REPRESENTATION OF OBJECT-CENTERED SPACE BY NEURONS OF THE SUPPLEMENTARY EYE FIELD

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The supplementary eye field (SEF) is a region of cortex located on the dorsomedial shoulder of the frontal lobe, considered to be involved in the control of eye movements. SEF neurons show spatially selective activity during visually- and memory-guided saccades. The selectivity exhibited by SEF neurons has been described as being related to an eye- or head-centered reference frame. We have previously shown that SEF neurons exhibit selectivity in an object-centered reference frame: neurons will fire selectively when saccades are directed to one end of a bar or another, irrespective of the absolute location of the bar in space.

It is not well known how SEF neurons display selectivity for object-centered locations. In order to better understand the mechanism of this phenomenon, we performed three studies. In the first study, we asked how SEF neurons encode locations in both egocentric and object-centered reference frames. We recorded from single SEF neurons while monkeys performed tasks requiring spatial representation in either eye-centered or object-centered reference frames. Different SEF neurons encoded locations in eye-centered coordinates only, object-centered coordinates only, or in complex combinations of the two.

In the second study, we tested whether object-centered selectivity is an innate property of SEF neurons or whether it is acquired through learning. We recorded the activity of SEF neurons before and after training monkeys to perform an object-centered task. Some SEF neurons exhibited object-centered selectivity before training. Following training, this number was increased, as was the intensity of object-centered spatial selectivity.

In the third study, we investigated whether the object-centered selectivity seen in SEF neurons during performance of an object-centered task is reduced during performance of a non-object-centered task. We recorded from SEF neurons while monkeys performed either an object-centered task or a color matching task with an object as a target. An equivalent number of neurons showed object-centered selectivity in both tasks, but the strength of selectivity was slightly higher during performance of the object-centered task. We conclude from the results of these studies that neurons in the SEF are critically involved in the dynamic representation of locations using multiple spatial reference frames.

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1. General Introduction

1.1. Spatial reference frames

1.1.1. What are spatial reference frames?

Visual perception and the accurate direction of behavior both rely upon the ability of the brain to represent locations in space. Critical to the representation of space is the reference frame used: the origin, axes, and boundaries relative to which positions in space are distributed. The brain does not represent locations in an absolute spatial reference frame. Rather, spatial reference frames must be defined in reference to something. For example, if I wish to reach for a cup of coffee that is located to the right, one of the first questions that must be addressed is "to the right of what?" The right could be described in multiple different reference frames: right relative to the direction of my gaze, relative to the position of my body, relative to the boundaries made by the perimeter of an object, or relative to the environment as a whole (Fig. 1A). More often than not these reference frames are not aligned, and the visuomotor systems of the brain must account for these differences in order to accurately locate an object and direct a behavior to it. A second example makes this clear. If my desk is to the right of my gaze but the coffee cup is on the left side of the desk, there is a dissimilarity between reference frames (Fig. 1B). In a reference frame related to the direction of my gaze, both the desk and the cup are to the right. In a reference frame related to the desk, however, the cup is on the left. If I am told to reach for the cup on the left, I will ignore the reference frame related to my gaze (since there are no cups to my gaze-related left), and select the cup on the left side of the desk, thereby using the reference frame centered on the desk: an object-centered reference frame.

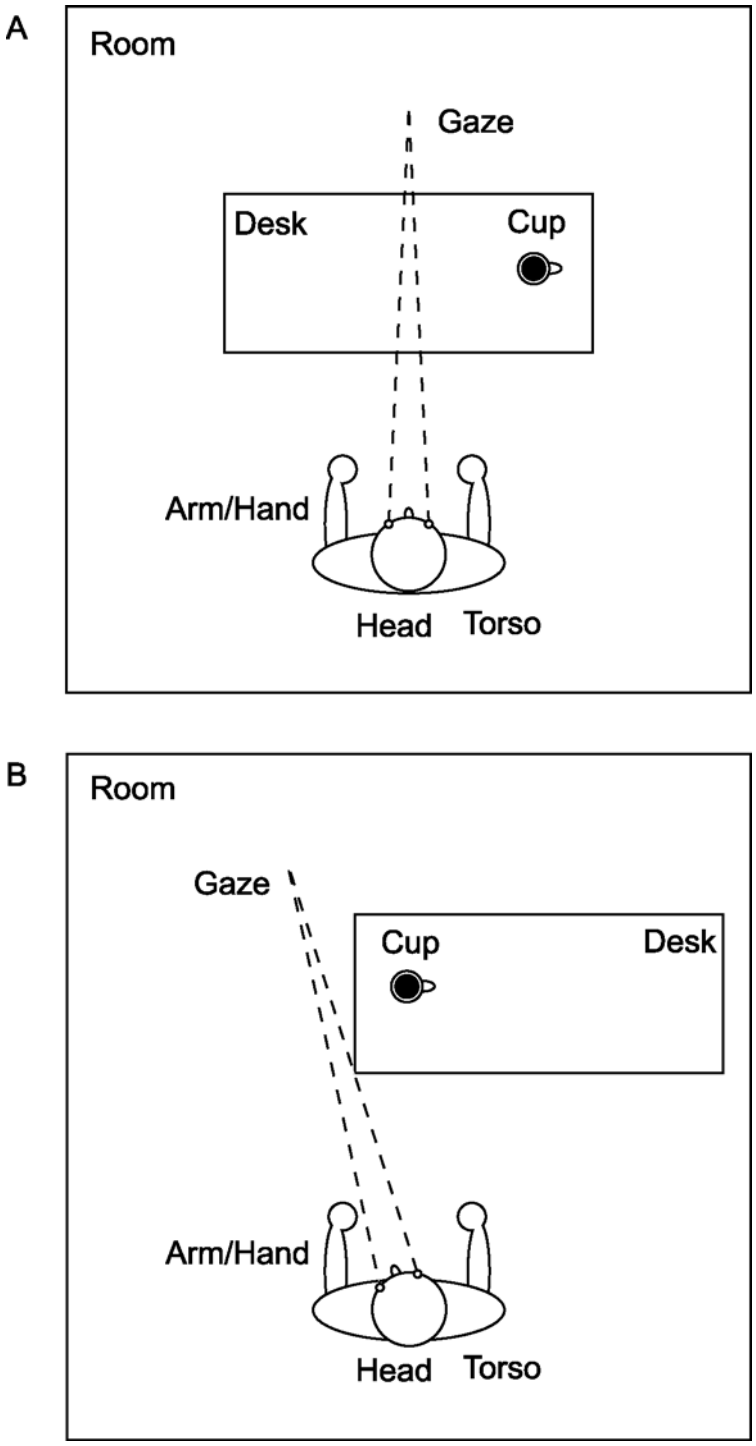

Fig. 1. Reference frame schematic.

Both figures show a variety of different objects that could be used as the focus of a reference frame. A. All reference frames are aligned. The location of the cup can be described as being on the right side of the room, the viewer, the viewer's gaze, and the desk. B. Reference frames are not aligned. The cup is in the center of the room, at the viewer's midline, to the right of the viewer's gaze, and on the left side of the desk. In a circumstance like this, the brain would have to determine the location of the cup using different reference frames depending on behavioral requirements.

1.1.2. What are object-centered reference frames?

The examples above characterize the distinction between *egocentric* (or viewer-centered) reference frames, in which spatial locations are defined relative to the viewer or to some body part attached to the viewer (e.g., the eyes, head, torso, etc.), and *allocentric* reference frames, in which spatial locations are defined relative to something external to the viewer (e.g., the environment, an object within the environment). One important and ubiquitous set of allocentric spatial representations are those related to objects. Spatial reference frames related to objects are described as object-centered and object-aligned. The term *object-centered* refers to the fact that a spatial location is centered on the boundaries defined by the object and maintains the same location relative to the object, even if the object is moved to another location. For example, the cross on the letter "t" is located at the top of the object in object-centered coordinates, regardless of where the letter may be moved in viewer-centered space. The term *object-aligned* refers to the fact that a spatial location is aligned with the intrinsic axis of an object and maintains the same location relative to the axis of the object, even if the object is rotated to another orientation. One recognizes that the cross on the letter "t" is on the top of the letter even if the letter is rotated.

1.1.3. Why use object-centered reference frames?

Spatial representation using egocentric reference frames is more basic and thus, one would think, more fundamental than object-centered spatial representation. The ubiquity of neural signals related to egocentric reference frames seems to confirm this assumption. For example, many cortical and subcortical areas involved in transforming locations in visual space into saccade target locations. These areas contain neurons whose receptive fields are *retina-centered*

or *eye-centered* (e.g., posterior parietal cortex (Colby et al. 1995; Duhamel et al. 1992), frontal eye field (FEF) (Goldberg and Bruce 1990; Schall 1991a), supplementary eye field (SEF) (Russo and Bruce 1996, 2000), and superior colliculus (Mays and Sparks 1980; Sparks et al. 2000; Sparks 1989; Sparks and Porter 1983)). Neurons have also been shown with *head-centered* receptive fields (e.g., posterior parietal cortex (Duhamel et al. 1997) and SEF (Bon and Lucchetti 1992; Lee and Tehovnik 1995; Schall 1991a, b; Schlag and Schlag-Rey 1985; Schlag et al. 1992)). Additionally, neurons with eye-centered receptive fields have been shown to be modulated by changes in eye, head, or body position (e.g., posterior parietal cortex (Andersen et al. 1990b; Andersen et al. 1985; Andersen and Mountcastle 1983; Brotchie et al. 1995; Sakata et al. 1980; Snyder et al. 1998)), providing examples of how complex spatial representations can arise from the interaction of purely egocentric reference frames.

Egocentric sensorimotor transformations are conceptually simpler than object-centered sensorimotor transformations as well. Given that the eye is used in both the perception and the action (in eye movements to visual targets), the alignment between locations in a retina-centered spatial map and locations in an ocular spatial map could be one-to-one: neurons in the visual system with receptive fields at locations in an egocentrically-defined reference frame could simply activate neurons in the saccadic system with receptive fields at the same location in an equivalent egocentric reference frame. Though this process is, in reality, more complex than described, it seems obvious that transforming spatial locations from an object-centered map to an ocular spatial map does not have the same type of similarity, and is likely more complicated.

Given that so much of the visuomotor brain appears to represent space using egocentric reference frames, and given the relative simplicity of transforming egocentric sensory signals to egocentric behavioral signals, why would the brain need to use object-centered reference frames?

One important answer relates to cognitive complexity. Primitive behaviors, such as reaching, pointing, and orienting, involve a limited number of cognitive processes and likely can be performed using exclusively egocentric reference frames. Humans, however, are capable of more cognitively demanding behaviors that require complex, object-centered spatial representations. Behaviors such as drawing, reading, writing, construction, and the use of tools or maps all require some degree of object-centered spatial representation and can not be performed using exclusively egocentric representations (Olson 2003). Even basic processes, such as the recognition of an object from multiple viewpoints, require the representation of space in an object-centered reference frame. One of the first formal characterizations of the object-centered reference frame was used to explain how the visual system represents objects (Marr 1982; Marr and Nishihara 1978).

It seems clear that the brain should encode object-centered spatial locations, but is human behavior actually influenced by the use of object-centered representations? If so, are there areas in the brain that actually encode locations in object-centered reference frames to support these behaviors? The rest of the introduction will address these questions, focusing almost exclusively on the direction of object-centered attention and eye movements, given that the neural systems controlling these behaviors appear to be tightly connected (Corbetta et al. 1998; Kustov and Robinson 1996). First, we will describe psychophysical investigations in humans in order to show that object-centered reference frames can guide behavior (1.2). Next we will describe what has been revealed so far regarding the neural basis of object-centered representations in humans based on studies of the behavior of patients with localized brain damage (1.3) and studies using functional imaging (1.4). We will then discuss studies of object-centered signals in single neurons of multiple areas of the macaque visuomotor brain (1.5), and focus on the supplementary

eye fields of the frontal cortex, where a preponderance of these signals have been observed (1.6). This overview should provide substantial evidence that there are, indeed, object-centered signals in the brain that permit the performance of object-centered behaviors. Following the overview, we will summarize the goals of the present set of studies, which attempt to further refine our understanding of these neural signals (1.7).

1.2. Psychophysical studies of object-centered spatial representation

1.2.1. Object-centered attention

Studies of object-centered attention in normal human subjects have established that humans do refer to object-centered reference frames, and not only egocentric reference frames, in directing behavior. Multiple groups have demonstrated, in normal subjects, that attention is capable of being directed to and following one part of an object even as the object moves through space. Attention can track a cued location on a rotating cube (Gibson and Egeth 1994; Umilta et al. 1995), or to a single member of a rotating (Tipper et al. 1999; Tipper et al. 1994) or translating (Ro and Rafal 1999) array of connected or nearby items. Subjects can be made to be quicker (Maljkovic and Nakayama 1996) or more accurate (Kristjansson et al. 2001; Kristjansson and Nakayama 2003) in responding to the same object-centered location even when the object as a whole is placed at a different location in egocentric space. Object-centered effects can be seen using static stimuli as well. Reuter-Lorenz and colleagues showed that, if subjects are asked to detect a gap in one edge of a square, the object-centered location the gap in the square affects how well subjects are able to detect it (Reuter-Lorenz et al. 1996).

1.2.2. Object-centered eye movements

Object-centered reference frames also influence the direction of saccadic eye movements, though there are few explicit studies of object-centered influences on saccades. The influence of the object-centered reference frame has been shown indirectly in studies of reading. During reading, saccades directed to each word are localized in object- (here word-) centered space. Investigators have found that saccades tend to be directed near the center of each word (Inhoff et al. 1992; Mcconkie et al. 1988; O'Regan 1992; Vergilino and Beauvillain 2001; Vitu et al. 1990). This reliable word-centered landing position maximizes the amount of information acquired in reading the word and prevents multiple within-word refixations (O'Regan 1992), suggesting that an object-centered representation is critical in guiding the process of reading (Vergilino and Beauvillain 2001).

Exogenous cues in general can be influential in the direction of saccades. The presence of landmarks in the visual field can influence the direction of saccades to a remembered target, in some cases making the saccade more accurate (Dassonville et al. 1995; Hayhoe et al. 1992; Karn et al. 1993; Karn et al. 1997). Additionally, it has been observed both in monkeys and in humans that the presence of a stable pattern in the visual field improves saccadic accuracy (Gnadt et al. 1991). These results are not explicitly object-centered in that they do not examine localization using a coordinate system within an object, but they do show that allocentric factors can influence eye movements, which provides a sort of foundational support for object-centered encoding.

Studies have also been performed on humans performing explicitly object-centered eye-movements. Edelman and colleagues showed that subjects, instructed by a left- or right-pointing arrow at the center of the screen, could rapidly and accurately direct saccades to one or another

end of a horizontal bar or array of annuli, even when the location or size of the object varied across trials (Edelman et al. 2001, 2002). The saccadic accuracy suggests that object-centered behaviors are natural in normal human subjects. The speed with which subjects were capable of transforming an object-centered cue into a spatial saccade argues that there are areas of the brain capable of performing such an abstract, object-centered computation.

1.3. Neuropsychological studies object-centered spatial representation

The results presented above support the idea that object-centered behavior can be as rapid and precise as egocentric behavior. We now ask whether there is a direct neural correlate of object-centered spatial representation. One way to address this issue is to determine if damage to particular areas in the brain results in an inability to process spatial locations using an object-centered reference frame. This type of deficiency has been observed in patients exhibiting spatial neglect: a disorder in which the patients are unaware of contralesional locations in space. Neglect has been typically described as resulting from lesions to the right parietal cortex , but instances of neglect have been observed after both unilateral and bilateral lesions to frontal, parietal, and temporal cortical regions, areas in the basal ganglia and thalamus, and combinations of these areas (Behrmann et al. 2004; Doricchi and Tomaiuolo 2003; Leibovitch et al. 1998; Maguire and Ogden 2002; Mesulam 1999; Parton et al. 2004; Vallar 1998; Vallar et al. 2003). The precise anatomical locus of damage that produces spatial neglect is currently a debated topic (Karnath et al. 2004; Karnath et al. 2001; Karnath et al. 2002; Mort et al. 2003), and the exact nature of the neglect varies somewhat depending on the location and extent of the lesion. The unifying characteristic across neglect patients, however, is the unawareness of contralesional space.

A disorder of spatial representation immediately brings to mind the question of reference frames: in what reference frame is contralesional space neglected, and can this neglect be object-centered? A number of studies have described egocentric neglect, in which patients neglect locations on the opposite side of the eyes (Behrmann et al. 2002), head (Vuilleumier et al. 1999), trunk (Chokron and Imbert 1995; Karnath et al. 1993; Karnath et al. 1996; Karnath et al. 1991), or even arm or hand (Buxbaum and Permaul 2001) of the lesion. This variability in egocentric spatial reference frame affected in neglect patients underscores the complexity of interpretation of the disorder. What is important for the purposes of this discussion, however, is the consistently replicated observation that patients can exhibit neglect in both object-centered and object-aligned spatial reference frames.

As noted earlier, object-centered reference frames are critical to the performance of such behaviors as drawing or reading. Consequently, object-centered neglect can result in deficits to such behaviors. Many patients exhibit an inability to copy the contralesional half of an object. Gainotti and colleagues described patients who, when asked to copy a drawing of a complex image or scene, copied only the ipsilesional half of each object present (even when objects were contralesional in viewer-centered space) (Gainotti et al. 1972). Similar results have been seen in other paradigms requiring patients to reproduce drawings (Apfeldorf 1962; Behrmann and Plaut 2001; Doricchi and Galati 2000; Halligan and Marshall 1993; Hillis et al. 2005; Ishiai et al. 1996; Marshall and Halligan 1993; Ogden 1985).

In addition to drawing, reading provides clues as to how object-centered or object-aligned neglect can manifest in patients. Neglect related to words has been shown to be object-centered in some patients: they will neglect the letters on the left side of the normally-printed or mirror-reversed words (Hillis and Caramazza 1991). In other patients, word-related neglect is object-

aligned: they will neglect the letters on the left side of the normally-printed words (the word beginning), neglect the right side of mirror-reversed words (again, the word beginning), and show deficits for the beginning of vertically printed words (Caramazza and Hillis 1990a, b; Hillis and Caramazza 1990; Humphreys and Riddoch 1995). Neglect for locations within words persist even when eye movements are controlled and words are presented in the ipsilesional hemifield (Behrmann et al. 1990; Ellis et al. 1987; Katz and Sevush 1989; Kinsbourne and Warrington 1962a; Kinsbourne and Warrington 1962b; Nichelli et al. 1993; Riddoch et al. 1990; Subbiah and Caramazza 2000), arguing against a gaze-centered interpretation of the neglect.

Object-centered reference frames are also critical simply for accurate perception of visual stimuli. Neglect in an object-centered reference frame impairs this ability. Patients have been shown to exhibit object-centered neglect of the contralesional side of geometrical shapes (Boutsen and Humphreys 2000; Doricchi and Galati 2000; Driver et al. 1992; Egly et al. 1994; Halligan and Marshall 1994; Humphreys 1998; Humphreys and Riddoch 1994; Marshall and Halligan 1994, 1995), as well as of contralesional members of a horizontal array (Arguin and Bub 1993; Ladavas et al. 1990; Subbiah and Caramazza 2000) irrespective of the egocentric placement of these objects. Neglect patients presented with chimeric stimuli, in which two different half-images are appended and presented as a single object stimulus, will often neglect half of the image and report that they are being shown a full version of the non-neglected half (Buxbaum and Coslett 1994; Humphreys 1998; Peru et al. 1997; Subbiah and Caramazza 2000; Walker and Findlay 1997; Walker et al. 1996; Walker and Young 1996; Young et al. 1990; Young et al. 1992). The neglect is clearly object-centered in nature: placing a small separation between the two halves allows the patients to perceive both images (Buxbaum and Coslett 1994; Young et al. 1992). Furthermore, it persists during conditions of eye movement control (with

enforced fixation), rapid stimulus presentation (precluding fixation of the stimulus), or presentation of the stimulus in the ipsilesional hemifield (Arguin and Bub 1993; Ladavas et al. 1990; Pavlovskaya et al. 1997; Young et al. 1992 - see also citations regarding gaze control for object-centered neglect of words, above), arguing against a gaze-centered interpretation.

Studies using chimeric stimuli and asymmetrical figures have also been used to test whether changing the stimulus orientation affects the neglected part of the stimulus, i.e., whether neglect patients exhibit object-aligned neglect as well as object-centered neglect. A number of studies, using rotations of both complex images and chimeric stimuli have demonstrated instances of spatial neglect in an object-aligned reference frame (Behrmann and Moscovitch 1994; Driver et al. 1994; Driver and Halligan 1991; Hillis and Rapp 1998; Young et al. 1992) A series of studies by Behrmann and Tipper have described patients who neglect the same end of a barbell stimulus, whether it remains static or rotates 180º about its central axis (Behrmann and Tipper 1994, 1999; Tipper and Behrmann 1996). The authors also showed that the effect was not related to eye movements, and that the expression of both object-aligned and viewer-centered neglect could wax and wane by changing the probability that subjects would be expected to attend to either the moving end of the object or a fixed location on the screen (Behrmann and Tipper 1999; Tipper and Behrmann 1996). These findings led the authors to propose that locations in space can be represented in multiple reference frames, either simultaneously or in a task-dependent manner.

This final point underscores the idea that the brain is capable of representing locations in both egocentric coordinates and object-centered coordinates, possibly simultaneously. Exactly how this occurs is a debated topic. Some investigators believe that both reference frames are multiple aspects of the same representation, perhaps with the same neural underpinnings

(Niemeier and Karnath 2002a, b) , whereas others propose two separate mechanisms mediated by separate neural pathways, suggesting that egocentric and object-centered spatial processing are controlled by the right and left hemispheres respectively (Egly et al. 1994), or that egocentric neglect is a product of damage to the dorsal visual pathway and object-centered neglect is a product of damage to the ventral visual pathway (Humphreys 1998; Humphreys and Riddoch 1994, 1995). A recent study of neglect patients has provided particularly interesting support for this dual-stream account (Hillis et al. 2005), showing that patients with object-centered but not egocentric neglect primarily have damage to the superior temporal gyrus whereas patients displaying egocentric but not object-centered deficits exhibit damage primarily to the angular gyrus of the inferior parietal lobule. Similar dissociations have been made earlier in studies using a smaller number of patients (Ota et al. 2001; Ota et al. 2003). The results provide support for a neural basis for object-centered spatial representation that may be independent of egocentric spatial representations.

1.4. Functional imaging studies of object-centered spatial representation

Patients exhibiting neglect often show damage to overlapping neural structures, making anatomical localization of the neural basis of object-centered representations difficult. Another way to determine whether there are areas in the brain that are devoted to object-centered processing is to study the intact human brain using functional magnetic resonance (fMRI) or positron emission tomography (PET) imaging while subjects perform an object-centered task. Unfortunately, there have been very few studies of object-centered processing using functional imaging, and these studies have provided relatively inconclusive results. In study by Fink and colleagues, (Fink et al. 1997) subjects were asked to view a short horizontal line that was

presented to the right or left of fixation and report either the right or left location of the line (egocentric condition, what they call space-based) or else the location of a box that appeared on either the right or left end of the line (object-centered condition, what they call object-based). While the areas and degrees of activation were somewhat variable due to variations in task requirements, the general trend observed was that egocentric behavior increased areas in the parietal cortex, dorsolateral prefrontal cortex, and cerebellar vermis, and that object-centered behavior activated these regions as well as early ventral visual cortex. Other studies by the same group implicated a broad swath of neural structures related to object-centered processing: multiple occipital areas, dorsolateral and ventrolateral prefrontal cortex, superior and inferior parietal cortex, supplementary motor area (SMA), cingulate cortex, orbitofrontal cortex, cerebellum, and the thalamus and putamen (Fink et al. 2000a; Fink et al. 2000b; Fink et al. 2002; Fink et al. 2001). Most of these studies poorly control the reference frame used by the subject, however, and are only marginally informative.

Other functional imaging studies purporting to contrast object-centered with egocentric spatial encoding have seen a similar breadth of activation. A study by Honda and colleagues found heightened activation in a number of inferior occipitotemporal regions, as well as in the pre-supplementary motor area (pre-SMA), posterior parietal cortex, ventral premotor cortex, and dorsolateral prefrontal cortex, suggesting a role for these areas in object-centered processing (Honda et al. 1998). As above, there were flaws in controls for this study. However, the differential activation observed is suggestive of some sort of specialization for object-centered spatial representation and, as we shall see, it is supported in many ways by the results of single unit recording. Similar attempts at using functional imaging to determine the neural basis of

object-centered spatial processing have, for the most part, been equally poorly controlled and have, consequently, produced equally vague results (Committeri et al. 2004; Galati et al. 2000).

