (2002; 2004b; 2006). The authors proposed four possible explanations for the partial deficits. First, the inactivation of MD may not have been complete. Intact portions of the MD may relay corollary discharge information. Second, corollary discharge may be transferred from the SC through alternative thalamic structures. Third, the corollary discharge signal originated in the cortex. FEF neurons have similar response properties of SC neurons. When a lesion is made in the superior colliculus, eye movements are impaired (Schiller et al., 1974; Schiller et al., 1979;

Schiller et al., 1987). However, within weeks monkeys recover. Even with the lesion in the SC, monkeys are able to make corrective saccades after by stimulation to FEF causes an intervening eye movement (Schiller and Sandell, 1983). This indicates that the FEF has access to corollary discharge signals independent of the SC. This is a possible explanation for the parietal deficit. A fourth explanation is that the monkey uses signals other that corollary discharge to guide behavior, for example proprioceptive information about eye position.

On potential alternate pathway for corollary discharge originates in the cerebellum (Sommer, 2003). The output of the cerebellum is relayed to motor cortex through the ventral thalamus (Glickstein, 2000; Middleton and Strick, 2000a). The vermal lobules VIc and VII of the cerebellum are important for accurate saccadic eye movement (Fujikado and Noda, 1987; Noda and Fujikado, 1987a, b). The area has been designated the oculomotor vermis. Low level stimulation in the area evokes saccades. Cells in the oculomotor vermis project to cells in the fastigial oculomotor region (FOR), which in turn transmit information to the saccadic nuclei of the brain stem (Ohtsuka and Noda, 1990, 1991a, b). Through this pathway the cerebellum can influences saccade generation. A copy of motor command that is relayed through the FOR may be passed to cortex through the ventral thalamus (Fig. 46). The role of the cerebellum-thalamus needs to be further examined to determine if it is an alternate source of a corollary discharge signal.

A second alternative pathway originates in the basal ganglia (Sommer, 2003). The globus pallidus internal segment (GPi) and the substania nigra pars reticulate (SNr) send inhibitory projections to the thalamus (Fig. 46). The thalamus, in turn, projects to cortical areas including area FEF (Middleton and Strick, 1994, 1996, 2000b, a, 2002). SNr cells also have inhibitory projections to the SC. In order for a saccade to occur, the SNr must be inhibited.

However, inhibition of the SC may not be the only role of the SNr. Response properties of the SNr neurons are diverse. Some neurons decrease their activity in response to a visual stimulus, some neurons decrease their activity around the time of an eye movement and some neurons will increase their activity instead (Hikosaka and Wurtz, 1983b, c; Handel and Glimcher, 2000; Basso and Wurtz, 2002; Sato and Hikosaka, 2002). The neuronal properties of the SNr-thalamus-FEF pathway are unknown. Further studies need to be conducted to determine if it is a possible pathway for a corollary discharge signal.

5.1.2 Pathways for visual information required for remapping

There are many potential source of the motor signal required for remapping. What about the visual signal? Visual information is transmitted from the retina through the lateral geniculate nucleus to primary visual areas (Fig. 47). From striate cortex, visual information is further transmitted to both parietal and dorsal frontal cortex.

Early lesions studies in humans indicate that the parietal cortex is a critical brain area for spatial updating (Duhamel et al., 1992c; Heide et al., 1995a; Heide and Kompf, 1998). Patients with parietal damage have difficulty performing the double-step task when the second saccade is made to a remembered target. Once the first saccade is made, the position of the second target relative to eye in the orbit has shifted. Accurate performance depends on the patient's ability to update the representation, taking the first eye movement into account. Patients with parietal damage do not update their representations and make an inaccurate second saccade. This impairment is not a simple motor deficiency. The patients can perform the double-step task if the second target remains on. In contrast to patients with parietal damage, patients with damage to the frontal lobe cannot perform the double-step task even when the second saccade can be