Using a more controlled paradigm, one recent study has shown a striking difference in cortical activation between egocentric and object-centered reference frame use. Wilson and colleagues investigated the neural basis of direction of either object-centered or viewer-centered spatial attention using event-related fMRI (Wilson et al. 2005). The authors monitored neural activation while subjects attended either to the left or right end of a bar (object-centered conditions) or one of two dots on the screen (egocentric conditions). The direction of spatial attention in both conditions activated a frontoparietal circuit consisting primarily of the intraparietal sulcus, the dorsolateral prefrontal cortex, the frontal eye fields, a medial region around the SMA, and the insular cortex. The authors found heightened activation during object-centered conditions which was particularly notable in the left intraparietal sulcus and the medial SMA region. These results are particularly interesting for a number of reasons. First, this study is clearly the most rigorous functional imaging study of object-centered spatial attention to date. Second, the study lends support to the notion that different cortical areas are involved to different degrees in egocentric and object-centered behaviors. Finally, the results seem to dovetail nicely with those seen in investigations of single neurons in behaving primates.

1.5. Object-centered representations in single neurons

1.5.1. Encoding of object-centered features by neurons in ventral visual cortex

Given that neglect and functional imaging studies in humans have gestured towards a role for ventral visual cortical areas during performance of object-centered tasks, it would make sense to determine if neurons in these regions encode the location of visual features in object-centered coordinates. Indeed, a number of studies have indicated that this is the case. The activity of many single neurons in visual areas V1, V2, and V4 encode the locations of features relative to the rest of an object. Neurons in all three areas were shown to fire if their receptive field overlapped the edge of a square stimulus, but only if the stimulus edge was on the neuron's preferred side of the stimulus (Zhou et al. 2000). A collection of studies from the Connor laboratory has shown that many neurons in V4 respond to a particular object feature (such as a curve of a particular angle) only if the feature is located in a particular location relative to the rest of the object, strongly supporting the idea that single neurons in visual cortex are capable of representing feature locations in object-centered coordinates (Pasupathy and Connor 1999, 2001, 2002). A recent study by Brincat and Connor extended these findings by showing that that inferotemporal (IT) cortical neurons fire selectively for objects with a combination of multiple features located at different object-centered locations (Brincat and Connor 2004).

As can be seen from the studies presented here it is plausible that objects can be represented in the brain with part locations encoded in relation to the objects themselves as opposed to in relation to an egocentrically defined reference frame. Further support of this idea has come from years of study of the neural representation of objects in neurons of IT, where some neurons have been shown to respond selectively to particular objects or conjunctions of features, but to show invariance in their firing rate to changes in object location, object angle, or object scale (Booth

and Rolls 1998; Eifuku et al. 2004; Ito et al. 1995; Logothetis et al. 1995; Lueschow et al. 1994; Tanaka et al. 1991; Tovee et al. 1994). Similarly, neurons in the superior temporal cortex, which receives projections from both temporal and parietal cortex (Baizer et al. 1991; Morel and Bullier 1990; Seltzer and Pandya 1994), have been shown to be selective for conjunctions of visual features and invariant to egocentric spatial location in some cases, though sensitive to variations in egocentric spatial locations in others (Ashbridge et al. 2000; Bruce et al. 1981; Eifuku et al. 2004; Hasselmo et al. 1989; Perrett et al. 1989; Perrett et al. 1991). These studies support the idea that neurons in the ventral visual processing stream can encode object-centered locations of features, groups of features, and complex objects. The invariant encoding of feature and object location by visual cortical neurons could conceivably provide a representation of locations, centered on the object, that could be used as a map in the generation of targets for object-centered spatial behaviors.

1.5.2. Encoding of object-centered locations for targets of behavior

The studies above support the claim that there are neurons that are involved in representing object-centered feature locations. There are also neurons in a number of cortical areas, and at least one subcortical area, that exhibit object-centered spatial selectivity for the target of a behavior. One of the first instances of object-centered spatial selectivity was presented in an early study by Niki (Niki 1974). Recording from neurons in the dorsolateral prefrontal cortex, Niki demonstrated that some neurons displayed object-centered spatial selectivity: when monkeys reached for one of two targets in an array, certain neurons would fire selectively for reaches to either the left or right of the array, irrespective of the absolute spatial location of the array. The results of a study by Lebedev et al. support the claim of the existence

of object-centered spatial coding in prefrontal neurons (Lebedev et al. 2001), though the experiment was designed such that alternate explanations of the apparent object-centered neuronal activity were possible.

Given that many instances of object-centered neglect appear to involve lesions of human parietal lobe and that at least one imaging study in humans has shown activation of parietal cortex during performance of object-centered tasks, one might wonder whether parietal neurons encode locations in an object-centered reference frame. Sabes and colleagues recorded from the lateral intraparietal cortex (LIP) while monkeys directed saccades to remembered targets on a rotated complex stimulus (Sabes et al. 2002). Intriguingly, the authors found that very few neurons exhibited encoding in an object-aligned reference frame. Additional studies in which stimuli both translated and rotated found that only a small number of neurons exhibited object-centered/aligned selectivity, leading the authors to conclude that area LIP may not play a major role in the representation of object-centered space (Brezen et al. 2003). The existence of object-centered reference frames in the parietal cortex can not be entirely dismissed, however. Chaffee and colleagues recorded from neurons in parietal area 7a while monkeys performed a task requiring them to remember locations relative to a complex stimulus (Chafee et al. 2005). The authors found that many 7a neurons fired selectively for specific object-centered locations relative to the complex stimulus used in the task. The selectivity for object-centered locations persisted despite translational movements of the stimulus in egocentric space. Both the absence of object-aligned signals in LIP found by Sabes et al. (2002) and the presence of object-centered signals in area 7a seen by Chafee and colleagues support, to some degree, a report by Snyder and colleagues who found that neurons in area 7a can encode spatial locations in allocentric (described as world-centered) coordinates, whereas neurons in LIP tend more towards egocentric

representation (Snyder et al. 1998). These authors, however, did not test for object-centered or object-aligned signals. Why some regions of the parietal cortex are involved in object-centered spatial representations while others are not is unclear. Further studies using tasks of the same type are needed to disentangle the differing accounts.

Neurons in other visuomotor areas outside of parietal cortex do appear to exhibit object-centered spatial selectivity. In a study by Horowitz and Newsome, monkeys signaled the direction of a moving field of dots by directing a saccade to the right or left member of a horizontal pair of larger dots (Horwitz et al. 2004b). The authors found neurons in the superior colliculus that showed selective activity for saccades directed to either the left or right end of the pair of dots despite movement of the pair to multiple locations in the visual field. By dissociating the egocentric target location from the object-centered target location (right or left end of the pair), the results strongly support the hypothesis that superior colliculus neurons are capable of encoding locations in an object-centered reference frame. Additionally, the authors recorded from a small number of neurons in the SEF while monkeys performed the same task and found similar degrees of object-centered selectivity, confirming the results of a number of earlier studies of object-centered spatial encoding in the SEF (Olson and Gettner 1995, 1999; Olson and Tremblay 2000; Tremblay et al. 2002). Given that the SEF has been shown many times to contain neurons with object-centered response fields, and given that an examination of the object-centered response fields in neurons in the SEF is the main focus of the reports presented here, we now turn to an overview of the SEF, with an emphasis on the neuronal representation of object-centered space.

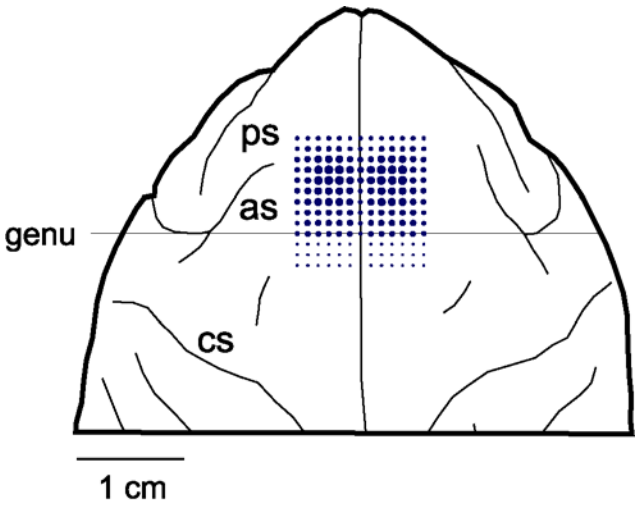

Fig. 2. Location of the macaque supplementary eye field.

Extent of the SEF as defined by mapping with intracortical microstimulation in studies from 10 laboratories listed in Table 1 of (Tehovnik 1995). Tehovnik brought results from different laboratories into register by use of two landmarks: for mediolateral register, the hemispheric midline and, for anteroposterior register, the genu of the arcuate sulcus, as marked by the horizontal line in this figure. For each study listed, Olson and Tremblay generated a rectangle encompassing, to the nearest mm, the anterior, posterior, lateral and medial limits of the region in which electrical stimulation elicited eye movements. Then, on each point in a 1 X 1 mm grid spanning the cortex, they superimposed a dot, the area of which was proportional to the number of rectangles including that point. The number of times a site was counted could range from 0 (not marked on this figure: sites not implicated by any study) through 1 (smallest dots visible in this figure: sites implicated by just 1 study) to 10 (largest dots visible in this figure: sites implicated by all 10 studies). as, arcuate sulcus; as, genu, genu of the arcuate sulcus; cs, central sulcus; ps, principal sulcus. Figure and legend adapted from (Olson and Tremblay 2000)

1.6. Supplementary eye field

1.6.1. SEF: Overview

The macaque SEF is a region of cortex located on the dorsomedial shoulder of the frontal cortex (Fig. 2), and is typically considered to be involved in the representation of spatial locations, primarily for the purpose of programming or control of eye movements. Microstimulation of the SEF at low current (~< 50 μA) elicits eye movements directed to specific locations (Fujii et al. 1995; Lee and Tehovnik 1995; Mann et al. 1988; Martinez-Trujillo et al. 2003a; Martinez-Trujillo et al. 2004; Martinez-Trujillo et al. 2003b; Missal and Heinen 2001, 2004; Mitz and Godschalk 1989; Russo and Bruce 1993; Schall 1991a; Schlag and Schlag-

Rey 1985, 1987a, b; Tehovnik and Lee 1993; Tehovnik et al. 1994; Tehovnik and Slocum 2000; Tehovnik et al. 1999; Tehovnik et al. 1998; Tehovnik and Sommer 1996, 1997; Tian and Lynch 1995). Additionally, a number of studies have shown that single neurons in the SEF are active preceding eye movements directed to specific locations (Bon and Lucchetti 1991, 1992; Chen and Wise 1995a, b, 1996, 1997; Coe et al. 2002; Fujii et al. 2002; Hanes et al. 1995; Lee and Tehovnik 1995; Mushiake et al. 1996; Olson and Gettner 1995, 1999, 2002; Olson et al. 2000; Olson and Tremblay 2000; Russo and Bruce 1996, 2000; Schall 1991a, b; Schlag and Schlag-Rey 1985, 1987b; Schlag et al. 1992; Schlag-Rey et al. 1997; Tremblay et al. 2002). The spatially-selective activity of an SEF neuron firing before a saccade is shown in Fig. 3.

Given the preponderance of studies linking the SEF to oculomotor behavior, one is tempted to conclude that the sole function of SEF is to control eye movements. This conclusion is not completely warranted, however. A number of studies in which the SEF has been inactivated, either temporarily or permanently, have reported only minor effects on the performance of oculomotor tasks (Schiller and Chou 2000a, b; Schiller and Chou 1998; Sommer and Tehovnik 1999). Furthermore, many neurons in the SEF show changes in firing related to aspects of motivated behavior besides the generation of eye movements. Neurons in the SEF have been shown to change their activity over the course of learning a stimulus-response association (Chen and Wise 1995a, b, 1996, 1997; Mann et al. 1988), to fire selectively during either erroneous saccade generation or correct withholding of a movement during a countermanding task (Stuphorn et al. 2000b), to fire more strongly preceding and during the execution of an internally-guided decision (Coe et al. 2002), and to fire either before, during, or after receipt of a juice reward (Amador et al. 2000; Stuphorn et al. 2000b). SEF neurons have also been shown to exhibit heightened activity during instances of stimulus-response

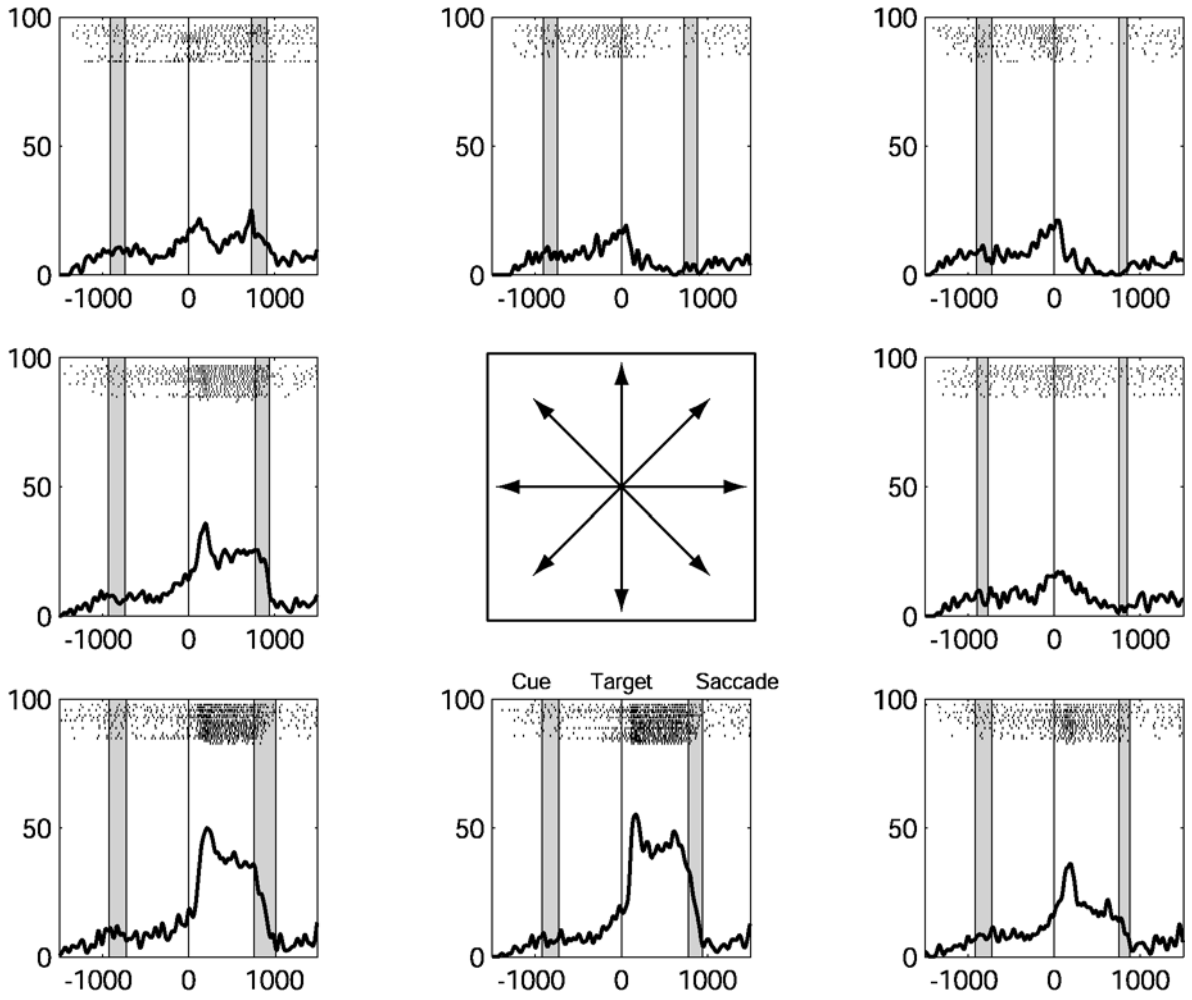

Fig. 3. Activity of an individual SEF neuron during a delayed saccade task.

Each panel shows rasters (top) and spike density functions (bottom, smoothed with Gaussian, SD=10ms) for a neuron recorded during performance of a delayed saccade task in eight directions. The saccade target was a single dot. The three timepoints (noted for the down position panel) represent the cue (in this case alerting the monkey to the fact that he is performing a delayed saccade task), the onset of the target at one of the eight locations (depicted in the center panel) and the onset of the saccade. Trials are aligned on target onset. Cue and saccade are represented as wide bars due to slight temporal variation between cue and target (for cue) and due to variability in saccade latency (for saccade). For more details of the task, refer to section 2.2. Clearly this neuron has a preferred direction that is down and to the left.

incompatibility (Amador et al. 2004; Nakamura et al. 2004; Olson and Gettner 2002; Schlag-Rey et al. 1997). Furthermore, neurons have been shown to fire more robustly during performance of pattern-guided saccades (Olson et al. 2000). SEF neurons additionally exhibit selectivity for specific visual patterns presented in and oculomotor responses performed in a sequence (Isoda

and Tanji 2002, 2003; Lu et al. 2002). Neurons in the SEF have even been shown to fire during planning of arm movements (Fujii et al. 2002; Mann et al. 1988; Mushiake et al. 1996). This diversity of neuronal response properties suggests that the SEF is involved many cognitive and behavioral functions outside of eye movement control.

Anatomical studies of the SEF provide support for the idea that the area is involved in oculomotor control as well as other aspects of different behaviors. The SEF is well-connected with other parts of the brain involved in spatial aspects of oculomotor control. The SEF receives projections from parietal area LIP (Cavada and Goldman-Rakic 1989; Huerta and Kaas 1990; Matelli et al. 1998), is densely interconnected with the frontal eye fields (Huerta and Kaas 1990; Schall et al. 1993), and sends robust projections to the superior colliculus (Huerta and Kaas 1990; Shook et al. 1990). Furthermore, the SEF sends projections to oculomotor regions of the caudate nucleus and putamen that largely overlap with projections from the frontal eye field (Parthasarathy et al. 1992; Shook et al. 1990). The SEF also sends projections to the majority of the oculomotor nuclei in the brainstem in addition to the superior colliculus. These projections converge to some degree with those from the FEF, though not precisely (Shook et al. 1990). Finally, in addition to input from cortical oculomotor-related regions, the SEF receives input from thalamic nuclei VAmc and MDmf as well as from area X (Matelli and Luppino 1996; Shook et al. 1991), all of which emphasize the placement of the cortical area in the "oculomotor circuit" described by Alexander and colleagues (Alexander et al. 1986).

The assignment of the SEF to the category of a purely oculomotor region based on these anatomical results, however, belies the complex connectivity of the region, much of which underscores the high degree of variability in the response properties of neurons recorded there. Huerta and Kaas examined the connectivity of physiologically-defined SEF and demonstrated

that the SEF is connected, not only to areas involved in visuomotor function, but to areas involved in higher cognitive functions and skeletomotor control as well (Huerta and Kaas 1990). In addition to being reciprocally connected to supplementary motor areas in the dorsomedial frontal cortex, the SEF is also reciprocally connected with cingulate cortical areas, and exhibits a particularly strong degree of connectivity with both dorsolateral and ventrolateral prefrontal cortex (Huerta and Kaas 1990; Luppino et al. 2003). Thalamic connectivity with the SEF is similar in some ways to that with lateral prefrontal cortex, most notably in the strong connectivity between MDpc and both the lateral prefrontal cortex (Goldman-Rakic and Porrino 1985) and the SEF (Huerta and Kaas 1990). Furthermore, the SEF receives a particularly robust projection from the superior temporal sulcus (Huerta and Kaas 1990; Luppino et al. 2001; Matelli et al. 1998). Two of these connections to the SEF are notable in regard to encoding of object-centered spatial locations: dorsal and ventral lateral prefrontal cortex, in which many neurons have been described exhibiting selectivity for visual objects (O'Scalaidhe et al. 1997; Rao et al. 1997; Wilson et al. 1993), and superior temporal sulcus, in which neurons are selective for complex visual stimuli and occasionally exhibit invariance to egocentric locations (see citations in section 1.5.1). While the functions of these projections to the SEF have not been studied, it is conceivable that object-related signals from these areas could provide a substrate which could be integrated by neurons in the SEF in order to form object-centered spatial representations.

1.6.2. SEF: Egocentric reference frames

That many neurons in the SEF encode locations in space, whether for the direction of eye movements or for other behaviors, raises the question of what reference frame is employed by

SEF neurons. A number of studies have been performed addressing which egocentric coordinate system is used by neurons in the SEF, often arriving at somewhat different conclusions.

During initial the characterization of the SEF, Schlag and Schlag-Rey determined that activation of the SEF with microstimulation evoked a continuum of saccades types defined by two extremes: fixed-vector saccades (a saccade with the same metrics was elicited regardless of initial gaze angle), and converging saccades (saccades differed in metrics depending on initial gaze angle, but converged at the same endpoint) (Schlag and Schlag-Rey 1985, 1987a, b). The authors concluded that different populations of neurons in the SEF may represent different stages of saccadic specification: areas related to fixed-vector saccades could represent the encoding of saccade direction in eye-centered coordinates whereas areas related to converging saccades could represent goal specification potentially represented in head-centered coordinates. Studies from other laboratories have largely supported these conclusions. Microstimulation of the SEF has been shown to evoke both fixed vector (eye-centered) and converging (head-centered) saccades (Bon and Lucchetti 1992; Lee and Tehovnik 1995; Mann et al. 1988; Mitz and Godschalk 1989; Schall 1991a; Schlag and Schlag-Rey 1985, 1987a, b; Tehovnik and Lee 1993; Tehovnik et al. 1994; Tehovnik and Slocum 2000; Tehovnik et al. 1999; Tehovnik et al. 1998; Tehovnik and Sommer 1996, 1997). In many cases, investigators found that prolonged microstimulation enforced fixation at the saccade goal (Schall 1991a; Tehovnik and Lee 1993), suggesting that the goal location in head-centered coordinates is encoded by SEF neurons.

Single-unit recording studies have also provided evidence that the SEF encodes saccade targets with relation to the eyes and/or the head. Schlag and Schlag-Rey recorded the activity of single neurons during visually-guided and spontaneously executed saccades, and found that activity preceded saccade initiation in both head-fixed and head-free animals, and that the

preferred direction of each neuron was unchanged with head position, suggesting an eye-centered representation (Schlag and Schlag-Rey 1985, 1987b). In contrast, SEF neurons have also been described whose activity is modulated by fixations at different eye positions (Bon and Lucchetti 1992; Lee and Tehovnik 1995; Schall 1991a, b; Schlag and Schlag-Rey 1985; Schlag et al. 1992), and investigators have described neurons that fire equivalently for saccades of different metrics that bring the eyes to the same target in head-centered space (or body- or world-centered space, as heads were fixed during the studies) (Mann et al. 1988; Schall 1991b). If SEF neurons encoded locations strictly in eye-centered coordinates, saccades of the neuron's preferred direction would elicit activity irrespective of the starting point of the saccade, and neurons would be unable to use information about the position of the eyes relative to the head to alter firing rate. The existence of fixed target response fields in SEF neurons instead supports a reference frame other than one yoked to the retina or eyes.

The conclusion that SEF neurons encode spatial locations in some non-oculocentric coordinate system is not uniformly accepted. Russo and Bruce conducted parametric measurements of the spatial response properties of SEF neurons using both microstimulation and single-unit recording techniques (Russo and Bruce 1993, 1996, 2000). The authors arrived at the conclusion that SEF neurons encode locations in space in oculocentric, and not craniocentric, coordinates. The authors provide multiple explanations for the apparent discrepancies between their results and those of other investigators. First, they suggest that studies claiming to see head-centered response properties in SEF neurons are actually recording from areas outside the SEF. Regarding the observation of goal-directed saccades following SEF stimulation, the authors propose that the artificial nature of microstimulation produces saccades that are not truly representative of natural eye movements and therefore only appear head-centered.

A series of recent studies from the Crawford laboratory seems to have brought these conflicting results into register. Using a microstimulation paradigm in head-free monkeys, the authors determined that activation of neurons in the SEF encodes three dimensional gaze commands consisting of simultaneous movements of head-in-space and eyes-in-head (Martinez-Trujillo et al. 2003a; Martinez-Trujillo et al. 2003b). The authors then used the technique to characterize the reference frame in which the SEF encodes locations, focusing on contrasting, in three dimensions, eye-centered, head-centered, and body-/space-centered (bodies were immobilized in space) reference frames (Martinez-Trujillo et al. 2004). The authors determined that a continuum encompassing each of the three types of reference frame is represented across the extent of the SEF. This result is notable, not only for the technical advance of incorporating eye and head movements in three dimensions into the spatial encoding structure of the SEF, but also for the implications of the results: that the SEF as a whole is capable of representing locations in multiple reference frames.

1.6.3. SEF: Object-centered reference frames

SEF neurons have also been shown to encode locations in object-centered coordinates (Olson and Gettner 1995, 1999; Olson and Tremblay 2000; Tremblay et al. 2002). We have trained monkeys to perform a bar task in which they are instructed to direct a delayed saccade to either the left or right end of a bar that can be located at multiple locations in egocentric space. In this way, object-centered location (right or left end of the bar) can be decoupled from eye-centered location (right or left side of the screen), allowing us to dissociate object-centered neural signals from eye-centered neural signals. During performance of the bar task, we have shown that a large proportion (anywhere from approximately 25% to more than 50%) of

neurons recorded in the SEF display object-centered selectivity during performance of the bar task: when a monkey is required to remember one end of a bar or another, many SEF neurons will fire selectively for a particular location on the bar, irrespective of the location of the bar in relation to other reference frames, that is, no matter where the bar is located in eye- or retina-centered space (for our studies the terms are used interchangeably). An example of an SEF neuron exhibiting object-centered selectivity in the bar task is shown in Fig. 4.

Object-centered selectivity is not dependent on the type of cue used to instruct the saccade. The object-centered instruction cue can be either a small sample bar with the left or right end of the bar highlighted (Olson and Gettner 1995; Olson and Tremblay 2000; Tremblay et al. 2002), or a color cue, where one color is associated with one end of the uniformly gray target bar, and the other color is associated with the other (Olson and Gettner 1999). SEF neurons display selectivity for object-centered location following either type of cue, supporting the idea that this selective activity represents the object-centered target location, and was not simply a visual response to the cue. Object-centered selectivity is also invariant to the visual structure of the target object. Robust object-centered selectivity has been seen across changes in target object size (Olson, unpublished observations), when the target object is either a vertical or horizontal bar (Olson, unpublished observations), when the target array is a horizontal array of dots that creates the appearance of a virtual object (Olson and Tremblay 2000), and even when the target is a face image (Olson, unpublished observations). The fact that SEF neurons encode locations using an object-centered reference frame despite variations in both cue and target structure strongly supports the robustness of the phenomenon.

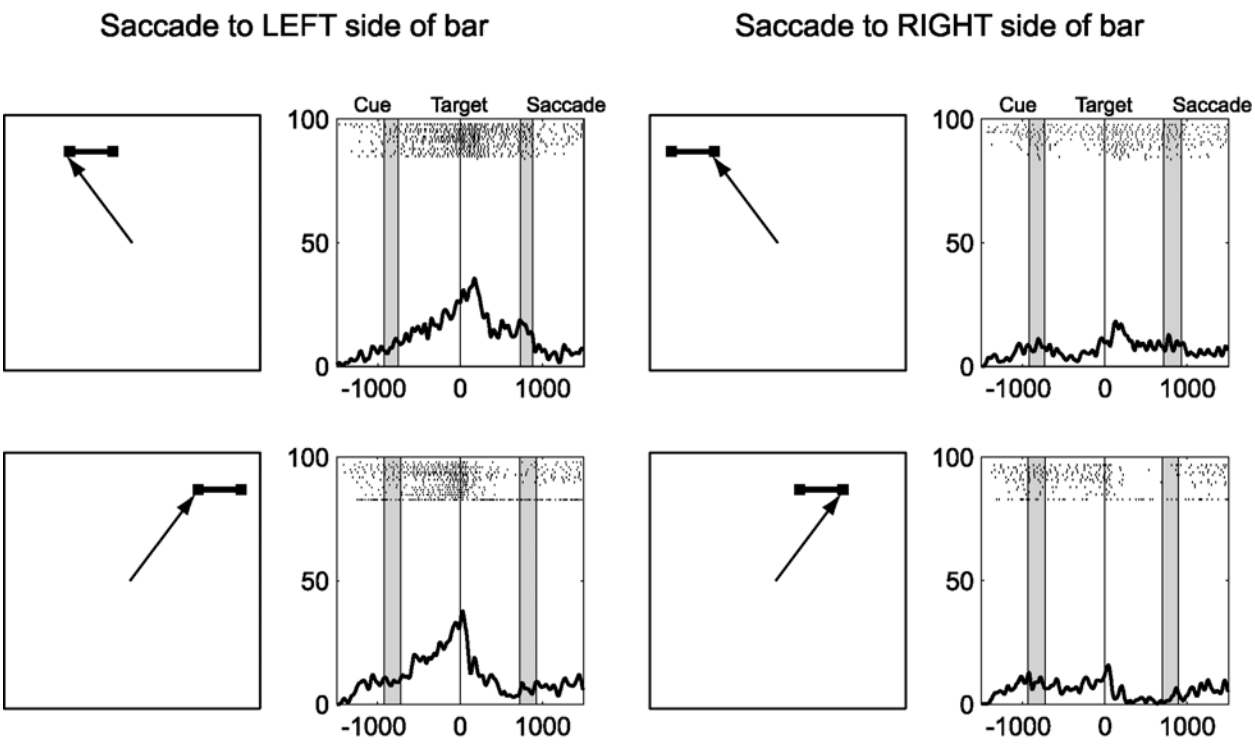

Fig. 4. Activity of an individual SEF neuron during an object-centered task.

Same neuron as in Fig. 2, here during performance of the object-centered bar task. Left two columns show trials in which saccades were directed to the left side of the bar. Right two columns show trials in which saccades were directed to the right side of the bar. Top panels show saccades directed to the left of the screen. Bottom panels show saccades directed to the right side of the screen. Conventions for plotting data are as in Fig. 2, with the exception that the cue in this task was a green or red square indicating whether the target would be on the left or right side of the bar. Activity was recorded for saccades directed to bars placed in both the upper and lower hemifield, but data from only the upper hemifield is shown for simplification. For more details of the task, refer to section 2.2. As is clear from the figure, this neuron demonstrated robust object-centered selectivity following the onset of the colored cue (marked Cue in the figures), preferring locations to the left in an object-centered reference frame. This neuron also shows an interesting property whereby activity of the neuron following the bar onset (marked Target in the figures) changed depending on the direction of the saccade, preferring saccades directed to the left side of the bar that is additionally on the left side of the screen (compare top left and bottom left activity panels). This complex interaction between object-centered selectivity and retina-centered selectivity will be addressed in Aim 1.

The encoding of object-centered locations is also largely insensitive to changes in the rule used to guide the object-centered saccade. Tremblay and colleagues trained monkeys to direct saccades to one or the other end of a bar when following one of two rules (Tremblay et al. 2002). In the color matching rule task, a colored cue on the end of a sample bar instructed the monkey to direct a saccade to the matching colored end of a two-colored target bar. In the object-

centered rule task, the object-centered location of the cue on the sample bar would instruct the monkey to direct a saccade to a specific end of a uniformly gray target bar. Critical to this study was the fact that, in the color matching task, the cue and target colors could appear on either end of the bars, dissociating color and object-centered location and requiring the monkey to follow a color-matching rule. In both of these conditions, neurons in the SEF signaled the object-centered location of the impending saccade, supporting the hypothesis that SEF neurons encode object-centered locations irrespective of the rule used guide the behavior. This differentiates the object-centered selective activity seen in SEF neurons from more general rule selective activity seen in neurons other cortical areas (e.g., Asaad et al. 2000; Stoet and Snyder 2004; Wallis et al. 2001; Wallis and Miller 2003).

All of the experiments described above strongly support the existence of a neural representation for object-reference frames. Research from other groups have produced very similar instances of object-centered selectivity in single neurons using slightly different task paradigms (Breznen et al. 2004; Horwitz et al. 2004b). The work from our laboratory and from these other laboratories has characterized many of the circumstances under which SEF neurons are capable of exhibiting object-centered selectivity. A number of issues remain to be resolved regarding the existence of object-centered spatial coding by SEF neurons. We have been, up to this point, uncertain as to how object-centered and egocentric signals in the SEF coexist. Furthermore, we have been uncertain as to how object-centered signals in the SEF develop and whether they persist over time. Given that such a considerable number of studies have established *that* the phenomenon of object-centered spatial coding by SEF neurons exists, the work presented in this report seeks understand *how* this spatial reference frame is encoded by SEF neurons.

1.7. Experimental aims

1.7.1. Aim 1: Interaction of retina-centered and object-centered signals in SEF neurons

As noted above, some studies have shown that SEF neurons represent spatial locations in egocentric coordinates, while others have shown that SEF neurons exhibit selectivity for object-centered spatial locations. The fact that both reference frames are used by neurons in the SEF leaves us with a critical set of questions that must be addressed. First, can individual neurons display both egocentric and object-centered reference frames? Second, if so, under what circumstances do neurons exhibit one or the other? Finally, if so, how is the manifestation of the two signals related at the level of the single neuron? Previous work from our laboratory has shown that single neurons do appear to be capable of representing space in both reference frames (Olson and Gettner 1995; Olson and Tremblay 2000), but a more comprehensive study of the subject is required to understand the precise nature of the interaction. The hypothesis that we sought to test in this aim, based on previous work in our laboratory (Olson and Gettner 1995; Olson and Tremblay 2000), is that SEF neurons are capable of encoding locations using both egocentric and object-centered reference frames.

1.7.2. Aim 2: The effect of learning on object-centered signals in SEF neurons

As noted above, single neurons in the SEF encode object-centered locations even when the monkey is not explicitly following an object-centered rule (Tremblay et al. 2002), suggesting that object-centered spatial encoding is an inherent property of SEF neurons. The monkeys used in the experiment in which this was demonstrated, however, had previously learned to follow an

object-centered rule, directing saccades to object-centered target locations. It is possible that neurons in the SEF had become tuned for object-centered location as a product of the monkeys having previously learned to discriminate object-centered locations on the bar. It is therefore of interest to determine whether SEF neurons exhibit object-centered spatial selectivity *before* learning to perform the bar task. The hypothesis that we sought to test in this aim, based on the results of previous studies from our laboratory (Tremblay et al. 2002) is that SEF neurons innately encode object-centered locations, both before and after training on the object-centered task.

1.7.3. Aim 3: Automatic encoding of object-centered space in SEF neurons

Tremblay and colleagues (2002), showed that when monkeys perform interleaved trials of object-centered tasks and non-object-centered tasks, SEF neurons show selectivity for object-centered locations in both tasks. This result suggests that the neural representation of object-centered locations is always present, persisting even in tasks in which it is not needed for correct performance. This persistence may be a reflection of a permanent induction of object-centered selectivity in SEF neurons following extensive object-centered training. On the other hand, this persistence may have been due to the close temporal proximity of the two task types (because of task interleaving) and the inability of neurons to rapidly switch from one spatial representation to another. The goal of Aim 3 was to understand two components of this persistent object-centered selectivity. First we sought to determine whether SEF neurons show object-centered selectivity on non-object-centered tasks following a shorter duration of training on the object-centered task than was used in the study of Tremblay et al. (2002). Second, we addressed the question of whether the separation of object-centered and non-object-centered tasks into long blocks of non-

interleaved trials would decrease the strength of object-centered signals observed during performance on the non-object-centered task. The hypothesis that we sought to test, based on previous research from our laboratory (Tremblay et al. 2002) and the results from Aim 2, is that object-centered selectivity, once induced through learning, is consistently expressed, and is exhibited during performance of multiple blocks both the object-centered task and the non-object-centered color-matching task.

2. Interaction of Retina-Centered and Object-Centered Signals in SEF Neurons

2.1. Introduction

The macaque SEF, an area on the dorsomedial shoulder of the frontal lobe, has been proposed to be involved in the generation of saccadic eye movements. This is indicated by the fact that intracortical microstimulation at levels of current elicits eye movements (Fujii et al. 1995; Lee and Tehovnik 1995; Mann et al. 1988; Martinez-Trujillo et al. 2003a; Martinez-Trujillo et al. 2004; Martinez-Trujillo et al. 2003b; Missal and Heinen 2001, 2004; Mitz and Godschalk 1989; Russo and Bruce 1993; Schall 1991a; Schlag and Schlag-Rey 1985, 1987a, b; Tehovnik and Lee 1993; Tehovnik et al. 1994; Tehovnik and Slocum 2000; Tehovnik et al. 1999; Tehovnik et al. 1998; Tehovnik and Sommer 1996, 1997; Tian and Lynch 1995). It is also indicated by the fact that single neurons are active during the planning and execution of eye movements toward targets in restricted response fields (Bon and Lucchetti 1991, 1992; Chen and Wise 1995a, b, 1996, 1997; Coe et al. 2002; Fujii et al. 2002; Hanes et al. 1995; Lee and Tehovnik 1995; Mushiake et al. 1996; Olson and Gettner 1995, 1999, 2002; Olson et al. 2000; Olson and Tremblay 2000; Russo and Bruce 1996, 2000; Schall 1991a, b; Schlag and Schlag-Rey 1985, 1987b; Schlag et al. 1992; Schlag-Rey et al. 1997; Tremblay et al. 2002).

The contribution of the SEF to eye movement generation, however, probably occurs at the level of cognition rather than of motor programming. This is indicated by the fact that neuronal activity reflects many factors other than the parameters of saccades (Amador et al. 2000, 2004; Chen and Wise 1995a, b, 1996, 1997; Coe et al. 2002; Fujii et al. 2002; Isoda and Tanji 2002,

2003; Lu et al. 2002; Mann et al. 1988; Mushiake et al. 1996; Nakamura et al. 2004; Olson and Gettner 2002; Olson et al. 2000; Schlag-Rey et al. 1997; Stuphorn et al. 2000b).

The sophistication of functions performed by the SEF is underscored by the fact that neurons represent saccade direction with respect to multiple spatial reference frames. Electrical stimulation at some sites elicits saccades of fixed direction regardless of initial gaze angle (suggesting that the representation of saccade direction is retinocentric or oculocentric) while electrical stimulation at other sites elicits saccades to a fixed end-point regardless of initial gaze angle (Bon and Lucchetti 1992; Lee and Tehovnik 1995; Mann et al. 1988; Mitz and Godschalk 1989; Schall 1991a; Schlag and Schlag-Rey 1985, 1987a, b; Tehovnik and Lee 1993; Tehovnik et al. 1994; Tehovnik and Slocum 2000; Tehovnik et al. 1999; Tehovnik et al. 1998; Tehovnik and Sommer 1996, 1997). The latter observation has been taken as suggesting that saccadic end-points are represented relative to a head-centered reference frame but there are alternative interpretations (Russo and Bruce 1993, 1996, 2000). The idea that SEF neurons are sensitive to locations as defined in head-centered coordinates is concordant with reports that the firing of some neurons reflects the angle of gaze as defined relative to the head (Bon and Lucchetti 1992; Lee and Tehovnik 1995; Schall 1991a, b; Schlag and Schlag-Rey 1985; Schlag et al. 1992) and that some neurons fire equivalently for saccades that bring the eyes to the same target in head-centered space from different directions (Mann et al. 1988).

That the SEF is involved in cognitive as distinct from motor processes has emerged particularly strikingly from studies in our laboratory showing that around half of SEF neurons are selective for the object-centered location of a saccade target, firing differentially before saccades to the right or left end of a horizontal bar even when the properties of the saccade are held constant (Olson and Gettner 1995, 1999; Olson and Tremblay 2000; Tremblay et al. 2002),

a finding supported by recent results from other laboratories (Breznen et al. 2004; Horwitz et al. 2004b). In our previous studies, the location of the bar was varied from trial to trial so as to allow counterbalancing the retina-centered location of the target against its object-centered location. This allowed demonstrating that neurons were indeed sensitive to object-centered as distinct from retina-centered location. However, because the range of variation was limited, with the bar always confined to the upper quadrant of the visual field, the results left several questions unanswered, including, notably: (a) how is a neuron's selectivity for object-centered location affected by the direction of the saccade and (b) how is a neuron's selectivity for saccade direction affected by the object-centered location of the target? To answer these and related questions, we monitored neuronal activity in the SEF while monkeys planned and executed saccades in directions distributed around the clock to targets that included dots and the right and left ends of horizontal bars.

2.2. Methods

2.2.1. Subjects

Two adult male rhesus monkeys were used (Macaca mulatta; laboratory designations Bi and Ro hereafter referred to as M1 and M2). Experimental procedures were approved by the Carnegie Mellon University Animal Care and Use Committee and were in compliance with the guidelines set forth in the United States Public Health Service Guide for the Care and Use of Laboratory Animals.

2.2.2. Preparatory surgery

At the outset of the training period, each monkey underwent sterile surgery under general anesthesia maintained with isofluorane inhalation. The top of the skull was exposed, bone screws were inserted around the perimeter of the exposed area, a continuous cap of rapidly hardening acrylic was laid down so as to cover the skull and embed the heads of the screws, a head-restraint bar was embedded in the cap, and scleral search coils were implanted on the eyes, with the leads directed subcutaneously to plugs on the acrylic cap (Robinson 1963). Following initial training, a 2-cm-diameter disk of acrylic and skull, centered on the midline of the brain approximately at anterior 21 mm (Horsley-Clarke coordinates), was removed and a cylindrical recording chamber was cemented into the hole with its base just above the exposed dural membrane.

2.2.3. Task

Each trial of the bar-dot task proceeded through the following stages: attainment of central fixation (Fig. 5B1), presentation of a foveal cue instructing the monkey whether the saccade target would be the left or right end of a bar or a dot Fig. 5B2), a pre-target-onset delay period (Fig. 5B3), onset of a target display, either a bar or a dot, which remained visible during a post-target-onset delay period (Fig. 5B4), offset of the central fixation spot (Fig. 5B5) and execution of a saccade (Fig. 5B6) followed at a random interval in the range 0-300 ms by disappearance of the display and juice delivery. The central and peripheral fixation windows were 5° x 5°. The 24 conditions (eight dot, eight bar-left and eight bar-right: Fig. 1A) were interleaved randomly subject to the constraint that one trial conforming to each condition had to be completed successfully before the beginning of the next block of 24 trials. Data collection continued until

16 trials had been completed under each condition unless the neuron was lost. In the event of the neuron's being lost, the data were retained and included in the database for subsequent analysis if at least eight trials had been completed successfully under each condition.

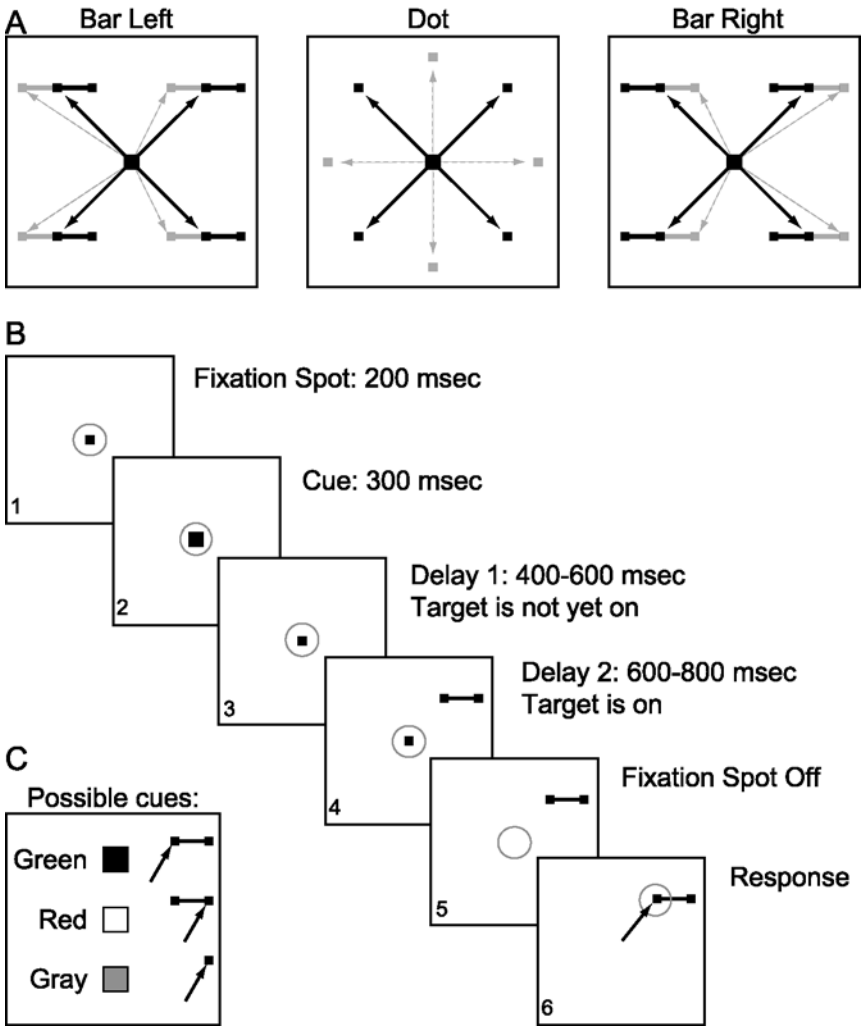

Fig. 5. Bar-dot task.

A. There were eight conditions in which the target was at the left end of a bar, eight in which the target was a dot and eight in which the target was at the right end of a bar. Data analysis focused on twelve conditions (shown in black) in which the saccade was directed along one of the 45° obliques to a location that could be occupied by a target of any of the three types. B. Sequence of events during the trial. 1) A white fixation spot appeared at the center of the screen and monkey achieved foveal fixation. 2) After 200 ms, the fixation spot was replaced by a cue the color of which instructed the monkey whether to prepare a saccade to the left end of a bar, a dot, or the right end of a bar. 3) A delay ensued. 4) The target display (in this example, a bar in the upper right quadrant) appeared and remained on during an ensuing delay period. 5) Offset of the fixation spot served as an imperative cue. 6) The monkey was required to make a saccade directly to the target. C. A green, gray or red foveal cue instructed the monkey to prepare a saccade to the left end of a bar, a dot or the right end of a bar.

2.2.4. Stimuli

Geometry. The displays (Fig. 5) were identical for the two monkeys but the distance from the eyes to the monitor was less for M2 by a factor of 0.96. In analyzing saccade trajectories, we scaled up data from M2 by a factor of 1.04 so as to achieve register with data from M1. The values given here are for M1. The fixation spot was a 0.43° x 0.43° white square presented at the center of the screen. The foveal color cue was a 1.7° x 1.7° gray, green, or red square. The bar display consisted of two 1.3° x 1.3° gray squares centered on the ends of a horizontal gray bar 5.7° long and 0.28° thick. The bar display was centered at one of eight locations 11.4° above or below the zero degree horizontal meridian and 8.5° or 14.2° degrees to the right or left of the zero degree vertical meridian. The dot display consisted of a single 1.3° x 1.3° gray square placed at a location 16.1° eccentric along one of eight rays emanating from the fixation point at 45° intervals. In consequence of the above constraints, there were four points, located at 16.1° eccentricity along 45° oblique rays emanating from the fixation point, at which could appear a solitary dot target, a dot forming the left end of a bar or a dot forming the right end of a bar. This design feature was critical because it allowed analyzing neuronal activity accompanying a saccade to the same dot as a function of whether the dot was solitary or at the left end of a bar or at the right end of a bar.

Luminance and hue. The fixation point had a luminance of 83 cd/m^2 and CIE x and y chromaticity coefficients of 0.28 and 0.32. The red cue and target had a luminance of 33 cd/m^2 and CIE x and y chromaticity coefficients of 0.33 and 0.17. The green cue and target had a luminance of 67 cd/m^2 and CIE x and y chromaticity coefficients of 0.25 and 0.66. The gray bar

and targets had a luminance of 57 cd/m^2 and CIE x and y chromaticity coefficients of 0.27 and 0.31.

2.2.5. Single-neuron recording

At the beginning of each day's session, a varnish-coated tungsten microelectrode with an initial impedance of several megohms at 1 KHz (Frederick Haer & Co., Bowdoinham, ME) was advanced vertically through the dura into the immediately underlying cortex using a hydraulic microdrive (Narashige, Tokyo, Japan). The electrode could be placed reproducibly at points forming a square grid with 1 mm spacing (Crist et al. 1988). Single neurons were isolated using both online and offline template-matching and principal components analysis sorting (Plexon Inc, Dallas, TX).