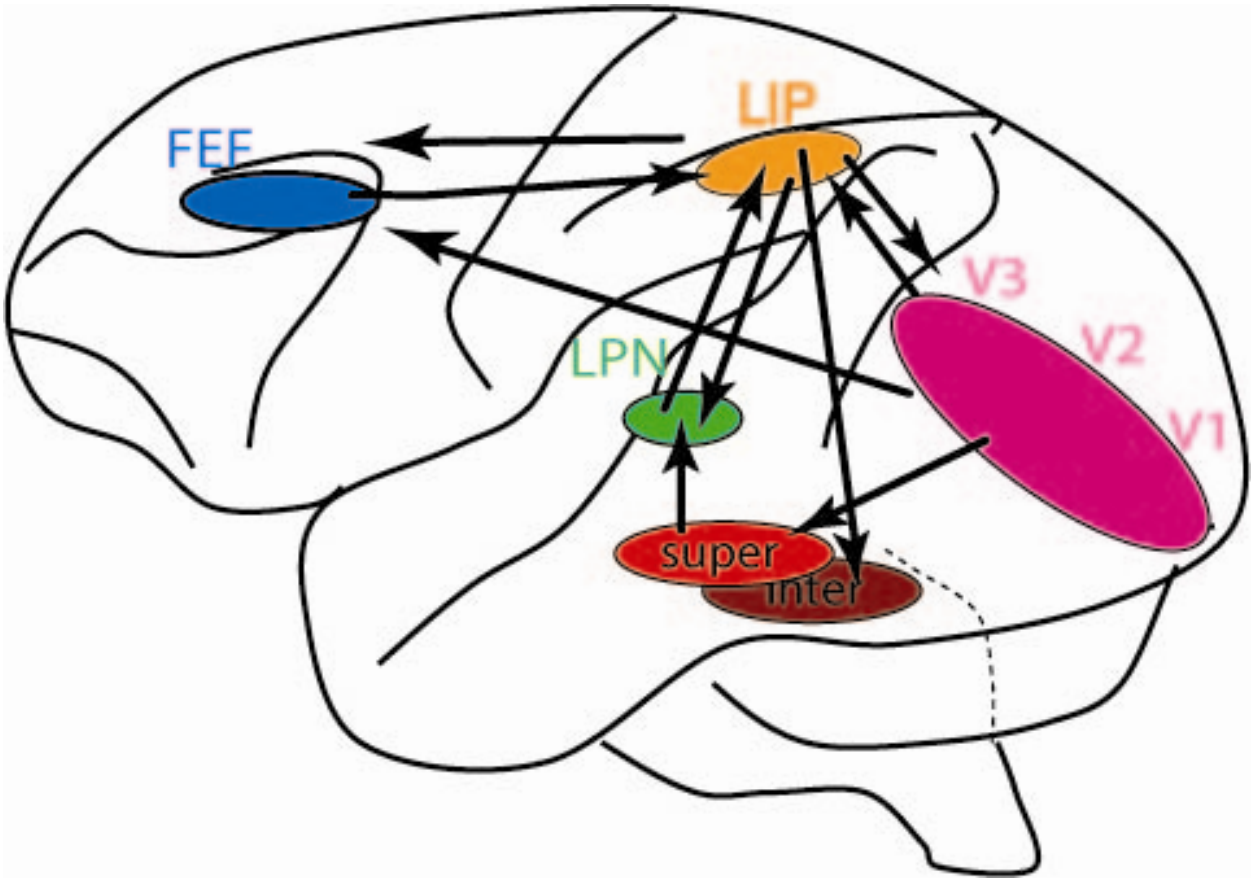


Figure 47. Possible pathways for visual signals required for remapping.

Lateral view of a macaque brain. Arrow represents possible projections that carry a visual or remapping signal. FEF, frontal eye fields. LIP, lateral intraparietal cortex. LPN, lateral pulvinar nucleus, Super, superficial layers of the superior colliculus. Inter, intermediate layers of the superior colliculus.

visually-guided (Heide et al., 1995a). This result for patients with frontal lobe damage suggests an inability to complete the double-step task independent of the need to spatially update. These studies do not eliminate the possibility that remapping activity originates in frontal areas. However, the difference between patients with parietal and frontal damage suggests that the two areas have different contributions to remapping.

Where remapping activity originates is unknown; however, it is unlikely that it originates in striate cortex. Neurons in V3, V2, V1 are capable of remapping (Nakamura and Colby, 2002). If we compare across areas, the proportion of neurons that remap decreases with each lower level. Additionally, the latency of remapping is much later in lower levels compared area LIP. These findings suggest that striate cortex is not the source of remapping, but receives information in a top-down fashion (Fig. 47).

Our current studies suggest that information is also passed from cortical areas to the intermediate layers of the SC. Remapping activity is altered in the intermediate layers of the SC in the split brain monkeys. The forebrain commissures connect the cortical hemispheres, directly affecting only activity in the cortex. Activity in the SC can only be altered if it is influenced by a cortical area.