2.2.6. Behavioral control and data collection

All aspects of behavioral procedure, including presentation of stimuli, monitoring of eye movements, and delivery of reward, were under the control of a Pentium-based computer running Cortex software (http://www.cortex.salk.edu). Eye position was monitored by means of a scleral search coil system (Riverbend Instruments, Inc., Birmingham, AL). The X and Y coordinates of eye position were stored at 10 ms intervals. Stimuli generated by an active matrix LCD projector were rear-projected on a frontoparallel screen 25.4 cm (M1) and 24.5 (M2) cm from the monkey's eyes. Reward in the form of 0.1 cc of juice was delivered through a spigot under control of a solenoid valve upon successful completion of each trial.

2.2.7. Analysis of behavioral performance

Behavioral data, including percent correct and reaction time, as well saccade velocity, amplitude, and landing points, were calculated for each trial in both tasks. These data were compared across tasks to determine the behavioral effect of changes in task requirements. In all cases, significant differences in behavioral data were assessed using t-tests or Kolmogorov-Smirnov tests ($p < 0.05$).

2.2.8. Analysis of saccade metrics

The aim of this step was to characterize the properties of the saccade executed on each trial. First, the direction of gaze was determined for each 10 ms bin during a 500 ms epoch beginning with offset of the fixation spot. Then the instant of maximal velocity was identified by finding the pair of adjacent 10 ms bins (B_m and B_{m+1}) for which the displacement of the eye in degrees of visual angle (ΔE_m) was maximal. The maximal velocity, in degrees of visual angle per second, was given by $100*\Delta E_m$. The start of the saccade was identified by moving backward in time until encountering a pair of bins, B_s and B_{s+1}, for which $\Delta E_s < \Delta E_m/4$. Saccadic reaction time was taken as the interval between offset of the fixation spot and the beginning of bin B_{s+1}. The finish of the saccade was identified by moving forward in time until encountering a pair of bins, B_f and B_{f+1}, for which $\Delta E_f < \Delta E_m/4$. Saccade amplitude was taken as the distance in degrees of visual angle between eye positions recorded at B_s and B_{f+1}. The final position of the eye was estimated on the basis of B_{f+7} so as to allow time for asymptotic deceleration without exceeding the minimal reaction time for any corrective saccade.

2.2.9. Analysis of neuronal activity

To characterize the dependence of neuronal activity on the retina-centered direction of the saccade and the object-centered location of the target, we carried out a series of ANOVAs as described in the text. Independent analyses were carried out on data from three epochs: a pre-target-onset epoch (cue onset + 100 ms to target onset + 100 ms), a post-target-onset epoch (target onset + 100 ms to fixation point offset + 100 ms), and a peri-saccadic epoch (saccade initiation +/- 150 ms). The criterion for significance was taken as $p < 0.05$ unless otherwise stated. In comparing counts of neurons exhibiting significant effects, we used a χ^2 test. In all such cases, if there was only one degree of freedom, we incorporated a Yates correction.

2.2.10. Multiple regression analysis

In order to determine whether firing rate was correlated with object-centered location independently of any effect arising from subtle variations in saccades between bar-left and bar-right trials, we performed a multivariate regression analysis, fitting three models to data collected from each neuron during trials in which the target (the right or left end of a bar) appeared at a given screen location:

1) $Y = \beta_0 + \beta_1 Obj + \beta_2 Lat + \beta_3 Vel + \beta_4 Amp + \beta_5 Xpos + \beta_6 Ypos$

2) $Y = \beta_0 + \beta_1 Lat + \beta_2 Vel + \beta_3 Amp + \beta_4 Xpos + \beta_5 Ypos$

3) $Y = \beta_0 + \beta_1 Obj$

where Y = firing rate measured during the post-target-onset period (target onset +100 ms to saccade initiation +100 ms), Obj = object-centered location (0 or 1 for bar-left or bar-right), Lat

= latency (from fixation spot offset), Vel = peak velocity, Amp = amplitude, and Xpos and Ypos = final x and y landing positions respectively. Having fitted the parameters of each model to a neuron's data, we determined, using an F-test, whether the full model (1), when compared to each of the reduced models (2, 3) accounted for significantly more of the variance in the data than could be explained by its larger number of degrees of freedom. If model 1 provided a significant improvement over model 2, we concluded that neuronal activity depended significantly on object-centered location independently of any tendency for saccade parameters to co-vary with object-centered location. If model 1 provided a significant improvement over model 3, we concluded, by similar reasoning, that neuronal activity depended significantly on variations in the saccade. We computed F as:

$$F_{k,m-(n+k)} = \frac{\left(\frac{SS_{red} - SS_{full}}{k}\right)}{\left[\frac{SS_{full}}{m-(n+k)}\right]}$$

where k = the difference in degrees of freedom between the two models, m = the number of trials, n = 1 was the number of neurons, and SS_{full} and SS_{red} were the residual sums of squares for the full model and the reduced model.

2.2.11. Characterization of recording sites

The location of the recording sites relative to gross morphological landmarks was assessed by analysis of structural MR images. Scanning was carried out in a Brükker 4.7 T magnet in which the anesthetized monkey was supported by an MR-compatible stereotaxic device. Fiducial marks made visible by means of a contrast agent included the centers of the ear bars and

selected locations inside the recording chamber. Frontoparallel and parasagittal slices of 2 mm thickness were collected over the entire extent of the cerebral hemisphere. To determine the location of recording sites relative to functional divisions of cortex, we mapped out regions under each chamber from which oculomotor responses could be elicited at low threshold (≤ 50 μA) by electrical microstimulation (1.65 ms biphasic pulses delivered through the recording microelectrode at a frequency of 300 Hz in trains 200 ms long).

2.3. Results

2.3.1. The bar-dot task

Data were collected in the context of a single task in which, on interleaved trials, the target could be either a dot, as in standard oculomotor tests, or the right or left end of a horizontal bar, as in previous studies demonstrating object-centered spatial selectivity (Fig. 5). A foveal cue presented early in each trial (Fig. 5B, panel 2) instructed the monkey (by its color) concerning the nature of the response required at the end of the trial, either a saccade to a dot (gray cue) or a saccade to the left or right end of a bar (green or red cue respectively). After a delay of 400-600 ms (Fig. 5B, panel 3), the target appeared – either a dot at one of eight possible locations (if the cue had been gray) or a bar at one of eight possible locations (if the cue had been green or red) (Fig. 5A). After a further delay of 600-800 ms, offset of the foveal fixation spot signaled the monkey to execute a saccade to the instructed location (Fig. 5B, panel 5).

The essential aim of using this task was to allow analyzing how neuronal activity depended on the combination of two independent factors: the retina-centered location and the object-centered location of the target. To allow characterizing neuronal selectivity for retina-centered

direction, the location of the target was allowed to vary around the clock – a feature unique to this study as compared to previous studies characterizing object-centered spatial selectivity in the SEF (Olson and Gettner 1995, 1999; Olson and Tremblay 2000; Tremblay et al. 2002). Within the full set of 24 trial conditions, there was a subset of twelve conditions (targets and saccade vectors indicated by dark shading in Fig. 5A) that represented the full crossing of four saccade directions (on the 45° obliques) with three target types (dot, bar-left and bar-right). Data analysis focused on this subset of conditions because, within it, saccade direction and the nature of the target were strictly counterbalanced.

2.3.2. Behavior

Percent Correct. In assessing behavioral performance, we confined our attention to a set of trial conditions across which retina-centered direction (one of four 45° obliques) and the nature of the target (dot, bar-left or bar-right) were fully counterbalanced (conditions represented by dark shading in Fig. 5A). We first assessed performance in terms of percent correct by considering a data base consisting of the percent-correct scores for dot, bar-left and bar-right trials during each electrophysiological data collection session. The score for each condition during each session was taken as the number of trials on which the monkey made a saccade to the correct target expressed as a percentage of all trials on which he made some saccade in response to the imperative command (offset of the fixation spot). The monkeys performed somewhat better under dot than under bar conditions. M1 and M2 scored 99% and 98% respectively under dot conditions whereas under bar-left conditions the scores were 96% and 89% and under bar-right conditions they were 94% and 86%. In both monkeys, the tendency for the percent correct score to vary across conditions was significant (Kruskal-Wallis, $P<0.01$) and

the significance was revealed by post hoc tests to depend on the comparison between dot and bar conditions (Kolmogorov-Smirnov, $P<0.01$) rather than on the comparison between bar-right and bar-left conditions (Kolmogorov-Smirnov, $P>0.05$). The slight difference between monkeys on dot trials was not significant (Kolmogorov-Smirnov, $P>0.05$) but the tendency for M1 to perform better than M2 on bar trials was significant (Kolmogorov-Smirnov, $P<0.01$). It is not surprising that performance was better overall on dot than on bar trials because the monkey could simply make a saccade to the single visible target on a dot trial whereas, on bar trials, he had to select one end of the bar on the basis of a rule conveyed by a cue presented early in the trial and held in working memory over the course of a 1000-1400 ms delay.

Reaction time. In assessing reaction time, we first took the mean for each session of the interval between when the fixation spot was extinguished and the saccade began (Methods: Saccade Metrics). The monkeys were free to respond as soon as the fixation spot vanished. We had introduced temporal jitter (in the range 400-600 ms) into the delay period between onset of the target and offset of the fixation spot so as to discourage anticipatory saccades. Nevertheless, it is clear from the short durations of the RTs that the monkeys were engaging in anticipatory behavior. In M1, the mean RTs on dot trials, bar-left trials, and bar-right trials were 118 ms, 101 ms and 106 ms respectively. In M2, the corresponding values were 139 ms, 105 ms and 80 ms. In each monkey, all pairwise differences between conditions achieved significance (Kruskal-Wallis with post hoc Kolmogorov-Smirnov, $P<0.01$). We have no ready explanation for the consistent tendency whereby responses were swifter on bar trials than on dot trials.

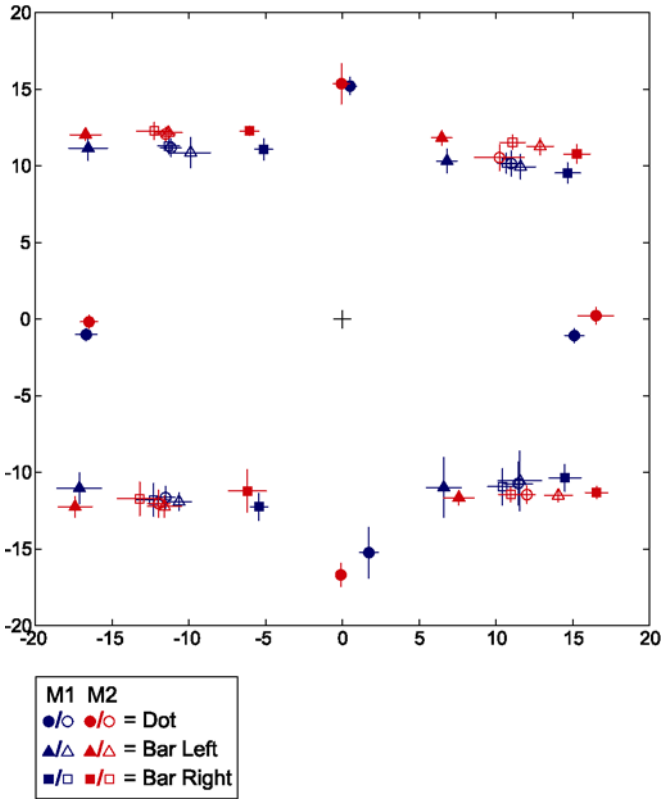

Fig. 6. Saccadic end-points.

For each trial condition in each monkey are shown the mean and the horizontal and vertical standard deviations of the landing position of the eyes (as obtained by computing the mean for each session and then taking the mean and standard deviations of the session means). Units on both axes are degrees of visual angle. Cross marks central fixation spot. Open symbols represent landing points under the twelve conditions on which most stages of data analysis were based (conditions in which the target lay on a 45° oblique ray emanating from fixation: black vectors in Fig. 5A). Filled symbols represent landing points under the other twelve conditions (gray vectors in Fig. 5A).

Saccadic landing position. To assess whether there was a consistent discrepancy between the landing point of the saccade and the location of the target, we computed the mean location of the landing point under each condition during each electrophysiological data collection session and then computed the means across sessions. We found, as expected, that saccades to a target at a given location tended to terminate close to each other regardless of the nature of the target (Fig. 6). However, there was a degree of systematic variability in the landing position on bar trials as reported previously (Olson and Tremblay 2000). In particular, the eyes deviated slightly from the end of the bar toward its center, with the result that they landed farther to the right on bar-left

trials than on bar-right trials under conditions in which the target dots on the ends of the bars occupied precisely the same location on the screen. The mean horizontal difference in landing position on bar-left and bar-right trials was 1.3° in M1 and 1.8° in M2. We assess below, through a multiple regression analysis, the degree to which the subtle differences in ocular trajectory between bar-left and bar-right trials affected the firing rates of neurons (section 2.3.6).

2.3.3. Recording sites

We recorded bilaterally from a total of 233 neurons in the SEFs of two monkeys (129 and 104 neurons in M1 and M2 respectively). All recording sites (as shown in Fig. 7) were within a region, straddling the interhemispheric midline 4-8 mm rostral to the genu of the arcuate sulcus, from which eye movements could be elicited by microstimulation at low levels of current ($\leq$ 50 μA). They thus met criteria for assignment to the SEF as established in classic studies (Russo and Bruce 1993, 2000; Schlag and Schlag-Rey 1985, 1987a, b).

2.3.4. Examples of spatially selective neurons

Some SEF neurons exhibited robust selectivity for the object-centered location of the target of a saccade. The neuron of Fig. 8A is an example. It fired much more strongly on trials in which the right end of a bar was the target than on trials in which the target was the bar's left end. It exhibited object-centered spatial selectivity both during the first delay period (following the cue conveying the object-centered instruction) and during the second delay period (following onset of the target bar). During the latter period, the neuron's firing rate continued to reflect the

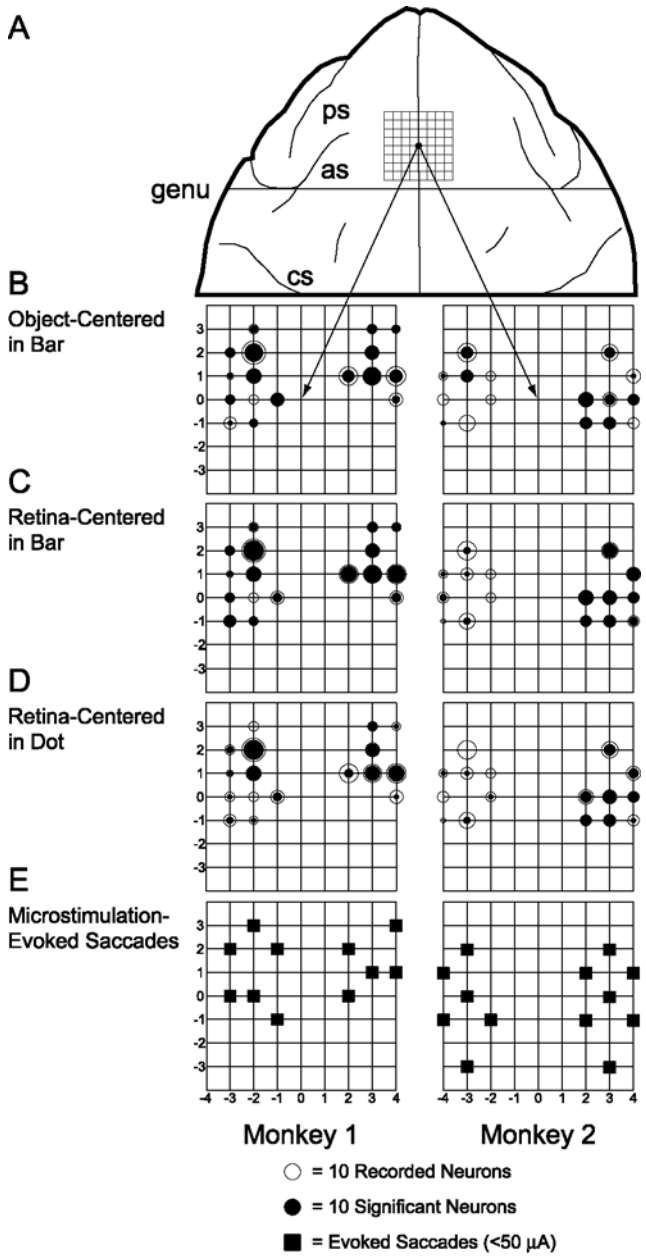

Fig. 7. Recording sites in the bar-dot task.

Recording sites in both monkeys were localized relative to gross morphological landmarks visible in structural MR images and relative to regions from which motor responses could be elicited by low-threshold electrical microstimulation (200 ms 300 Hz trains of 1.65 ms biphasic pulses at currents ≤50 μA). A. Schematic dorsal view of frontal lobe with recording grid superimposed on it. Points of intersection of grid lines (spaced at 1 mm intervals) represent possible recording locations. The center of the grid in each monkey was located within 0.5 mm of a point 5 mm rostral to the genu of the arcuate sulcus ("genu") and at the interhemispheric cleft. as: arcuate sulcus; cs: central sulcus; ps: principal sulcus. B-D. Distribution of neurons exhibiting object-centered spatial selectivity under bar conditions (B), retina-centered spatial selectivity under bar conditions (C) and retina-centered spatial selectivity under dot conditions (D). At each location, the area of the outer (open) bubble indicates the number of recorded neurons and the area of inner (filled) bubble indicates the number exhibiting selectivity. E. Distribution of sites at which electrical stimulation was demonstrated to elicit eye movements. Results for M1 and M2 are shown in left and right columns respectively.

object-centered location of the target - and not the retina-centered direction of the saccade - even though the direction of the saccade was determined by the presence of the bar in a particular quadrant.

Other SEF neurons were selective primarily for the retina-centered direction of a planned saccade. The neuron of Fig. 8B is an example. Following onset of the target, which determined the direction of the impending saccade, this neuron fired strongly in the event that the planned saccade was up and to the right but not otherwise. It did so regardless of whether the saccade was to be directed to a dot or to the right or left end of a bar – although firing persisted at a higher level on bar than on dot trials.

Yet other SEF neurons were markedly sensitive to both object-centered and retina-centered location. The neuron in Fig. 8C is an example. It fired following onset of the target in the left hemifield at a rate that depended on the identity of the target (highest on bar-left trials and lowest on bar-right trials).

2.3.5. Retina-centered selectivity on dot trials

Rationale. This phase of this analysis had as its aims (1) to identify neurons that fired at significantly different rates during planning of saccades to dot targets at different retina-centered locations and (2) to characterize parametrically the directional signals carried by these neurons.

Statistical assessment. In order to determine how many neurons were sensitive to the retina-centered location of the target during the performance of dot trials, we carried out, for each neuron, independent ANOVAs focused on (1) the post-target-onset epoch (100 ms after bar onset to 100 ms after fixation point offset) and (2) the peri-saccadic epoch (150 ms before to 150 ms

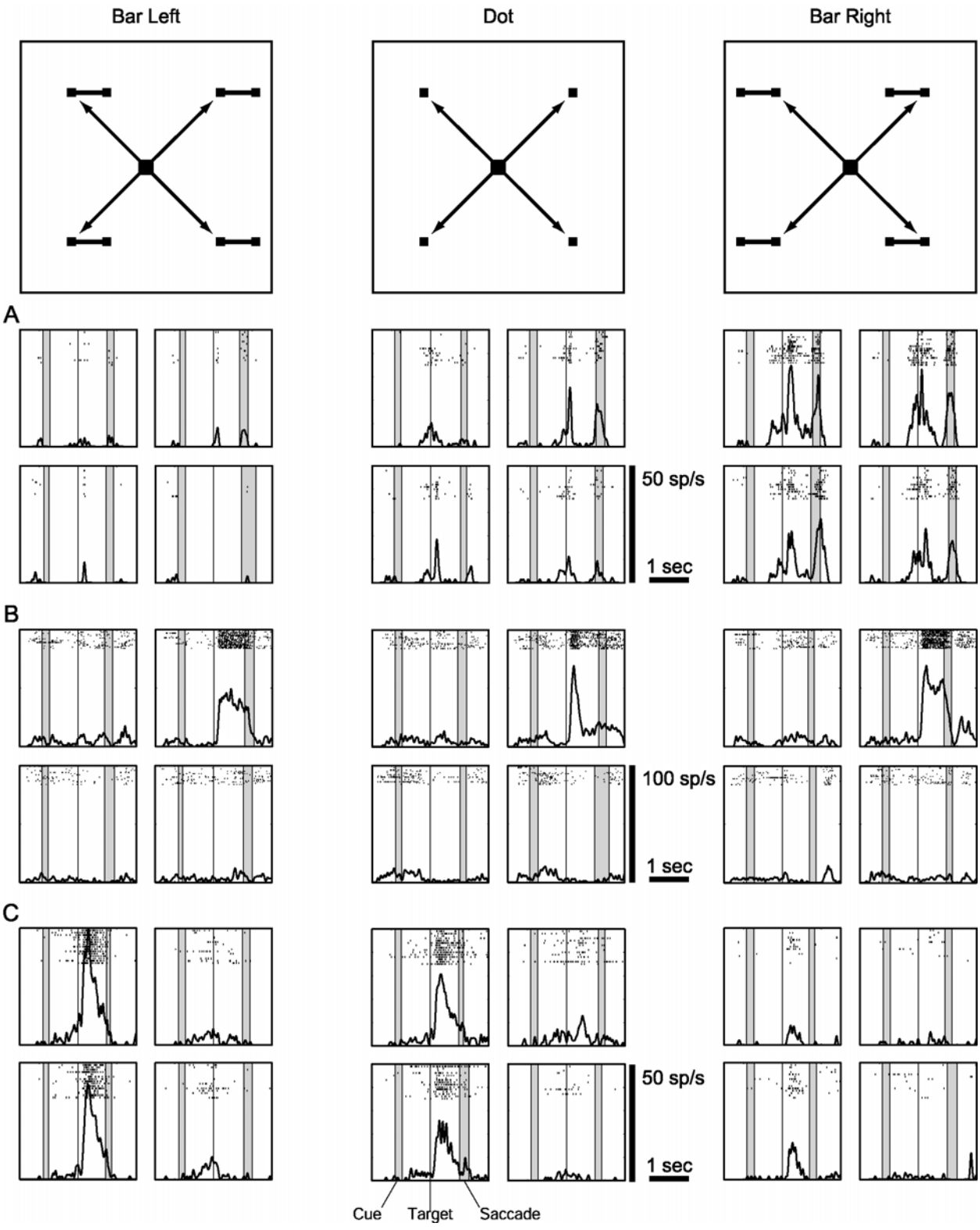

Fig. 8. Activity during the trial under twelve critical conditions for three representative neurons.

A. A neuron sensitive primarily to the object-centered location of the target, firing most strongly on bar-right and least strongly on bar-left trials. B. A neuron sensitive primarily to the retina-centered location of the target, firing

(Fig. 8, ctd.) most strongly before saccades up and to the right regardless of whether they are directed to the left end of a bar, a dot or the right end of a bar. C. A neuron markedly sensitive to both the object-centered and the retina-centered location of the target, firing most strongly when the target is the left end of a bar if the saccade is in a leftward direction. For each neuron, the three tetrads of panels represent data collected when the target was at the left end of a bar (left), was a dot (middle) or was at the right end of a bar (right). In each tetrad of panels, the location of each component panel corresponds to the direction of the required saccade, so that the panel up and to the right represents data collected under a condition requiring a saccade up and to the right and so on. In each panel, rasters from successive trials are shown at the top and spike density functions at the bottom. Both are aligned on the time of onset of the target display (either bar or dot). The times of cue onset and saccade initiation varied within the ranges indicated by the correspondingly labeled gray bars.

after saccade onset). These epochs were chosen to encompass the approximate times during which the SEF would have access to information about (1) the planned saccade and (2) the executed saccade. The offset of 100 ms from key events was included to take into account the approximate latency with which visual occurrences exert an impact on firing in the SEF. Each ANOVA treated firing rate as a function of the single factor retina-centered direction (with four levels corresponding to the four 45° oblique directions). Consideration was restricted to the four 45° oblique directions in order to ensure direct comparability between the results of this analysis and the subsequent analysis carried out on data from bar trials, in which saccades were executed only in those directions.

Incidence. The results, summarized in Table 1, indicate that retina-centered selectivity was common during both epochs. During the post-target-onset epoch, 105/233 = 45% of neurons exhibited significant retina-centered selectivity. During the peri-saccadic epoch, 89/233 = 38% of neurons did so. There was a bias favoring contraversive saccades during both epochs and in both monkeys. This attained significance in data from the two monkeys combined during the post-target-onset epoch (χ^2 test. $p = 0.011$).

Sufficiency of four directions. The rationale for basing the above analyses exclusively on data from trials requiring saccades in the four 45° oblique directions was to ensure strict

Monkey	Post-Target-Onset Epoch		Peri-Saccadic Epoch	
	C>I	I>C	C>I	I>C
M1 N = 129	39 (30%)	24 (19%)	36 (28%)	23 (18%)
M2 N = 104	27 (26%)	15 (14%)	16 (15%)	14 (13%)
Total N = 233	66 (28%)	39 (17%)	52 (22%)	37 (16%)

Table 1. Counts of neurons exhibiting retina-centered selectivity on dot trials

Results of ANOVAs carried out on data from 233 neurons with firing rate as the dependent variable and with the retina-centered location of the dot target (upper left, upper right, lower left or lower right) as a single factor. Independent analyses were carried out on data from the post-target-onset epoch (target onset + 100 ms to fixation point offset + 100 ms) and the peri-saccadic epoch (saccade onset +/- 150 ms). C>I (or I>C): main effect of retina-centered location, with stronger firing overall when the target was in the visual field contralateral (or ipsilateral) to the recording hemisphere. The criterion for significance was $p < 0.05$.

parallelism between the analysis of data from dot trials and of data from bar trials (in which saccades were made only in these directions. Sampling direction coarsely seemed reasonable because neuronal response fields in the SEF are large (Russo and Bruce 1996). Moreover, four directions spaced at 90° have been sufficient for the demonstration of robust directional tuning in prior studies of the SEF (Chen and Wise 1995a, b, 1996, 1997; Olson and Gettner 2002; Olson et al. 2000). Nevertheless, coarse sampling could conceivably result in inaccurate estimates of direction selectivity. To address this issue, we estimated the preferred direction of each neuron independently on the basis of the four directions on which the statistical analysis was founded (black arrows in the central panel of Fig. 5A) and also on the basis of all eight directions (black and gray arrows in the central panel of Fig. 5A). Each estimate was based on the neuron's firing rate during the post-target-onset epoch. It was generated by (a) multiplying the four (or eight) unit vectors pointing toward the four (or eight) target locations by the associated firing rates and (b) summing the resulting vectors. The summed vector contained information about both the magnitude of the directional signal (in its amplitude) and the preferred direction (in its direction). The results obtained by considering four directions were closely concordant with the results

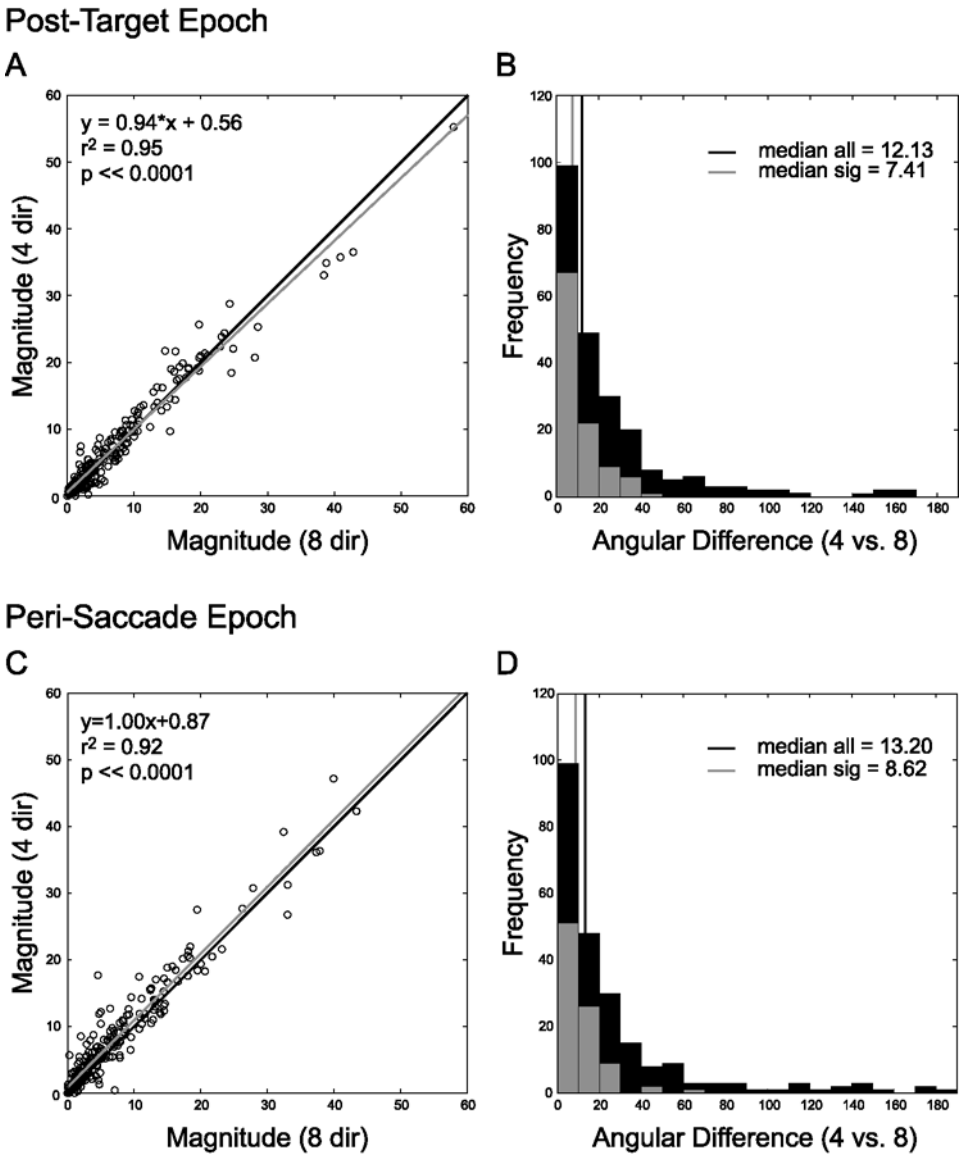

Fig. 9. Comparison of retina-centered selectivity for saccades directed to four or eight locations.

The pattern of retina-centered spatial selectivity of each neuron (as characterized on trials with dots as targets) could be well estimated from firing rates associated with saccades in only four directions (the four 45° obliques). This is indicated by the close correspondence across neurons between the estimate based on these four directions alone and the estimate based on all eight tested directions (Fig. 4A, middle panel). A. During the post-target-onset epoch (from 100 ms after target onset to 100 ms after fixation spot offset), the magnitude of the directional signal, as estimated on the basis of firing rates associated with saccades in four directions, was closely correlated with the magnitude as estimated on the basis of firing rates associated with all eight directions. Black: identity line. Gray: best-fit line. B. During the post-target-onset epoch, the estimate of preferred direction based on four trial conditions was in good agreement with the estimate based on eight trial conditions, as indicated by the fact that the distribution angular differences had a narrow peak close to zero. This was especially true for neurons exhibiting significant retina-centered spatial selectivity during this epoch (gray bars). C-D. Same for peri-saccadic epoch (from 100 ms before to 100 ms after saccade initiation).

obtained by considering all eight directions. The estimated magnitude of the directional signal was tightly correlated across the four- and eight-direction analyses during both the post-target-onset epoch (Fig. 9A) and the peri-saccadic epoch (Fig. 9C). Moreover, the difference between the estimate of the preferred direction based on four directions and that based on eight directions (Fig. 9B and D) had a median value of only 12-14° (for all neurons) or 7-9° (for neurons exhibiting significant selectivity for retina-centered direction in the statistical analysis described above, represented by gray bars in Fig. 9B and D).

Conclusion. On trials in which the monkey was preparing a saccade to a dot target, many SEF neurons were selective for the direction of the impending saccade as defined relative to a retina-centered reference frame. Retina-centered spatial selectivity was evident both during the delay period following onset of the target and during the period surrounding execution of the saccadic response. Firing rates measured in conjunction with planning and executing saccades spaced around the clock at 90° intervals provided a good estimate of retina-centered direction selectivity.

2.3.6. Object-centered selectivity on bar trials

Rationale. This phase of analysis had as its aims (1) to identify neurons that fired at significantly different rates on trials in which the monkey was required to execute a saccade to one end or the other of a bar and (2) to characterize the duration of object-centered signals over the course of the trial.

Statistical assessment. We carried out, for data collected from each neuron during the performance of bar trials, independent ANOVAs focused on three task epochs: (1) the pre-target-onset epoch (100 ms after cue onset to 100 ms after bar onset), (2) the post-target-epoch (100 ms

Monkey	Pre-Target-Onset Epoch					Post-Target-Onset Epoch					Peri-Saccadic Epoch				
	Retina		Object		Int	Retina		Object		Int	Retina		Object		Int
	C>I	I>C	C>I	I>C		C>I	I>C	C>I	I>C		C>I	I>C	C>I	I>C	
M1 N = 129	2 (2%)	3 (2%)	27 (21%)	28 (22%)	3 (2%)	45 (35%)	34 (26%)	20 (16%)	27 (21%)	39 (30%)	38 (29%)	30 (23%)	13 (10%)	17 (13%)	21 (16%)
M2 N = 104	1 (1%)	2 (2%)	22 (21%)	6 (6%)	2 (2%)	32 (31%)	20 (19%)	21 (20%)	8 (8%)	19 (18%)	24 (23%)	14 (13%)	18 (17%)	4 (4%)	18 (17%)
Total N = 233	3 (1%)	5 (2%)	49 (21%)	34 (15%)	5 (2%)	77 (33%)	54 (23%)	41 (18%)	35 (15%)	58 (25%)	62 (27%)	44 (19%)	31 (13%)	21 (9%)	39 (17%)

Table 2. Counts of neurons exhibiting retina-centered and object-centered selectivity on bar trials.

Results of ANOVAs carried out on data from 233 neurons with firing rate as the dependent variable and with the retina-centered location of the target (upper left, upper right, lower left or lower right) and the object-centered location of the target (bar-left or bar-right) as two factors. Independent analyses were carried out on data from the pre-target-onset epoch (cue onset + 100 ms to target onset + 100 ms), the post-target-onset epoch (target onset + 100 ms to fixation point offset + 100 ms) and the peri-saccadic epoch (saccade onset +/- 150 ms). "Retina": main effect of retina-centered location. "Object": main effect of object-centered location. "Int": interaction effect involving both retina-centered and object-centered location. C>I: stronger firing when the target was in the visual field contralateral to the recording hemisphere (in the case of retina-centered selectivity) or at the end of the bar contralateral to the recording hemisphere (in the case of object-centered selectivity). I>C: the opposite pattern. The criterion for significance was $p < 0.05$.

after bar onset to 100 ms after fixation point offset) and (3) the peri-saccadic epoch (150 ms before to 150 ms after saccade onset). These epochs were chosen to encompass the approximate times during which the SEF would have access to information about (1) the object-centered instruction alone, (2) the planned saccade and (3) the executed saccade. Each ANOVA treated firing rate as a function of two factors: object-centered direction (with two levels) and retina-centered direction (with four levels). Consideration was restricted to a set of trial conditions across which object-centered and retina-centered direction were fully counterbalanced (black arrows in Fig. 5A).

Incidence. During the pre-target-onset period, when the object-centered location of the target was known but its retina-centered location was not, around a third of neurons (83/233 = 36%) exhibited significant selectivity for object-centered location. During the post-target-onset period, when both the object-centered and the retina-centered location of the now visible target were known, the count remained at around a third (76/233 = 33%). During the peri-saccadic

period, it dropped to around a quarter (52/233 = 22%). Half of the recorded sample (117/233 = 50%) exhibited significant object-centered selectivity during at least one of the analysis epochs. These results are summarized in table 2.

Timing. The fact that object-centered signals were present throughout the trial does not imply that they were carried by the same neurons from the beginning to the end of the trial. It might have been the case, for example, that different populations were active during the pre-target-onset epoch, when only the object-centered instruction was known, and the later epochs, when the target was visible and, therefore, the retina-centered direction of the impending saccade was also known. To assess the temporal partitioning of object-centered activity, we first posed the question whether the tendency for a neuron to display object-centered selectivity in one epoch was correlated with its tendency to do so in other epochs. The results, shown in Fig. 10, indicate (a) that there was a significant tendency for neurons exhibiting significant object-centered selectivity during one epoch to do so during other epochs but (b) that this did not amount to a firm rule.

To pursue this issue further, unhindered by the division of the trial into arbitrary coarse epochs, we carried out an analysis at a much finer scale of temporal resolution. Focusing on data from 117 neurons in which there was a significant main effect of object-centered location during at least one trial epoch, we constructed a matrix of values in which each row corresponded to a neuron while the columns represented 300 successive 10 ms time bins, with time defined relative to a selected trial event. In each cell of the matrix, we entered a value corresponding to the mean firing rate on bar-right trials minus the mean firing rate on bar left trials for the corresponding neuron in the corresponding 10 ms time bin. We then carried out an analysis of the correlation

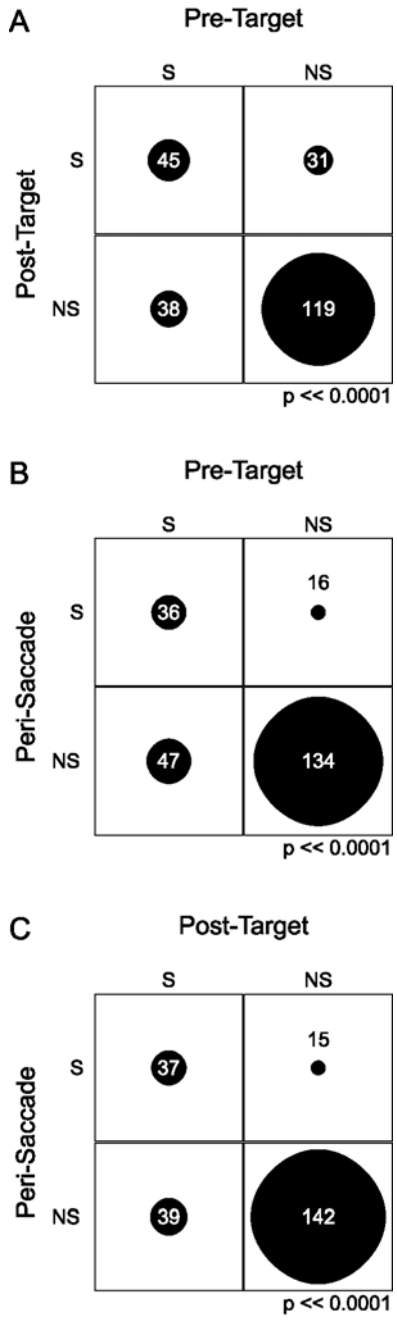

Fig. 10. Incidence of object-centered selectivity in different temporal epochs.

If a neuron exhibited object-centered selectivity in one epoch, then it tended to do so in other epochs as well. A. Counts of cases in which a neuron did (S) or did not (NS) exhibit significant selectivity for object-centered location during the pre-target-onset epoch and did (S) or did not (NS) do so during the post-target-onset epoch. N = 233 neurons. The number of counts along the match diagonal (S+S and NS+NS) was significantly in excess of the number expected on the basis of the null hypothesis that the two properties were distributed across neurons independently (χ^2 test, $p << 0.0001$). B. Same for pre-target-onset epoch vs. peri-saccadic epoch. C. Same for post-target-onset epoch vs. peri-saccadic epoch. Pre-target-onset epoch: 100 ms after onset of the foveal cue to 100 ms after onset of the target display. Post-target-onset epoch: 100 ms after onset of the target display to 100 ms after offset of the fixation spot. Peri-saccadic epoch: 150 ms before to 150 ms after saccade initiation.

between the values in every column (corresponding to a particular 10 ms time bin) and those in every other column. We represented the resulting correlation coefficients in 300x300 bin heat map smoothed by convolution with a Gaussian kernel with a standard deviation of 10 ms (Fig. 11).

The maps in Fig. 11A, B and C represent results obtained when data were aligned on cue onset, target onset and fixation-spot offset respectively. The fact that regions of warm color tend to form square domains in these maps is indicative of the tendency for the trial to contain continuous periods during which the pattern of object-centered selectivity across the neuronal population was consistent. The largest such domain encompasses the entire period from presentation of the cue to execution of the saccade. From its existence, we conclude that the pattern of object-centered activity across the population tended to be conserved from the beginning to the end of the trial. Within this large domain, there are three sub-domains of particularly strong internal correlation. Two occupy periods during which neurons had access only to the object-centered instruction: (1) the period immediately following presentation of the colored foveal cue and (2) a period straddling the instant of target onset. The third occupies (3) the middle part of the post-target-onset delay period, during which neurons had access to information about the location of the target and thus about the direction of the impending saccade. From the existence of these sub-domains, we conclude that neurons tended to fall into three populations representing object-centered location during the post-cue period, the target-anticipation period and the post-target-onset period respectively.

Independence of variability in saccades. It is conceivable that neurons might have appeared to be selective for object-centered location because they were sensitive to subtle variations in

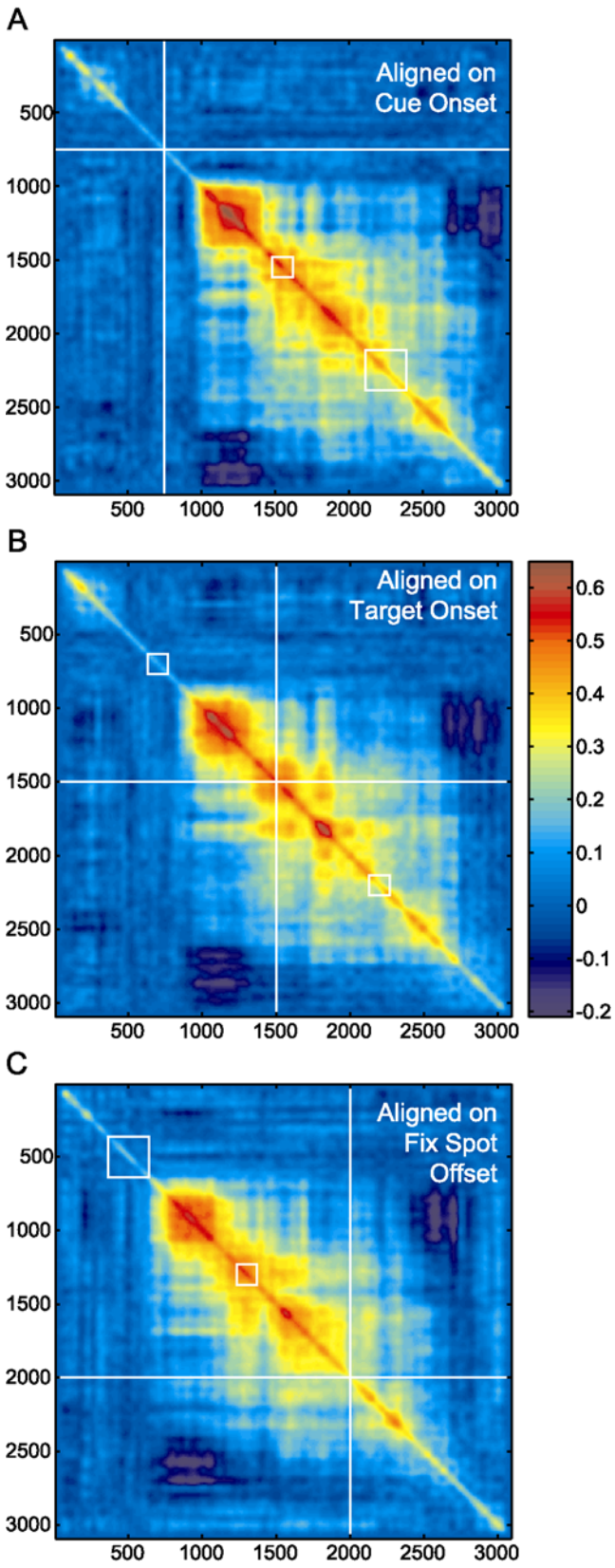
A
Aligned on
Cue Onset
500
1000
1500
2000
2500
3000
B
Aligned on
Target Onset
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
C
Aligned on
Fix Spot
Offset

Fig. 11. Temporal correlation of the object-centered signal

There were sub-domains of time within the trial during which object-centered signals, if present, tended to persist in a consistent form. The color at each point represents the degree of correlation, across all 233 neurons, between the object-centered signal (firing rate on bar-left trials minus firing rate on bar-right trials averaged across all four retina-centered directions) carried at a given time during the trial (horizontal axis) and that carried at each other time (vertical axis). The values are smoothed by convolution with a Gaussian kernel with a standard deviation of 10 ms. This explains the fact that values along the identity diagonal are less than one. A. Data are aligned on onset of the foveal cue (white lines). Range of times of target onset is indicated by the white square roughly at the center of the panel. Range of times of fixation spot offset is indicated by the white square toward the bottom right. B. Data are aligned on onset of the target display (white lines). Range of times of foveal cue onset is indicated by the white square toward the top left. Range of times of fixation spot offset is indicated by the white square toward the bottom right. C. Data are aligned on offset of the fixation spot (white lines). Range of times of foveal cue onset is indicated by the white square toward the top left. Range of times of target onset is indicated by the white square close to the center of the panel. Note the existence of three domains, visible, especially in B, as red squares, during which the pattern of object-centered selectivity tended to remain constant. One preceded target onset, one straddled the instant of target onset and one following target onset.

saccades directed to a given location on the screen when that location was occupied by the left vs. the right end of a bar. To address this issue, we carried out a multivariate regression analysis, fitting three models to data from each neuron: (1) a reduced model containing only a parameter for object-centered location, (2) a reduced model containing parameters for saccadic latency, velocity, amplitude, horizontal landing position and vertical landing position, and (3) a full model containing both sets of factors (see Methods). Having obtained the fits, we then asked, using an F-test, whether the amount of variance accounted for by the full model was significantly greater than the amount accounted for by the reduced object-centered model (in which case the properties of the saccade contributed significantly to determining the neuronal firing rate) and, conversely, whether the amount of variance accounted for by the full model was significantly greater than the amount accounted for by the reduced saccadic model (in which case the factor of object-centered location contributed significantly to determining the neuronal firing rate). This analysis was carried out independently for four sets of data from each neuron derived from trials in which the target was in the four quadrants. Thus it focused on trial-to-trial variations in

saccades that occurred despite the fact that the target was, in a formal sense, always at the same location.

By this approach, we analyzed firing rates during the post-target-onset epoch in 76 neurons exhibiting a significant main effect of object-centered location during this epoch. Each neuron contributed four sets of data. Thus the analysis concerned 304 cases. The general finding was that the neuronal firing rate was much more frequently dependent on object-centered location than on the parameters of the saccade. There was a significant dependence on object-centered location in 121 cases and on saccade parameters in 30 cases. In only 3 cases did firing depend solely on saccade parameters. In light of the fact that the neurons selected for analysis had all exhibited a significant main effect of object-centered location in an ANOVA based on the firing rate during the post-target-onset delay period, one might ask why there were cases in this analysis in which the firing rate was not dependent on object-centered location. The answer is that the multiple regression analysis, as described here, was less powerful than the ANOVA, on which the selection of neurons was based, because it concerned subsets of the full data set, each subset being confined to trials in which the saccade was directed to a single location on the screen. This resulted (a) in a smaller sample size for each analysis and (b) focusing of some analyses on saccade directions associated with low firing rates. We conclude that neuronal activity depended directly on the object-centered location of the target in a substantial number of cases and was not simply sensitive to oculomotor variables correlated with object-centered location.

Conclusion. On trials in which the monkey was preparing a saccade to one end or the other of a bar, many SEF neurons were selective for the location of the target as defined relative to an object-centered reference frame. Object-centered spatial selectivity was present during all

phases of the trial including the pre-target-onset epoch, when only the object-centered location of the target was known, and later epochs, when the retina-centered direction of the impending saccade was known as well. There was, however, a tendency for different populations of neurons to carry object-centered signals before and after onset of the target.