An alternative pathway for the visual signal required for remapping is from the retina to the superficial layers of the SC. Tracer studies demonstrated that the neurons in the pulvinar that receives connects from the SC in turn connect to LIP (Hardy and Lynch, 1992; Clower et al., 2001). The functional significance of the SC-pulvinar-LIP pathway is unknown; however, based on the anatomy it appears to be visual in nature. As stated above, the superficial layer is the main source of input to LIP. The superficial layer contains mainly visual neuron, which have no presaccadic response. It is unknown if pulvinar neurons that are part of the SC to LIP pathway

differ in response properties compared to the rest of the pulvinar population. The population on a whole closely resembles LIP neurons (Bender, 1981). It has neurons that are purely visual, neurons with visual and memory signals, as well as activity around the time of the eye movement. Humans with damage to the pulvinar have deficits in visual attention and spatial cognition, similar to deficit due to damage in parietal cortex (Rafal and Posner, 1987). It may be that visual information is transferred from the SC to cortex. Once the visual signal arrives in a cortical area, it is then remapped. Our current study suggests another possibility. Neurons in the superficial layers of the SC are capable of remapping. In addition to a visual signal, a remapped signal may also be transmitted to area LIP from the SC via the pulvinar (Fig. 47).

It is also possible that the pulvinar is part of the circuitry of remapping independent of the superior colliculus (Fig. 47). Most of the inputs to the pulvinar are from cortical areas, and the only output of the pulvinar is back to cortex (Asanuma et al., 1985; Hardy and Lynch, 1992; Shipp, 2003). What is the function of the Pulvinar nucleus? One possibility is that the projections from cortex to the pulvinar back to cortex provides a redundant circuitry that mirrors existing projections from one cortical area to another. Shipp hypothesized that instead of simply duplicating the cortical circuitry, the thalamic circuitry help coordinate the transfer of information (2003). One potential mechanism for remapping is that neurons representing the salient location before the eye movement passes information to neurons representing the salient location after the eye movement. The cortical-pulivnar-cortical connections may facilitate this transfer.

FEF, LIP and the SC are all structures where motor signal and visual signals converge. It is possible that remapping activity originates in one of the areas. It is also possible that

remapping originates in these areas independently. Further studies are needed to understand how each brain area contributes to remapping.

5.2 REMAPPING AND PERCEPTION

5.2.1 Remapping and Change blindness

One hypothesis of spatial constancy is that visual representations are dynamically updated in conjunction with every eye movement. This hypothesis implies that the entire visual field is shifted when the eyes move. However, many studies suggest that our perception around the time of an eye movement is extremely limited. Human subjects have a difficult time detecting spatial displacement of a visual stimulus when it occurs during a saccade (Bridgeman et al., 1975; McConkie and Currie, 1996). Even more surprisingly, subjects fail to notice large changes to visual scenes if they occur during a saccade--a phenomenon known as change blindness (for review see: Henderson and Hollingworth, 1999; Simons and Rensink, 2005). For example, in one of the original studies, 50% of the subjects failed to notice when two cowboys sitting on a bench exchanged heads (Grimes, 1996). The concept of change blindness was further studied in the lab using a flicker paradigm (Rensink et al., 1997). In this paradigm, the subject observed alternating presentations of an original photograph of a scene, and a modified version that contained a change to the scene. In between each display a brief blank scene was presented. The observers eventually found the difference between the two scenes, yet took on average 17 alternations of the images. In some case it took more than 80 alternations.

The results from change blindness studies seem to contradict the concept that we maintain a stable percept by updating representations with each eye movement. One way to reconcile the change blindness and remapping findings is to consider the importance of attention. One of the main conclusions from change blindness studies is that in order to detect the change, attention is required. It is possible that we only update portions of the visual scene that are salient. In other words, remapping only occurs for objects that we attend.