2.3.7. Retina-centered selectivity on bar trials

Rationale. The fact that neurons exhibited retina-centered direction selectivity on dot trials, as described above, cannot be taken to imply that they did so on bar trials. The aim of the next phase of analysis was to identify cases in which a neuron's firing rate did indeed, during bar trials, depend significantly on the retina-centered location of the target.

Incidence. In the ANOVA described at the beginning of the previous section, which included both object-centered and retina-centered location as factors, a substantial number of neurons exhibited a main effect of retina-centered location. The results, summarized in Table 2, indicate, as expected, that retina-centered selectivity was no more common than expected by chance (from type I errors) during the pre-target-onset epoch, when only the object-centered location of the target and not its location relative to the retina was known. However, retina-centered selectivity was common during both late epochs of the trial. During the post-target-onset epoch, 131/233 = 56% neurons exhibited significant retina-centered selectivity. During the peri-saccadic epoch, 106/233 = 45% of neurons did so. There was a bias favoring contraversive saccades during both epochs and in both monkeys, although this did not attain significance in any epoch or monkey (χ^2 test. $p > 0.05$).

Conclusion. A substantial number of neurons fired at significantly different rates as a function of the retina-centered direction of the saccade on trials in which the target was one end or the other of a horizontal bar.

2.3.8. Retina-centered selectivity on bar and dot trials compared

Rationale. This phase of analysis had as its aims (1) to determine whether neurons carrying retina-centered signals on bar trials also did so on dot trials and (2) to compare retina-centered selectivity on bar and dot trials by the use of parametric measures. The analysis focused on data from the post-target-onset delay period. Focusing on this period was motivated by two considerations: first, that both signals were present during it (as was not the case during the pre-target-onset interval) and, second, that it afforded a good signal-to-noise ratio by virtue of its extended duration (greater than the duration of the peri-saccadic interval).

Incidence. To determine whether neurons exhibiting retina-centered selectivity under the bar condition also did so under the dot condition, we compared results obtained in the two ANOVAs described above. We observed a strong (although not perfect) concordance between the tendency for a neuron to exhibit retina-centered selectivity on bar trials and its tendency to do so on dot trials (χ^2 test, $p << 0.0001$). This was true during both the post-target-onset epoch (Fig. 12A) and the peri-saccadic epoch (Fig. 12D). We conclude that a given neuron commonly was sensitive or not sensitive to the retina-centered location of the target regardless of the nature of the target (the end of a bar or a dot).

Parametric characterization. We generated, for each neuron, independent estimates of its directional tuning under the bar and dot conditions. The estimate for the bar condition was based on the average firing rate computed across bar-left and bar-right trials. To ensure that results

obtained under bar and dot conditions would be fully comparable, we based the comparison on trials requiring saccades in the four 45° oblique directions. Each estimate was generated by (a) multiplying unit vectors pointing toward the four target locations by the associated firing rates and (b) summing the resulting vectors.

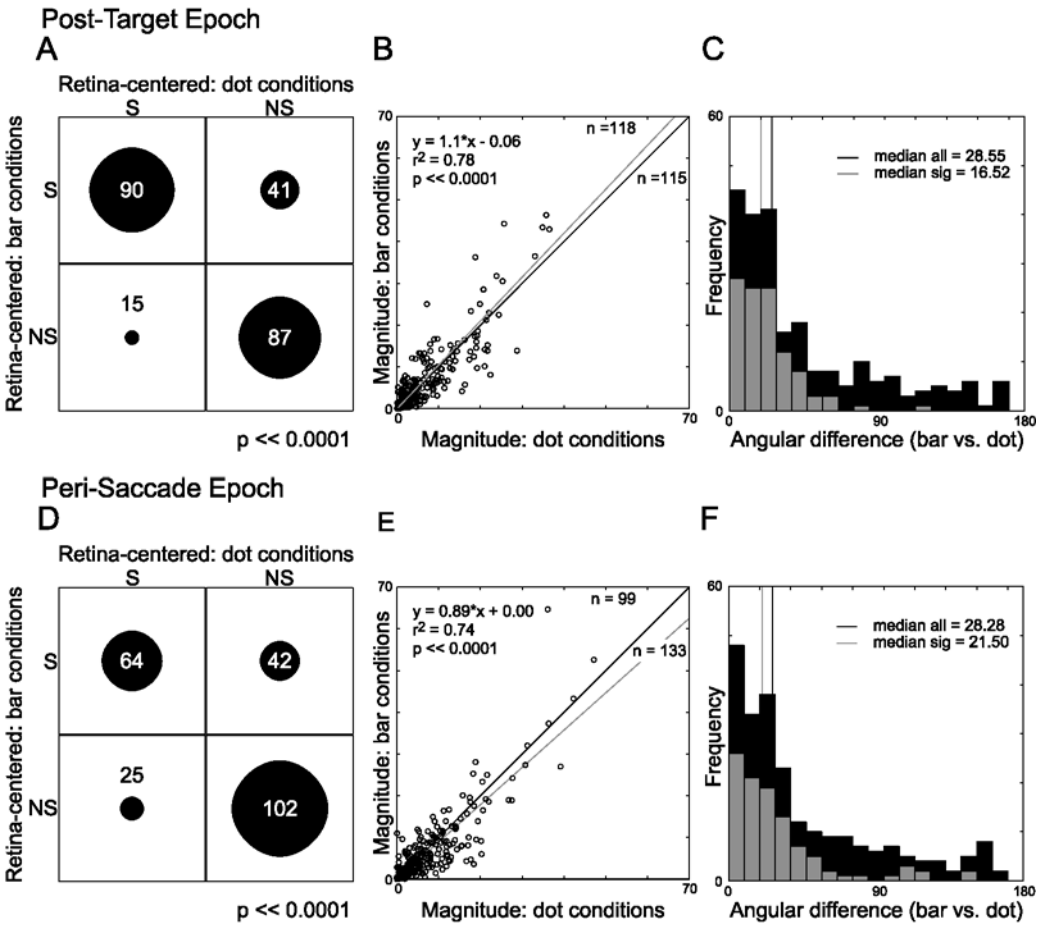

Fig. 12. Retina-centered selectivity compared in the dot and bar tasks.

Across all 233 neurons, there was a strong tendency for measures of retina-centered spatial selectivity obtained with bar targets to match measures obtained with dot targets. A. During the post-target-onset epoch, neurons exhibiting significant retina-centered selectivity (S) or not exhibiting it (NS) under bar conditions tended to do the same under dot conditions as indicated by the fact that counts on the match diagonal exceed the number expected on the basis of the null hypothesis that the two traits were distributed independently at a highly significant level (χ^2 test, $p << 0.0001$). B. Estimates of the magnitude of the retina-centered signal based on trials with bars and dots as targets were correlated at a highly significant level ($p << 0.0001$). C. Estimates of preferred direction based on firing rates from bar and dot trials were closely similar as indicated by the fact that the distribution of angular differences is narrowly peaked around zero. This was especially true for neurons selected according to the criterion that they exhibited significant retina-centered selectivity on dot trials. D-F. Same for peri-saccadic epoch.

Magnitude. To compare the strengths of the retina-centered directional signals observed on bar and dot trials, we plotted the magnitudes of the two signals against each other cross the entire recorded sample of neurons. During the post-target-onset epoch, we found that the magnitude of the directional signal observed under the bar condition was correlated at a highly significant level ($r^2 = 0.78$, $p << 0.0001$) with the magnitude of the signal observed under the dot condition (Fig. 12B). The same was true during the peri-saccadic epoch (Fig. 12E). In addition to the high degree of correlation, there existed, during the peri-saccadic epoch, a subtle tendency whereby retina-centered signals were stronger under the dot condition, as indicated by the preponderance of points below the identity line in the plot of Fig. 12E (133 points below, 1 point on and 99 points above the line, χ^2 test, $p = 0.03$).

Direction. To determine whether the preferred retina-centered direction on bar trials tended to match that on dot trials, we computed, for each neuron, the absolute angular difference between the vector based on dot trials and the vector based on bar trials. We found that the difference between the two estimates of preferred direction was small. During the post-target-onset epoch, the median angular difference was 29° across all neurons and 17° among neurons with significant retina-centered selectivity (Fig. 12C). A closely similar result was obtained during the peri-saccadic epoch (Fig. 12F). We conclude that there was a high degree of concordance between a neuron's preferred retina-centered directions as measured under the bar and dot conditions.

Conclusion. A majority of neurons exhibiting selectivity for a given retina-centered direction on dot trials also exhibited retina-centered selectivity (with the preferred direction conserved) on bar trials.

2.3.9. Object-centered selectivity compared to retina-centered selectivity on bar trials

Rationale. This phase of analysis, focused exclusively on bar trials, had as its aims (1) to determine whether a neuron's being selective for object-centered location was predictive of its being selective for retina-centered location, (2) to compare the strengths of the two signals and (3) to determine whether the direction of object-centered selectivity was related to the direction of retina-centered selectivity.

Incidence. We first asked whether the property of selectivity for object-centered location was correlated with the property of selectivity for retina-centered location. To answer this question, we considered the counts of neurons in four categories defined by crossing the status of the main effect of object-centered location (significant or not significant) with the status of the main effect of retina-centered location (significant or not significant) during the post-target-onset epoch (Fig. 13A) and the peri-saccadic epoch (Fig. 13E). There were unquestionably instances in which a neuron exhibited one form of selectivity without exhibiting the other. Nevertheless, during each epoch, the presence of one form of selectivity was highly significantly correlated with the presence of the other, as indicated by the fact that counts along the match diagonals are significantly in excess of the counts expected by chance if the two properties were independently distributed across neurons (χ^2 test, $p << 0.0001$).

Origin of the correlation. The significant positive correlation between object-centered and retina-centered selectivity could have arisen from either of two mechanisms. First, it might genuinely be the case that, among neurons with task-related activity, the possession of one trait was associated with possession of the other. Second, it might be the case that, among neurons with task-related activity, the two properties were distributed independently, but that a

correlation between the two arose through the inclusion, in the sampled population, of some neurons without task-related activity. According to the second scenario, the correlation between object-centered and retina-centered spatial selectivity was simply a secondary consequence of their both being correlated with the presence of task-related activity. On the basis of the counts alone, it is impossible to decide between these accounts. To resolve this issue, we defined task-related activity in a way that did not depend on the presence of spatial selectivity and then asked whether the two forms of spatial selectivity remained correlated within the sub-population of neurons classified as task-related. A neuron was categorized as exhibiting task-related activity if the difference in firing rate between the epoch in question (averaged across all conditions) and a baseline epoch (150 ms before to 150 ms after onset of the fixation spot) achieved a stipulated level of significance in a t-test. As the statistical criterion for task-relatedness was made progressively more stringent (from $p < 0.05$ to $p < 0.01$ to $p < 0.001$) there was a progressive decrease in the number of neurons classified as task-selective and a corresponding decrease in the level of significance of the correlation. However, in only one case (the peri-saccadic epoch under the most stringent criterion for task-relatedness) did the correlation cease to be significant and even in this case there was a trend toward correlation. We conclude that among task-related neurons, as defined by a change in mean firing rate between a given trial epoch and a baseline period, (a) some neurons were spatially selective and some were not and (b) that the spatially selective neurons tended to be sensitive to both object-centered and retina-centered location.

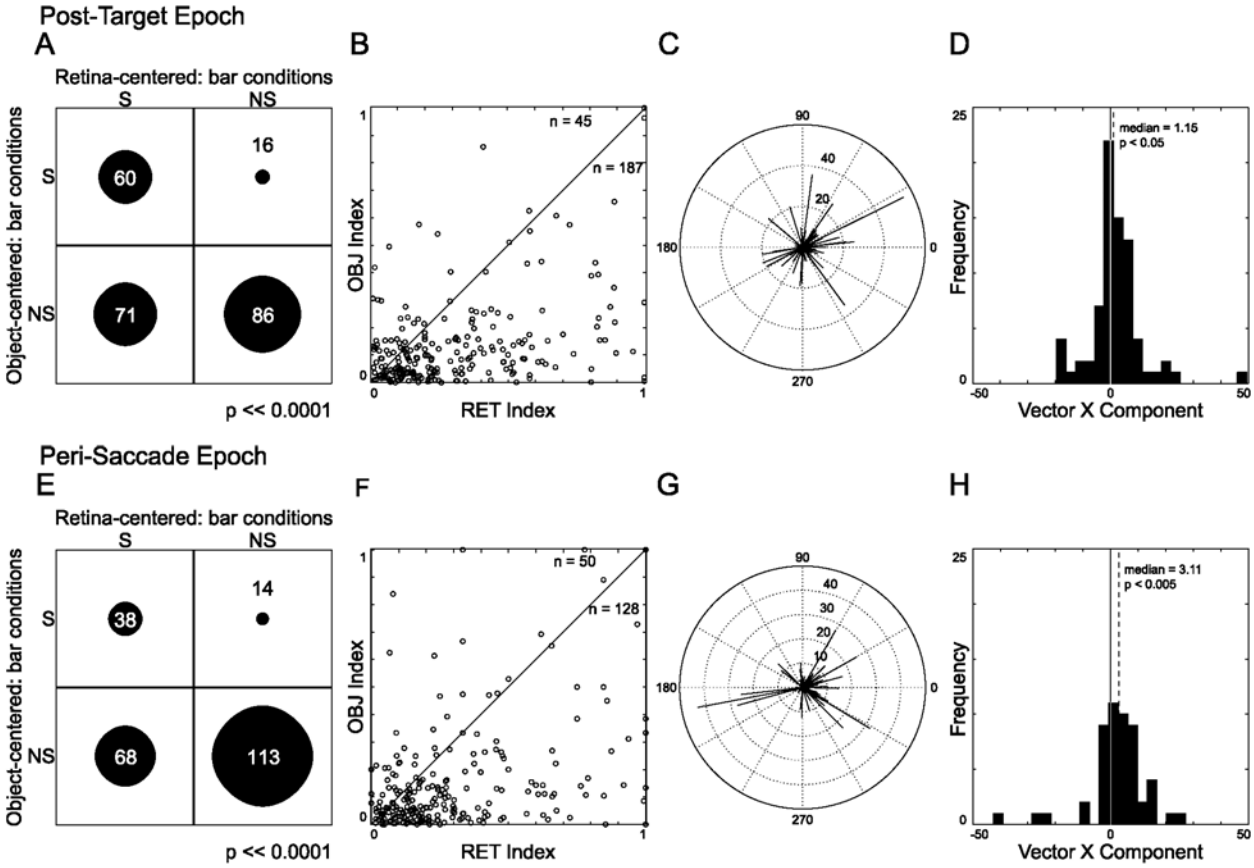

Fig. 13. Relation between measures of object-centered selectivity and measures of retina-centered selectivity, taken on data from bar trials.

A. During the post-target-onset epoch, neurons exhibiting (S) or not exhibiting (NS) significant dependence on the object-centered location of the target tended to do the same with respect to the retina-centered location of the target, as indicated by the fact that counts along the match diagonal exceed the number expected on the basis of the null hypothesis that the two traits were distributed independently at a highly significant level (χ^2 test, $p << 0.0001$). B. The magnitude of the object-centered signal is plotted against the magnitude of the retina-centered signal for all 233 neurons. The retina-centered signal tended to be stronger as indicated by the highly significant (χ^2 test, $p << 0.0001$) preponderance of points beneath the identity diagonal (counts above and below the diagonal sum to less than 233 because some points were on the identity line). RET index = Abs(B - O)/(B + O) where B was the firing rate for best retina-centered direction and O was the firing rate for opposite retina-centered direction as averaged across bar-left and bar-right conditions. OBJ index = Abs(L - R)/(L + R) where L was the firing rate on bar-left trials and R was the firing rate on bar-right trials as averaged across all four retina-centered directions. C. Vectors representing the estimated preferred retina-centered direction of each neuron exhibiting significant object-centered spatial selectivity during the post-target-onset epoch. Horizontal direction is depicted according to the convention that a vector points to the right for a match between preferred retina-centered and object-centered directions (as in the case of a neuron preferring rightward saccades and the right end of a bar) and to the left for a mismatch. The radial axis represents signal magnitude. Units along this axis are spikes per second. D. Distribution of the horizontal components of the vectors shown in C. Cases of matching object-centered and retina-centered direction selectivity were preponderant as indicated by the fact that the distribution is shifted significantly to the positive side of zero (Wilcoxon signed rank test, $p < 0.05$). E-H. The same for the peri-saccadic epoch.

Magnitude. To compare the strength of object-centered to retina-centered selectivity across the entire neuronal population, we computed for each neuron two indices of signal strength: an index of object-centered direction selectivity (the absolute value of the difference in firing rate between bar-left and bar-right trials scaled to the sum) and an index of retina-centered direction selectivity (the absolute value of the difference in firing rate between the best direction and the opposite direction scaled to the sum. The results for the post-target-onset epoch (Fig. 13B) and the peri-saccadic epoch (Fig.13F) make clear that retina-centered signals commonly were stronger than object-centered signals. In both cases, the excess of points beneath the identity diagonal (representing neurons with stronger retina-centered than object-centered direction selectivity) was significant ($p << 0.0001$).

Direction. To determine whether there was a consistent relation between the preferred object-centered direction (bar-left or bar-right) and preferred retina-centered direction, we carried out an analysis on the data from all 76 neurons exhibiting significant object-centered selectivity during the post-target-onset epoch and all 52 neurons doing so during the peri-saccadic epoch. For each neuron, using the firing rates measured on dot trials, we generated a vector representing by its magnitude the strength of the retina-centered signal and by its direction the retina-centered preferred direction. We then plotted the vectors according to a convention whereby 0° (to the right) represents a retina-centered direction matching the neuron's preferred object-centered direction and 180° (to the left) represents a retina-centered direction opposite the neuron's preferred object-centered direction. In plots depicting preferred retina-centered directions during the post-target-onset epoch (Fig. 13C) and the peri-saccadic epoch (Fig. 13G) it appears that there is a preponderance of vectors pointing to the right and thus representing cases in which a neuron's retina-centered preferred direction had a rightward (or leftward) component

and its preferred object-centered location was the right (or left) end of the bar. This trend was significant as indicated by the fact that the distribution of the horizontal components of the vectors was significantly offset to the right both during the post-target-onset epoch (Fig. 13D, (Wilcoxon signed rank test, $p < 0.05$), and the peri-saccadic epoch (Fig. 13H, $p < 0.005$).

Conclusion. Object-centered selectivity was somewhat less common than retina-centered selectivity and object-centered signals were somewhat less strong on average than retina-centered signals. Nevertheless, the two traits appeared to be related. Neurons that exhibited one trait also tended to exhibit the other. Moreover, there was a tendency for the preferred object-centered direction and the preferred retina-centered direction to match.

2.3.10. Firing rate on bar vs. dot trials: metric vs. categorical representation

Rationale. In tasks used previously to characterize object-centered selectivity, the monkey had to discriminate between only two locations: the right and left ends of a bar (Olson and Gettner 1995, 1999; Olson and Tremblay 2000; Tremblay et al. 2002). For this reason, it has never been clear whether the representation of object-centered location is categorical or metric. To make this distinction would require using at least three locations (for instance, the left end, the middle and the right end of a bar). Then we could ask whether three populations of neurons represent the three locations (in which case we would conclude that the representation is categorical) or, alternatively, whether neurons exhibit a preference for the right or left end of the bar and fire at an intermediate rate for the middle (in which case we would conclude that the representation is metric). The intermingling of dot and bar trials in this experiment afforded an opportunity to ask a related question, namely whether neurons with object-centered selectivity fired at an intermediate rate on dot trials (when the target was at the center of the object) as

compared to bar-left and bar-right trials. Examples of two neurons that clearly did so are shown in Fig. 8A and C.

Approach. To test whether this was a consistent trend, we computed, for each neuron with significant object-centered selectivity, the mean firing rate on bar-left, bar-right and dot trials and then counted instances in which the dot firing rate was between the bar-left and bar-right firing rates. We found that the dot firing rate was intermediate in 43/76 = 57% of neurons. This fraction was highly significantly in excess of the one third expected by chance (χ^2 test, $p < 0.0001$).

Conclusion. That the firing rate on dot trials tended to be intermediate between the firing rates on bar-left and bar-right trials suggests that SEF neurons represent object-centered location metrically rather than categorically.

2.3.11. Influence of retina-centered location on object-centered tuning

Rationale. This phase of analysis had as its aim to determine how consistently neurons expressed object-centered selectivity as the retina-centered location of the targets varied around the clock. The analysis focused on 76 neurons exhibiting a significant main effect of object-centered location during the post-target-onset epoch on bar trials (Table 2). The occurrence of a main effect in itself was uninformative because it could have arisen from strong object-centered selectivity for targets at one or two locations (as in Fig. 8C) or from object-centered selectivity at all locations (as in Fig. 8A).

Incidence. To determine at how many locations each neuron exhibited object-centered selectivity, we divided the data into four categories by visual-field quadrant. We then used a t-test to determine whether, for targets in each quadrant, the firing rates on bar-left and bar-right

trials, as measured during the post-target-onset epoch, were significantly different ($p < 0.05$). The firing rate depended significantly on object-centered location in 0, 1, 2, 3 and 4 quadrants in 16, 23, 20, 7 and 10 neurons respectively. Thus, even in a test of limited power resulting from the division of the database into quarters, around half of the neuronal population exhibited significant object-centered selectivity in more than one quadrant.

Strength. As a complement to the statistical approach, we carried out an index-based analysis. In each of the 76 neurons, we ranked the quadrants according to the strength of the object-centered signal: $Abs(R - L)/(R + L)$, where R and L were mean firing rates on bar-right and bar-left trials respectively. Then we normalized the signed signal in each quadrant – $(R – L)/(R + L)$ – to the signed signal in the best quadrant (the quadrant in which the absolute value of the signal was greatest). This resulted in a value of +1 for the best quadrant and a value in the range -1 to + 1 for the three other quadrants. The distributions of values for the second, third and fourth best quadrants are shown in Fig. 14A-C. In quadrants of all ranks, the median of the distribution was shifted significantly away from zero in a positive direction (signed rank test, $p < 0.05$), indicating a tendency for the preferred object-centered direction to match the one measured in the best quadrant. Moreover, for the second and third best quadrants, the effect was very nearly total (75/76 and 70/76 neurons). We conclude from this analysis that for a neuron to exhibit the same object-centered preference in three quadrants was the norm and to exhibit it in four quadrants was not uncommon.

Conclusion. SEF neurons sensitive to object-centered location exhibited this sensitivity for targets at a wide range of retina-centered locations commonly encompassing three or four quadrants.

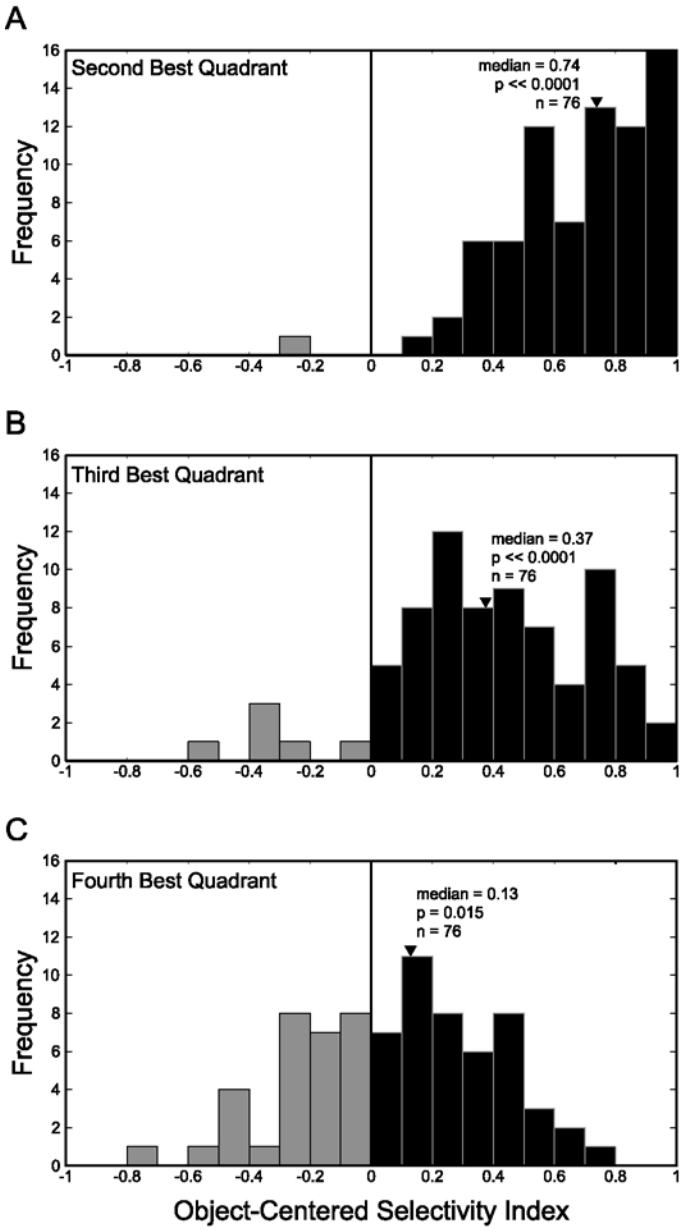

Fig. 14. Distribution of object-centered indices for each of the four quadrants of the visual field.

Neurons exhibiting object-centered spatial selectivity tended to do so when the target was in multiple visual field quadrants. For all 76 such neurons, we ranked the four quadrants by the absolute value of the object-centered signal: Abs(R – L)/(R + L), where R and L were firing rates on bar-right and bar-left trials respectively. Then we normalized the signed object-centered signals, (R – L)/(R + L) in the second-, third- and fourth-ranked quadrants, to the signed object-centered signal in the first-ranked quadrant. The strength of the normalized signal in the first-ranked quadrant had a value of one by definition. Shown here are the distributions of the normalized signals in the second-ranked (A), third-ranked (B) and fourth-ranked (C) quadrants. In all quadrants, the distribution was significantly shifted in a positive direction from zero, indicating a tendency for neurons to prefer the same object-centered direction in all four quadrants.

2.3.12. Influence of object-centered location on retina-centered tuning

Rationale. This phase of analysis had as its aim to determine how neuronal tuning for retina-centered location (as established on dot trials) was affected by placing the target on the end of a bar. Theoretical interest attaches to this question. It has been suggested that SEF neurons are able to mediate the transformation from pure object-centered commands to retina-centered motor output by virtue of forming a basis set representing all possible combinations of saccade direction and object-centered location (Deneve and Pouget 2003). For SEF neurons to function in this capacity would require that the interaction between object-centered and retina-centered signals be multiplicative (the analogue equivalent of a logical "and" function) or, in other words, that the retina-centered spatial tuning curve be modulated up or down by a multiplicative gain constant associated with each object-centered location

Approach. In any neuron selective for retina-centered saccade direction, the firing rate associated with a saccade to a dot is some function of target location. For example, in the hypothetical case of Fig. 15A, the neuronal response field has the form of a two-dimensional Gaussian with its peak at the preferred target location. For any given condition under which the target is not a dot (for example if it is the left end of a bar) one can pose the question: under this new condition, what transformation is imposed on the response field mapped out with dot targets? We present three hypothetical models in Fig. 15B-D, models in which the firing rate measured on dot trials (A) is multiplied by a constant associated with the bar-left condition (B), has added to it a constant associated with the bar-left condition (C), or is replaced by a constant associated with the bar-left condition (D). We refer to the third model as embodying "pure" object-centered selectivity because, when the target is at the left end of a bar, the firing rate depends purely on this fact independently of retina-centered direction.

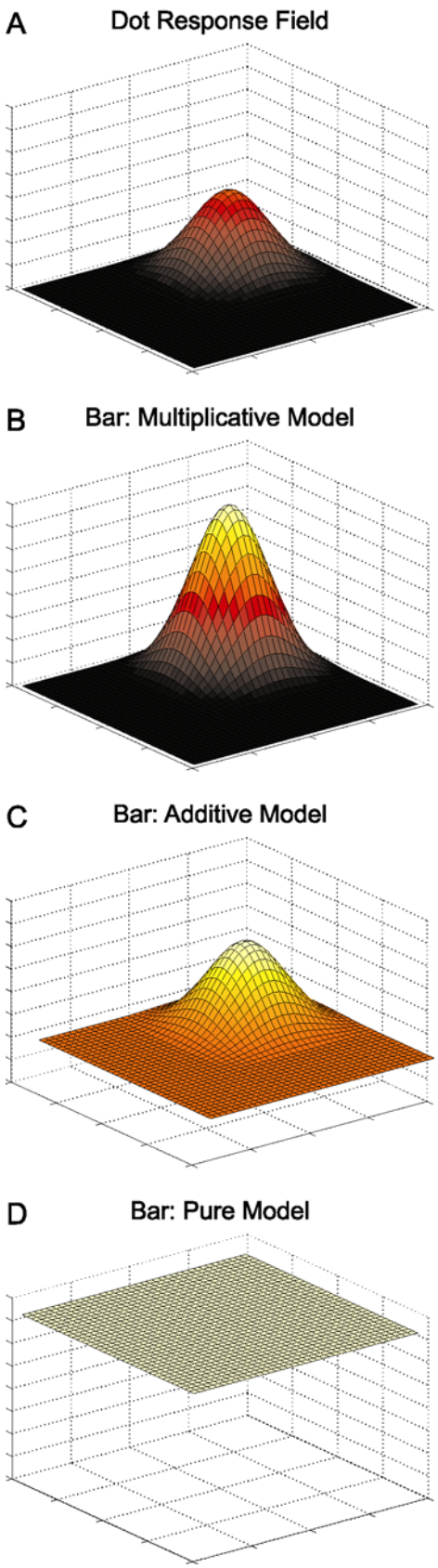
A
Dot Response Field
B
Bar: Multiplicative Model
C
Bar: Additive Model
D
Bar: Pure Model

Fig. 15. Functions by which the retina-centered response field on dot trials might be transformed on trials in which the target is a particular end of a bar.

A hypothetical response field, as mapped out on dot trials (A), could be transformed, on dot trials, through multiplying each firing rate by a bar-related constant (B), through adding to each firing rate a bar-related constant (C), or through replacing each firing rate with a bar-related constant (D). In each plot, the horizontal axes represent x and y position in a quadrant of the visual field with the fovea to the left and height represents the firing rate associated with planning or executing a saccade to the corresponding location.

Although we did not sample retina-centered space finely and so cannot plot out response fields approximating those in Fig. 15, nevertheless, we did sample four widely spaced retina-centered directions. On the basis of firing rates associated with saccades in those four directions, it is straightforward to pose the question: which of the models shown in Fig. 15B-D best describes the relation between the firing rates measured under the bar-left (or bar-right) condition and the firing rates measured under the dot condition. We set out to apply this approach to data from 52 neurons (Fig. 17A) exhibiting significant object-centered selectivity on bar trials (in consequence of which we knew object-centered location affected the firing rate) and exhibiting significant retina-centered selectivity on dot trials (in consequence of which we knew that there was a retina-centered tuning curve subject to modulation).

Model fitting. For each neuron, we plotted the firing rate on each trial under a given bar condition (for example, bar-left) as a function of the mean firing rate associated with saccades in the corresponding direction under the dot condition (a hypothetical case is shown in Fig. 16A). Then we computed the values of the parameters (α and β) that minimized the sum of squared differences between the data and each of the following five models: full linear ($y = \alpha * x + \beta$), multiplicative ($y = \alpha * x$), additive ($y = x + \beta$), pure ($y = \beta$) and identity ($y = x$). The parameters α and β could assume independent values from one model to the next. Applying this approach separately to bar-left and bar-right data from 52 neurons yielded 104 sets of five solutions. The five solutions based on data from a hypothetical case are shown in Fig. 16A.

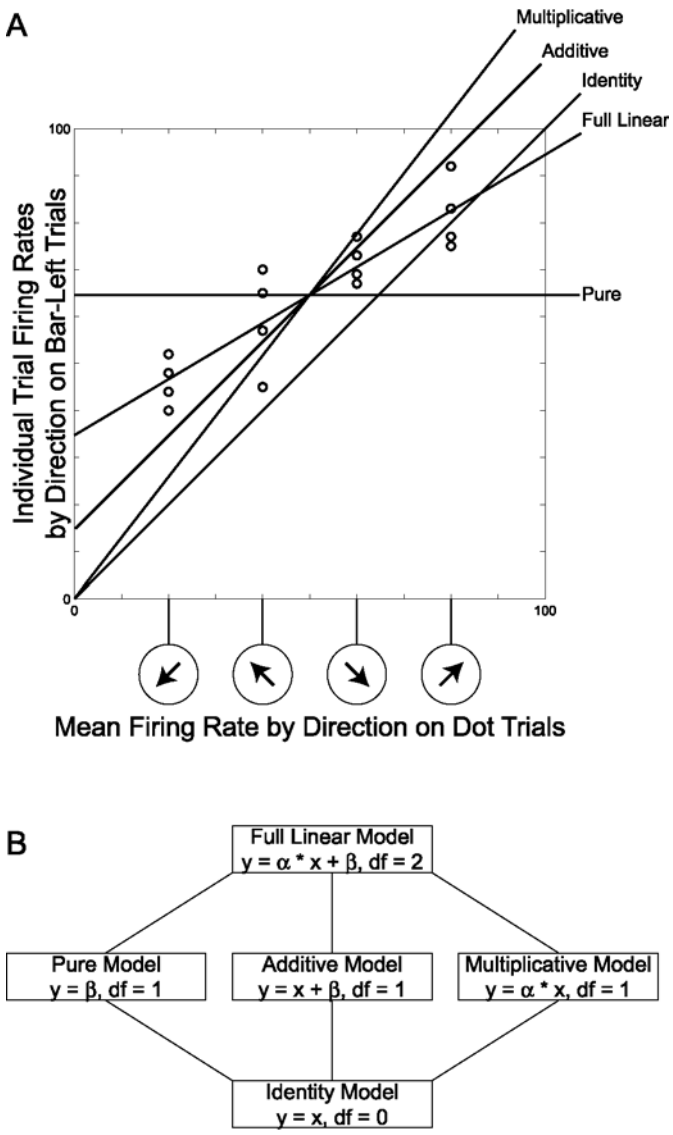

Fig. 16. Method for fitting to the data from a given neuron five models governing the transformation from firing rates on dot trials to firing rates on bar trials.

A. There are as many points as there were trials in which the target occupied a particular end of the bar. On each trial, the saccade was in one of four retina-centered directions. The location of the point is determined by the mean firing rate associated with saccades in this direction on dot trials (horizontal axis) and by the firing rate actually observed on this bar trial (vertical axis). B. The five models organized according to their degrees of freedom.

Ability of multiplicative, additive and pure models to fit the data. In assessing the ability of the multiplicative, additive and pure models to account for the data from each case, we compared them to the identity and full linear models, taking into account the differences in the number of free parameters (Fig. 16B). 1) We assessed (using an F-test) whether each one-

degree-of-freedom model (multiplicative, additive or pure) was significantly ($p < 0.05$) superior to the identity model in the sense that it accounted for more of the variance in the data than could be explained merely by its possessing an additional degree of freedom. 2) We assessed in an analogous manner whether the full linear model was significantly superior to each one-degree-of-freedom model (multiplicative, additive or pure). Out of 104 cases, there were 43, 37 and 17 cases in which the multiplicative, additive and pure models met the dual criteria that they accounted for the data better than the identity model and no worse than the full model (Fig. 17B). There were cases in which more than one model met these dual criteria (Fig. 17C). In each such case, we identified the single model which accounted for the greatest fraction of variance in the data as the winner. This resulted in classifying 32, 24 and 13 cases as being best fit by the multiplicative, additive and pure models respectively, with 35 cases remaining unclassifiable because for no one-degree-of-freedom model did they meet the dual criteria that that model should be superior to the identity model and not demonstrably worse than the full linear model (Fig. 17D).

Lack of strong concordance between different object-centered locations. In the analysis presented up to this point, bar-left and bar-right conditions were treated as independent cases. We next asked whether the nature of the outcome was consistent, for a given neuron, between conditions in which the target was on different ends of the bar. For each neuron, we first identified the "best" and "worst" ends of the bar, those associated with stronger and weaker firing respectively. We then compared the outcome obtained in the model-based analysis when the target was at the best object-centered location to the outcome obtained when it was at the worst location. We identified cases as best and worst, rather than as left and right, because it seemed plausible that different transformations might underlie increases and decreases in firing

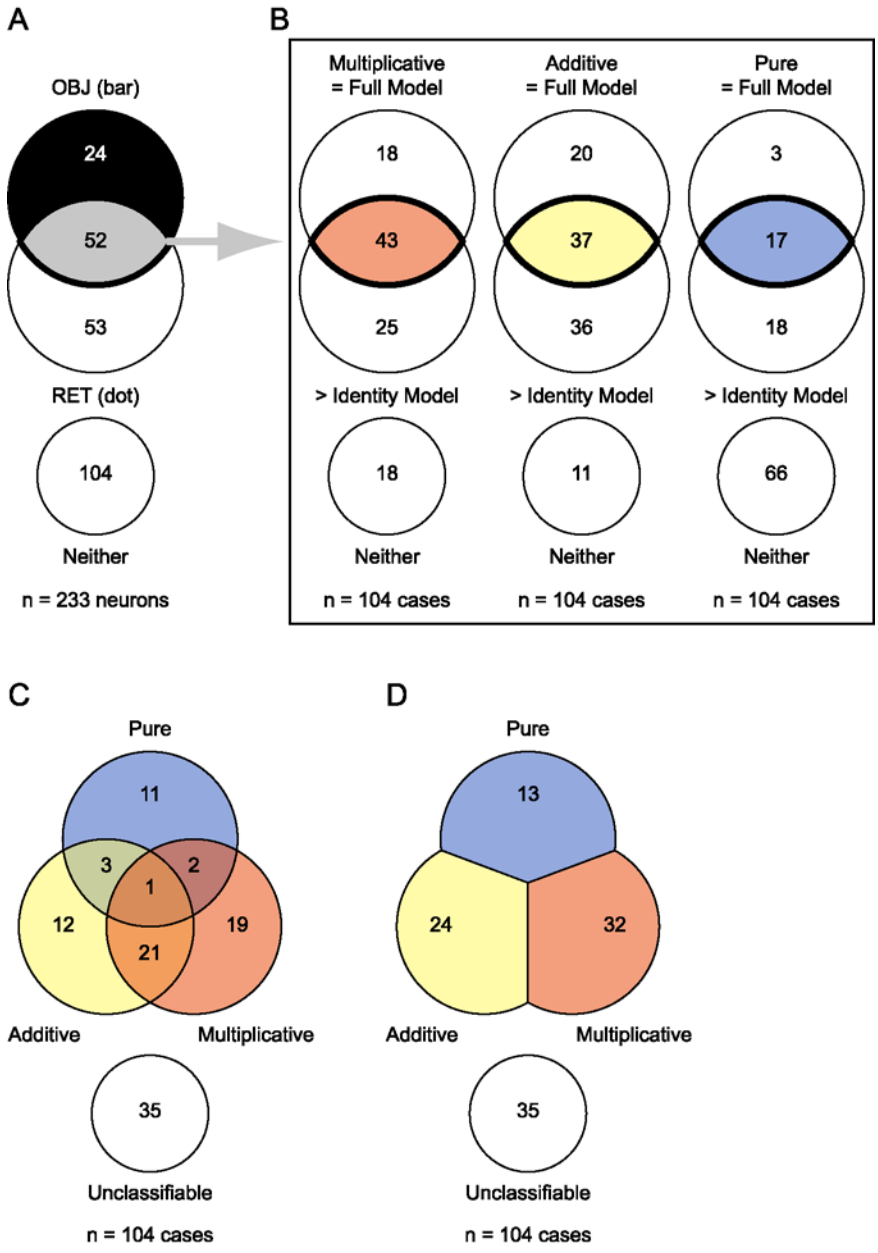

Fig. 17. Successive steps in determining which model best approximated the transformation function relating retina-centered selectivity on bar trials to retina-centered selectivity on dot trials.

A. The full population of 233 neurons was first sorted on the basis of the outcomes of ANOVAs assessing sensitivity to object-centered and retina-centered location (Tables 1-2). Shown here are counts of neurons exhibiting a significant main effect of object-centered location on bar trials, OBJ(bar), and of retina-centered location on bar trials, RET(dot). Subsequent steps of analysis focused on 52 neurons exhibiting both traits (gray sector). B. The next step of analysis involved determining (for 104 cases representing the crossing of 52 neurons with two object-centered locations) whether each one-degree-of-freedom model (multiplicative, additive or pure) met two criteria: (1) accounting for the data significantly better than the zero-degree-of-freedom identity model and (2) accounting for the data not significantly worse than the two-degrees-of-freedom full linear model. C. In some cases, more than one model met both criteria. D. In these cases, the model accounting for the greatest fraction of variance was deemed the winner.

rate. The results are given in Table 3. Counts along the match diagonal were slightly elevated compared to counts expected if the "best" and "worst" outcomes were uncorrelated; however the effect did not even approach significance (χ^2 test, $p > 0.05$). Likewise, the difference between "best" and "worst" cases in the distribution of counts across the four categories did not achieve significance (χ^2 test, $p > 0.05$). We conclude that which model provided the best fit for a given object-centered location was not related either (1) to the outcome for the opposite location or (2) to whether this location was preferred.

		Best				
		Multiplicative	Additive	Pure	Unclassified	**Total**
Worst	Multiplicative	7	2	1	7	**17**
	Additive	3	2	5	6	**16**
	Pure	2	1	1	2	**6**
	Unclassified	3	3	0	7	**13**
	Total	**15**	**8**	**7**	**22**	**52**

Table 3. Results of model-based analysis for each neuron's best vs. worst object-centered location.

For each of 52 neurons analyzed by the model-fitting approach, this table compares the nature of the outcome for trials in which the preferred ("best") end of the bar was the target to the nature of the outcome for trials in which the non-preferred ("worst") end of the bar was the target. These data represent a breakdown (for 52 neurons x 2 object-centered directions) of data (from 104 cases) in Fig. 17D.

Population activity of neurons classified by model-fitting. To assess whether the classification of neurons by a model-based approach captured genuine differences in the transformation function relating retina-centered selectivity on bar trials to retina-centered selectivity on dot trials, we computed the group-averaged firing rate as a function of object-

centered and retina-centered location for neurons in different categories. The group averages were achieved by the following steps. 1) For each neuron, we identified the "best" retina-centered direction (the direction associated with strongest firing on dot trials), defined two other directions as "middle" (those separated from the best by 90°) and defined one other direction as "worst" (that separated from the best by 180°). 2) For each neuron, we identified "best" and "worst" object-centered locations (associated, respectively, with stronger and weaker firing on bar trials). 3) We then computed the group-averaged firing rate under the six conditions obtained by crossing three retina-centered directions (best, middle or worst) with two target types (dot and bar).

In Fig. 18 are shown the results for (A-B) 32 cases classified as multiplicative, (C-D) 24 cases classified as additive, (E-F) 13 cases classified as pure and (G-H) 48 cases from 24 neurons excluded from the model-based analysis because, although they carried significant object-centered signals on bar trials, they did not carry significant retina-centered signals on dot trials. We additionally show a subset of (I-J) 26 cases from 13 neurons that showed significant object-centered selectivity, but no retina-centered selectivity in either the bar or dot task. Upon examination of the population histograms, it is evident that firing rate changes with retinal location in a pattern roughly conforming to expectation based on which model gave the best fit. In multiplicative cases (A-B), there is a marked tendency for the difference between the firing rate on bar trials and dot trials to be greatest at the retinal location associated with strongest firing on dot trials. In additive cases (C-D), the difference approximates more closely to a uniform upward or downward shift independent of retinal location. In pure cases (E-F), although firing is not constant under the bar condition regardless of retinal location, as expected if the case perfectly conformed to the model, nevertheless there is considerable interference with the retinal

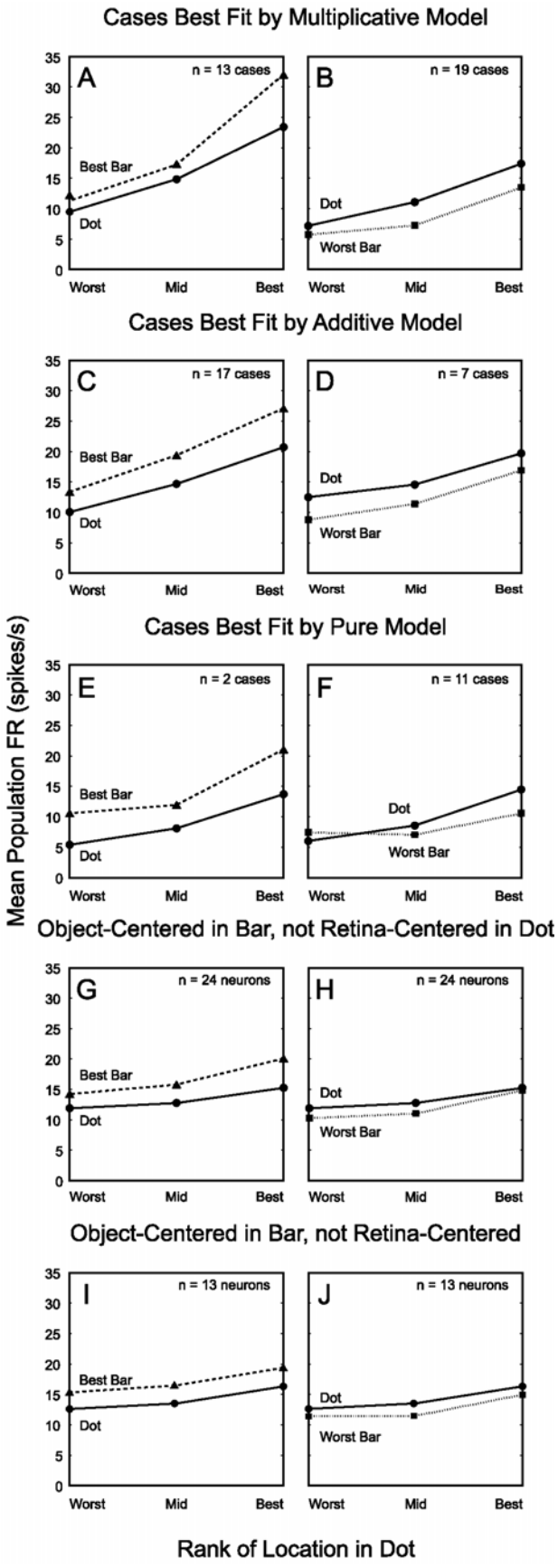
Cases Best Fit by Multiplicative Model
A
n = 13 cases
Best Bar
Dot
B
n = 19 cases
Dot
Worst Bar
Cases Best Fit by Additive Model
C
n = 17 cases
Best Bar
Dot
D
n = 7 cases
Dot
Worst Bar
Cases Best Fit by Pure Model
E
n = 2 cases
Best Bar
Dot
F
n = 11 cases
Dot
Worst Bar
Mean Population FR (spikes/s)
Object-Centered in Bar, not Retina-Centered in Dot
G
n = 24 neurons
Best Bar
Dot
H
n = 24 neurons
Dot
Worst Bar
Object-Centered in Bar, not Retina-Centered
I
n = 13 neurons
Best Bar
Dot
J
n = 13 neurons
Dot
Worst Bar
0
5
10
15
20
25
30
35
Worst
Mid
Best
Rank of Location in Dot

Fig. 18. Population firing rates for categories of neurons based on modeling and statistical analysis.

Mean population firing rate as a function of retina-centered direction for cases in which a multiplicative model (A-B), an additive model (C-D) or a pure model (E-F) provided the best fit to the data (cases from the red, yellow and blue sectors of Fig. 13D). Shown in the same format (G-H) are data from 24 neurons exhibiting object-centered selectivity on bar trials but excluded from analysis because they did not exhibit retina-centered selectivity on dot trials (neurons from the black sector of Fig. 17A). Shown in the same format (I-J) are data from 13 neurons exhibiting object-centered selectivity on bar trials and no retina-centered selectivity on either dot trials or bar trials. These neurons are a subset of the neurons shown in (G-H). Firing rate (in spikes per second) is plotted as a function of direction, with direction defined as "best" (associated with strongest firing on dot trials), "mid" (90° off from best) and "worst" (180° off from best). Cases are divided into those in which the target was at the object-centered location preferred by the neuron (panels in the left column: "best bar") and those in which the target was at the opposite object-centered location (panels in the right column: "worst bar"). Solid curves: trials in which the target was a dot. Broken curves: trials in which the target was one end of a bar.

tuning curve established on dot trials, as evidenced by a higher than expected firing rate at the worst retinal location. In the case of neurons exhibiting significant object-centered selectivity but not exhibiting significant retina-centered selectivity in the dot task (G-H), we note that there is a consistent modulation of firing rate across retinal locations, weak, indeed weaker than the modulation associated with object-centered location, but still present. This modulation by retina-centered location is further weakened into nonexistence when we focus our analysis on neurons that show significant object-centered selectivity in the bar task but no retina-centered selectivity in either task (I-J).