5.2.2 Remapping and Attention

Physiological evidence supports the hypothesis that spatial updating occurs only for salient stimuli. In addition to its importance in spatial updating, LIP has also been implicated in the guidance of spatial attention. Multiple studies have demonstrated that visual responses in LIP were modulated when the stimulus was important for behavior (Robinson et al., 1978; Bushnell et al., 1981; Colby et al., 1996). This was the case even if no eye movement was made to the stimulus (Colby et al., 1996). Attentional modulation was easily shown by comparing activity of an LIP neuron in two tasks. In the first task, the monkey passively fixated while a stimulus was presented in the RF of the neuron (Fig. 48A). The stimulus was irrelevant to the animal's behavior, and therefore did not require spatial attention. In the second task, the monkey also fixated while a stimulus was presented in the RF (Fig. 48B). While the monkey fixated the stimulus dimmed slightly. The monkey had to respond to the dimmed stimulus by releasing a lever. In this task the stimulus was important, and therefore required spatial attention. Figure 48 shows an example LIP neuron recorded while the monkey performed each task. The neuron fired more during the peripheral attention task compared to the fixation task. This attentional modulation was a general characteristic of LIP neurons (Fig. 48C). The importance of area LIP

in attention has been confirmed by reversible inactivation studies and single-unit recording studies while monkeys performed tasks that require covert attention (Bisley and Goldberg, 2003; Wardak et al., 2004; Balan and Gottlieb, 2006; Bisley and Goldberg, 2006).

Attention not only modulates the activity of LIP neurons it is also necessary for remapping. In the standard remapping task, the single-step task, the flashed stimulus was

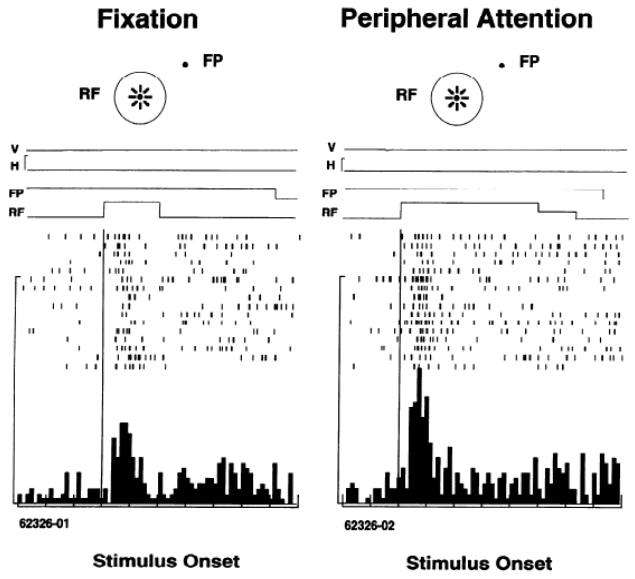


Figure 48. Attentional modulation in an LIP neurons of a behaviorally relevant stimulus.

The configuration of the task is represented at the top. The monkey fixates (FP) while a stimulus (asterisk) is presented in the receptive field (RF) of the neuron. The histograms and rasters are aligned on stimulus onset. The timing of the task is represented directly above the fasters. During the fixation tasks, the stimulus is turn on, then off again. In the peripheral attention task, the stimulus dims slightly. The dimming of the stimulus is a cue to the monkey to release a lever. When the stimulus becomes critical to the task, the firing rate of the LIP neuron increases. Adapted from Colby et al. 2006.

irrelevant to the monkey. The stimulus was never a target for behavior, however it does attract attention. Sudden stimulus onsets automatically attract attention through bottom-up mechanisms (Yantis and Jonides, 1984; Jonides and Yantis, 1988). In order to study the importance of attention to the process of remapping, Gottlieb and colleagues designed a new task (Gottlieb et al., 1998). In this task, a stable array of stimuli remained on the screen during the entire experiment. There was no sudden appearance of a stimulus. The monkey made an eye

movement so that the receptive field would land on one of the stable stimuli. The stimulus had no relevance to the monkey, and no sudden onset. Therefore the stimulus did not attract attention. Neurons in LIP did not remap during this stable array task. If the monkey's attention was directed towards the stimulus in the stable array, either by making it behaviorally relevant or by briefly flashing it, LIP neurons would showed remapping activity. These observations indicate that attention is a prerequisite for remapping.

5.2.3 Remapping and Mislocalization

As discussed above, subjects often fail to perceive changes to a visual scene around the time of an eye movement. Further studies in humans also indicate that if an object that is present around the time of an eye movement is perceived, the perception is often inaccurate. The types of error in perception can be classified into two categories. First, the visual space around the saccade target is compressed (Honda, 1989, 1991; Morrone et al., 1997; Ross et al., 1997; Burr et al., 2001). This compression occurs in the presence of visual references (Lappe et al., 2000). If the targets are flashed in the absence of visual reference the direction of the mislocalization depends on the timing (Honda, 1989, 1991; Dassonville et al., 1992; Schlag and Schlag-Rey, 1995, 2002). Second, targets flashed before or at the beginning of the saccade are mislocalized in the direction of the saccade. Targets flashed after the saccade are mislocalized in the opposite direction.

Can remapping activity explain the perceptual mislocalization around the time of an eye movement? There is one important property of remapping that indicates a relationship between neural activity and perceptual localization. The latency of remapping is highly variable. Some neurons remap before the saccade, some remap at or just after the saccade. Because of the variability in latency, some neurons can represent the target at the original location, and other

neurons can represent the target at the new location. This dual responsiveness can be demonstrated even in a single neuron. The timing of remapping has been examined in V3A, LIP and FEF neurons; an example V3A neuron is represented in Figure 49 (Nakamura and Colby, 2002; Kusunoki and Goldberg, 2003; Sommer and Wurtz, 2006). The top row of histograms represents the response of the neuron to a stimulus presented at four different time points in the

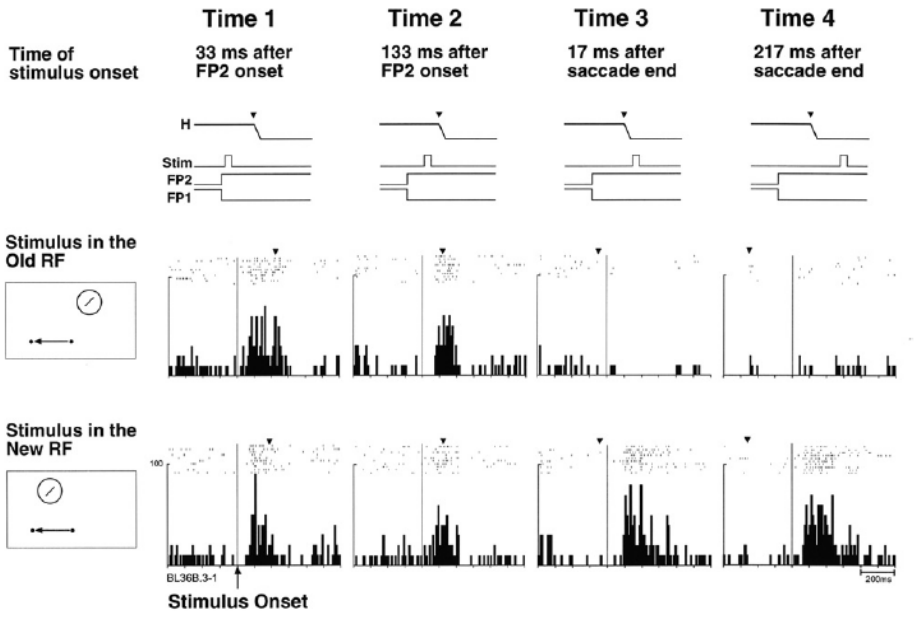


Figure 49. Timing of remapping in a V3A neuron.

The stimulus was presented at either the original "old " receptive field (middle panel), or at the new receptive field (bottom panel) at four different timings. Data are aligned on stimulus onset. The inverted triangle show the beginning of the saccade. The neuron responds to stimuli at the new RF long before the initiation of the saccade. Then neuron also responds simultaneously at the old receptive field. From Nakamura and Colby, 2002.

original RF ('old RF location'). The bottom row of histograms represents the response of the neuron to a stimulus presented at the location where the RF will be after the completion of the saccade ('new RF location'). The dual responsiveness is best illustrated at the second time point.

The neurons fire an equivalent amount when the stimulus is presented at the new or at the old RF. The benefit of remapping is that it provides an updated representation of the visual stimuli without the delay required if the brain had to rely only on a reafferent visual signal. This benefit may come at the expense of perceptual mislocalization of stimuli flashed briefly around the time of the saccade.

5.2.4 Summary

These experiments were designed to examine different mechanisms of spatial updating in monkeys when the forebrain commissures have been transcected. When the primary pathway through the forebrain commmissures is disrupted, alternative brain circuits can be utilized to control behavior. It is possible that these alternative circuits could control behavior independent of LIP, yet this is not the case. Even in the split brain monkey, remapping activity in LIP is significantly related to behavior. LIP activity also appears to affects remapping activity in other brain areas, specifically the intermediate layers of the SC. In contrast, activity in the superfical layers of the split brain monkey remain intact, and may be a source of across-hemifield activity in LIP.

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