In all analyses up to this point, we have ignored the issue of whether, in a given neuron, there was a significant interaction between object-centered location and retina-centered location on bar trials. A significant interaction effect could arise (a) from multiplicative interaction of retina-centered and object-centered signals or (b) from some other form of interaction entirely. If a neuron fired only for a single object-centered location at a single retinal location (a form of multiplicative interaction), this would likely give rise to an interaction effect combined with main effects of both object-centered and retina-centered location. If a neuron fired for one object-centered location at one retinal location and for the opposite object-centered location at the opposite retinal location (a form of non-multiplicative interaction), this would likely give rise

to an interaction effect in the absence of a main effect of either object-centered or retina-centered location. To pursue this issue, we repeated the model-based analysis on neurons included in the previous analysis but now subdivided according to whether they exhibited an interaction effect on bar trials (blue sector of Fig. 19A) or did not do so (red sector of Fig. 19A). A third group consisted of neurons exhibiting an interaction effect on bar trials but excluded from the previous analysis because they did not meet the dual criteria of exhibiting object-centered selectivity on bar trials and retina-centered selectivity on dot trials (yellow sector of Fig. 19A). The results (Fig. 19B-D), presented in the same format as those of the previous analysis (Fig 17D), reveal that cases in which the multiplicative model provided the best fit to the data were especially frequent in neurons exhibiting main effects of both object-centered and retina-centered location and an interaction effect in bar trials (Fig. 19C). Because the numbers were small, however, the differences between groups did not achieve significance χ^2 test, $p > 0.05$). The critical implication of these findings is that we did not artificially deflate the estimate of the incidence of multiplicative interactions by excluding from the previous analysis some neurons that exhibited an interaction effect in bar trials (those occupying the yellow sector in Fig. 19A and represented in Fig. 19D).

Conclusion. The question of whether the transformation of the retinal tuning curve on bar as compared to dot trials conforms to a multiplicative pattern consistent with a gain-field mechanism turns out to have a complicated answer. There are some cases in which the transformation is primarily multiplicative (Fig. 18A-B), some in which it is primarily additive (Fig. 18C-D) and some in which it is more complex (Fig. 18E-F). Moreover, there are cases in which signals reflecting object-centered location are markedly stronger than those reflecting

retina-centered location, with the result that even asking how the retina-centered tuning curve is transformed on bar trials seems problematic (Fig. 18G-J).

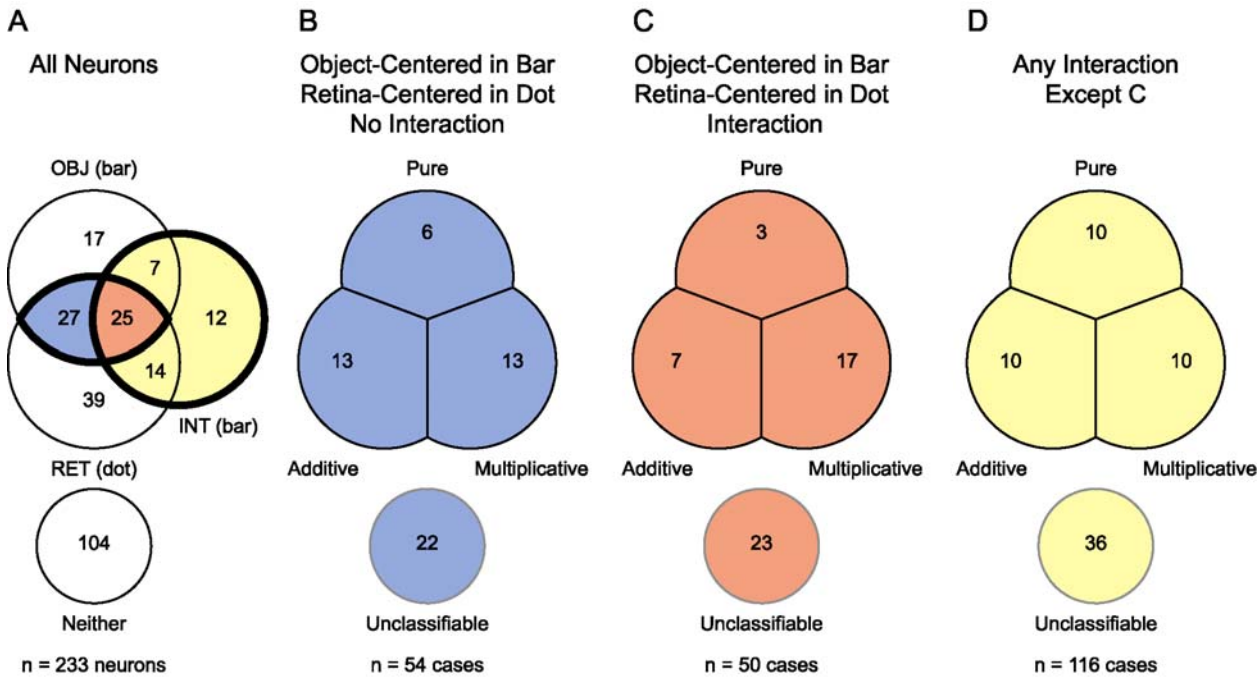

Fig. 19. Model-based analysis performed on neurons sorted by whether or not they exhibited an interaction effect.

On the principle that neurons exhibiting an interaction between object-centered direction and retina-centered direction on bar trials might be especially likely conform to the predictions of the multiplicative model, we repeated the model-based analysis on data sorted according to the presence or absence of an interaction effect. A. The red and blue sectors represent neurons considered together in the previous analysis (gray sector of Fig. 17A) but now sorted according to whether they did (red) or did not (blue) exhibit an interaction effect on bar trials. The yellow sector represents neurons excluded from the previous analysis but included here because they showed an interaction effect on bar trials. B, C and D show the results for neurons in correspondingly colored sectors of A, using a format identical to that of Fig. 17D. Among neurons considered in the previous analysis, there is a tendency for multiplicative effects to be more common in cases where there was an interaction effect (C) than in cases where there was not (B). However the numbers were small and the difference did not achieve significance (χ^2 test, $p > 0.05$).

2.4. Discussion

2.4.1. Overview

The focus of previous studies of object-centered spatial selectivity in the SEF was on demonstrating that neurons carry object-centered as distinct from retina-centered signals (Olson and Gettner 1995, 1999; Olson and Tremblay 2000; Tremblay et al. 2002). For this purpose, it was necessary to vary the retina-centered location of the target across trials so as to allow counterbalancing of retina-centered against object-centered location. However, the range of variation was small, with locations always restricted to the upper quadrant of the visual field. While this approach was adequate for distinguishing object-centered from retina-centered selectivity, it was not adequate for characterizing retina-centered selectivity. To do so would have required allowing target location to vary around the clock as in the present study. This, then, is the first study to address the question of how object-centered and retina-centered signals combine at the single-neuron level in the SEF. The essential answer is that the same neurons carry both kinds of signal although there is some variability with respect to the relative strength of the two signals and with respect to the rule by which the signals combine.

2.4.2. Consistency of retina-centered selectivity across bar and dot trials

In a previous study of neuronal activity during performance of a task in which (a) only the ends of bars were targets and (b) the bars were presented only in the superior quadrant of the visual field, fewer SEF neurons were found to be sensitive to the retina-centered location of the target than to its object-centered location (Olson and Gettner 1995). This result might have

arisen from any of several causes: a genuine preponderance of neurons sensitive to object-centered location, a damping of retina-centered selectivity in the context of the object-centered task or the use of a limited range of retina-centered locations. From results obtained in the present study, we can now conclude that the third possible explanation (use of a limited range of locations) was the actual one. When retina-centered location was allowed to vary around the clock, neurons exhibiting retina-centered selectivity moderately outnumbered neurons exhibiting object-centered selectivity (Tables 1-2). The impact on retina-centered selectivity of requiring the monkey to select a target by an object-centered rule rather than to plan a saccade to a dot was minimal. During the period of the trial following onset of the target, instances of significant retina-centered selectivity were actually more numerous on bar than on dot trials (Tables 1-2). This may, however, have been a consequence of greater statistical power arising from the inclusion of twice as many trials in the bar database. An index-based measure indicated a small but significant reduction in the strength of retina-centered selectivity on bar as compared to dot trials during the peri-saccadic epoch (Fig. 12E). Finally, there was a very strong concordance between measures of retina-centered tuning on bar and dot trials. We conclude that retina-centered selectivity as observed in a standard paradigm involving dots as targets generally was conserved under conditions in which the monkey was required to select the target by an object-centered rule.

2.4.3. Consistency of object-centered selectivity across visual field locations

In previous studies utilizing a narrow range of target locations in the upper visual field, it was not possible to assess the dependence of object-centered spatial selectivity on object location (Olson 2003; Olson and Gettner 1995, 1999; Olson and Tremblay 2000; Tremblay et al. 2002).

Neurons exhibiting object-centered selectivity in these studies might have been generalists, representing object-centered location regardless of the location of the object in the visual field, or specialists, concerned solely with operations in the upper visual field. The results of the current study resolve this issue by demonstrating that most neurons selective for object-centered location exhibit consistent selectivity in most or all visual field quadrants (Fig. 14). This is an important observation because it rules out the possibility (Deneve and Pouget 2003) that SEF neurons represent the object-centered location of the target only if it is within a narrowly defined retina-centered response field. However, it does not rule out a form of conjunctive representation involving very large retina-centered response fields, as discussed in the next section.

2.4.4. Functional significance of combined object-centered and retina-centered signals

Deneve and Pouget (2003) have described a simulated neural network, consisting of several layers of units, that is able to perform the object-centered task. Critical to the operation of this network is a hidden layer in which each unit represents a particular combination of object-centered and retina-centered locations. Mechanistically, these units operate by a gain-field or multiplicative mechanism, becoming active only if two conditions are met simultaneously: (a) one active input line signals that the neuron's preferred end of the bar is in the response field and (b) another active input line signals that the instruction on this trial is to move to the preferred end. Computationally, the population of units as a whole can be thought of as forming a basis set representing all possible combinations of object-centered and retina-centered locations. Deneve and Pouget suggest that the hidden layer in their network corresponds to the SEF. They argue that if this is so then the representation of object-centered space in the SEF is not explicit, which

is to say, not pure. How well does their argument bear up in light of results from the present study?

Gain fields. Do SEF neurons have object-centered gain fields? In answering this question, it is helpful to begin by considering the classic case from which the idea of gain fields arose: modulation of visual responses by angle-of-gaze signals in parietal cortex. In parietal areas 7a and LIP, neurons respond to visual stimuli within fixed retina-centered receptive fields and also exhibit changes in firing rate in conjunction with changes in the direction of gaze (Andersen et al. 1990b; Andersen et al. 1985; Andersen and Mountcastle 1983; Brotchie et al. 1995; Sakata et al. 1980; Snyder et al. 1998). The function relating firing rate to gaze angle (typically a monotonic function peaking as the gaze achieves maximal eccentricity in some direction) has been described as a "gain field" to capture the idea that what varies as the angle of gaze changes is not the baseline firing rate (which may remain flat) but rather the gain of the visual response (which can be thought of as being modulated by a multiplicative coefficient dependent on gaze angle). This description is subject to two serious qualifications. 1) There is a substantial number of neurons in which the baseline firing rate does depend on gaze angle (and in which, consequently, a gaze signal can be thought of as being added to the neuron's firing rate rather than as acting through multiplicative modulation of the visual response). 2) Gaze-angle signals and visual signals do not necessarily influence neuronal activity through qualitatively different mechanisms, as might be inferred from terming the zone of visual influence a "receptive field" and the zone of gaze influence a "gain field." There are neural net models, replicating at the hidden-layer level the interactions observed in parietal cortex, in which visual and gaze signals to hidden layer units act identically, summing at the input stage, and in which the nature of the observed interaction depends on a non-linearity introduced at the stage of the logistic activation

function (Andersen and Zipser 1988; Zipser and Andersen 1988). If the hidden unit is in the intermediate quasi-linear domain of its dynamic range, then the interaction of visual and gaze signals appears additive whereas, if it is outside that domain, then the interaction may appear multiplicative. In particular, if gaze signals are too weak to produce significant activation in their own right, and if visual signals bring the unit into a domain of the activation function in which small changes in input produce large changes in activation, then it will appear that gaze signals modulate the visual responses multiplicatively.

Against this backdrop, we can now answer the question of whether SEF neurons have object-centered gain fields. On one hand, it is true that object-centered and retina-centered signals interact in the SEF in a manner rather like that in which angle-of-gaze signals and visual signals interact in parietal cortex. On the other hand, it would be misleading to assert that object-centered signals act through gain modulation of retina-centered responses. It would be misleading for at least three reasons. 1) In a substantial number of cases, the signals combine according to an additive rather than a multiplicative rule (Fig. 17D). 2) In a substantial number of cases, neurons exhibit a main effect only of object-centered location (Fig. 17A) or carry object-centered signals that are stronger than retina-centered signals (Fig. 13B, F). 3) Insofar as the observed effects can be accounted for in principle by linear summation at the input stage to a logistic activation function, then it is parsimonious to assume that they act in a qualitatively identical way rather than in a mode whereby one modulates responses to the other.

Basis sets. Do SEF neurons form a basis set embodying all possible combinations of object-centered and retina-centered location, and do they, thereby, mediate the transformation from object-centered commands to retina-centered motor signals? This appealingly simple explanation for the combined presence of object-centered and retina-centered signals in the SEF

seems plausible on its face. The properties of SEF neurons as documented in this study of course do not replicate precisely to the properties of units in the hidden layer of Deneve and Pouget's model, deviating from the predictions of the model in at least three ways. 1) SEF neurons are not sharply selective for particular conjunctions of object-centered and retina-centered space, often exhibiting object-centered selectivity over several visual-field quadrants (Fig. 14). 2) The interaction of object-centered and retina-centered signals is additive or complex rather than multiplicative in numerous cases (Fig. 17D). 3) The representations of object-centered and retina-centered space are not orthogonal insofar as neurons preferring a given direction in object-centered space tend to prefer the same direction in retina-centered space (Fig. 13D, H). However, the mere fact that the two kinds of signal are combined in the SEF, whatever the exact principles governing their combination may be, seems to argue that the area is at a transitional functional stage between pure object-centered commands and retina-centered motor output.

Explicit representation. We have found that most SEF neurons carry a combination of object-centered and retina-centered signals. Most neurons classified on the basis of statistical analysis as exhibiting a main effect of object-centered location (Fig. 17A) do, as a population exhibit weak sensitivity to retina-centered location (Fig. 18G-H). However, included in this population is a small group of neurons exhibiting significant object-centered selectivity and no retina-centered selectivity in either the bar or the dot task (Fig. 18 I-J). Thus it is true, as predicted by Deneve and Pouget (2003), that the representation of object-centered space in the SEF is, for the most part, not "explicit." Of course, by the same logic, the representation of edge orientation in primary visual cortex is not explicit in the sense that orientation-selective neurons are subject to influence by other stimulus dimensions such as contrast and direction of motion. The fact that the representation is not pure no more detracts from the significance of object-centered

selectivity in the SEF than it does from the significance of orientation selectivity in V1. Furthermore, we do see examples of "explicit" object-centered representation, albeit in a small group of neurons. Their existence suggests that the response properties of SEF neurons may be more heterogeneously distributed than would be predicted by the basis function model account.

3. The Effect of Learning on Object-Centered Signals in SEF Neurons

3.1. Introduction

The macaque SEF, an area on the dorsomedial shoulder of the frontal lobe, is involved in aspects of the control of saccadic eye movements. This is indicated by the fact that intracortical microstimulation at levels of current elicits eye movements (Fujii et al. 1995; Lee and Tehovnik 1995; Mann et al. 1988; Martinez-Trujillo et al. 2003a; Martinez-Trujillo et al. 2004; Martinez-Trujillo et al. 2003b; Missal and Heinen 2001, 2004; Mitz and Godschalk 1989; Russo and Bruce 1993; Schall 1991a; Schlag and Schlag-Rey 1985, 1987a, b; Tehovnik and Lee 1993; Tehovnik et al. 1994; Tehovnik and Slocum 2000; Tehovnik et al. 1999; Tehovnik et al. 1998; Tehovnik and Sommer 1996, 1997; Tian and Lynch 1995). It is also indicated by the fact that single neurons are active during the planning and execution of eye movements toward targets in restricted response fields (Bon and Lucchetti 1991, 1992; Chen and Wise 1995a, b, 1996, 1997; Coe et al. 2002; Fujii et al. 2002; Hanes et al. 1995; Lee and Tehovnik 1995; Mushiake et al. 1996; Olson and Gettner 1995, 1999, 2002; Olson et al. 2000; Olson and Tremblay 2000; Russo and Bruce 1996, 2000; Schall 1991a, b; Schlag and Schlag-Rey 1985, 1987b; Schlag et al. 1992; Schlag-Rey et al. 1997; Tremblay et al. 2002).

The involvement of the SEF in saccade generation occurs at a comparatively high level probably best regarded as cognitive rather than motor. Among the indications that this is so is the observation that around half of neurons firing in conjunction with the planning and execution of saccades are sensitive to the object-centered location of the target, firing differentially before saccades to the left or right end of a horizontal bar even when the properties of the saccade are

held constant (Olson 2003; Olson and Gettner 1995). Object-centered signals in the SEF represent the location of the target relative to the object independently of concrete factors such as the nature of the cue conveying the instruction (Olson and Gettner 1999) or the physical properties of the object (Olson and Tremblay 2000). Many SEF neurons represent object-centered location over a wide or even unlimited range of saccade directions (Moorman and Olson 2005a, Aim 1). Object-centered signals do not even depend on the active use of an object-centered rule to select the target. In monkeys performing a task in which, on each trial, a saccade must be directed to one end of a horizontal bar or the other and in which, on interleaved trials, the rule for target selection is location-based (select the left or right end of the bar) or color-based (select the red or green end of the bar), SEF neurons signal the object-centered location of the target even when a color rule is in use (Tremblay et al. 2002).

The fact that SEF neurons in the monkeys studied by Tremblay et al. (2002) represented the object-centered location of the target even when the target was selected by color indicates that the representation of object-centered space was automatic in these monkeys but not necessarily that it was innate. Before ever performing the color-based task, each monkey had been trained extensively on a task requiring the selection of targets by an object-centered rule. Object-centered selectivity might have developed in the SEF in response to object-centered training even though ultimately it was expressed automatically outside the training context. To determine to what degree object-centered spatial selectivity is innate and to what degree it is a product of training was the aim of the experiment described here. To resolve this issue, we carried out single-neuron recording at two stages of training. We first trained monkeys on a color delayed-match-to-sample (DMS) task in which they had to select as target on each trial the red or green end of a horizontal bar. Following training, we monitored neuronal activity in the

SEF during task performance. Then we proceeded to train them on a task in which they had to select one end of the bar or the other on the basis of its object-centered location and again recorded in the SEF. The results indicate that object-centered spatial selectivity is present in the SEF before monkeys have learned to select targets on the basis of an object-centered rule but is enhanced by training on the use of such a rule.

3.2. Methods

3.2.1. Subjects

Two adult male rhesus monkeys were used (Macaca mulatta; laboratory designations Bi and Ro hereafter referred to as M1 and M2). Experimental procedures were approved by the Carnegie Mellon University Animal Care and Use Committee and were in compliance with the guidelines set forth in the United States Public Health Service Guide for the Care and Use of Laboratory Animals.

3.2.2. Preparatory surgery

At the outset of the training period, each monkey underwent sterile surgery under general anesthesia maintained with isofluorane inhalation. The top of the skull was exposed, bone screws were inserted around the perimeter of the exposed area, a continuous cap of rapidly hardening acrylic was laid down so as to cover the skull and embed the heads of the screws, a head-restraint bar was embedded in the cap, and scleral search coils were implanted on the eyes, with the leads directed subcutaneously to plugs on the acrylic cap (Robinson 1963). Following initial training, a 2-cm-diameter disk of acrylic and skull, centered on the midline of the brain

approximately at anterior 21 mm (Horsley-Clarke coordinates), was removed and a cylindrical recording chamber was cemented into the hole with its base just above the exposed dural membrane.

3.2.3. Tasks

The monkeys were first trained to perform the color DMS task and later trained to perform the color-conditional object-centered task (Fig. 20). The tasks were identical with respect to the timing of events and the geometry of the stimuli. They differed only with respect (1) to the coloring of the target bar (red on one end and green on the other in the color DMS task vs. uniformly gray in the object-centered task) and (2) the rule by which the monkey selected one end of the bar as the target for a saccade (the end of the same color as the cue in the color DMS task vs. the end associated with the color of the cue – left for green and right for red – in the color-conditional object-centered task). Each trial began with presentation of a central fixation spot and attainment of fixation in an approximately 5° x 5° fixation window. After a series of intervening events, including presentation of a foveal instructional cue and onset of an eccentric target display, the fixation spot was turned off, whereupon the monkey was required to make a saccade to the target (the left or right end of a horizontal bar), landing within a 5° x 5° window centered on it and maintaining gaze on it for an interval that varied randomly across trials in the range 0-300 ms. Upon termination of this interval, the display was extinguished and juice reward was delivered. The twelve conditions in the color DMS task (Fig. 20B, before training) or the six conditions in the object-centered task (Fig. 20C, after training) were interleaved randomly subject to the constraint that one trial conforming to each condition had to be completed successfully before the beginning of the next block of twelve or six trials. Data

collection continued until 16 trials had been completed under each condition unless the neuron was lost. In the event of the neuron's being lost, the data were retained and included in the database for subsequent analysis if at least eight trials had been completed successfully under each condition.

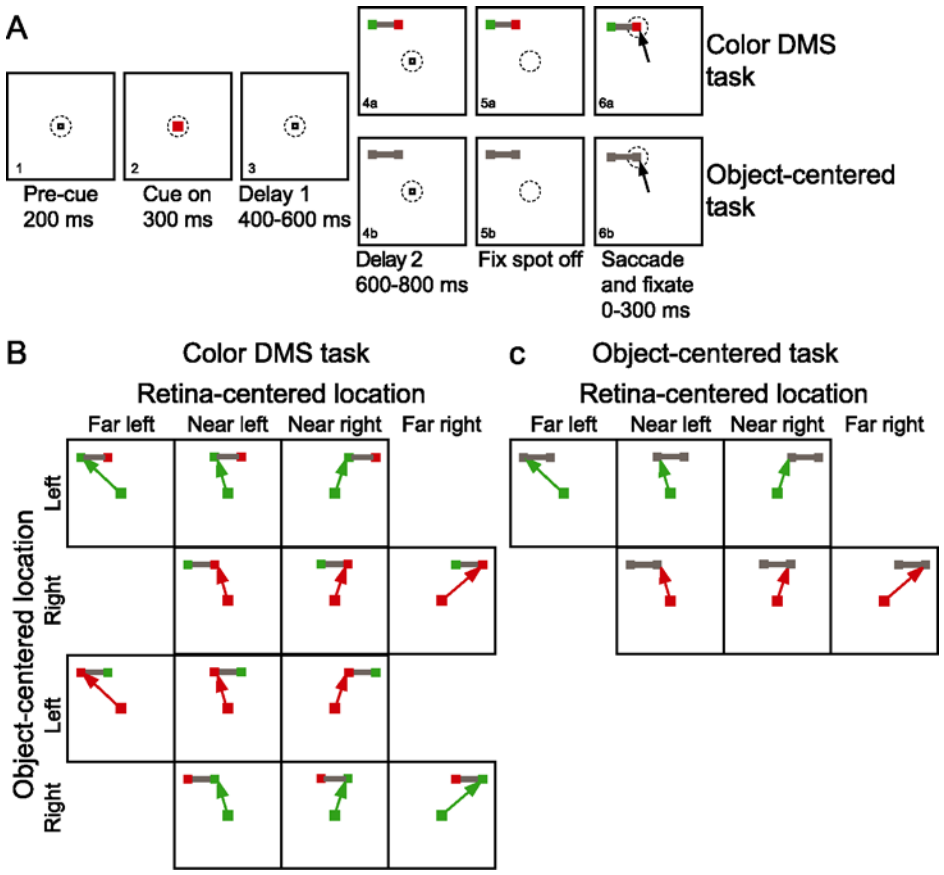

Fig. 20. Task design.

A. Sequence of events in the color delayed match-to-sample task (top) and color-conditional object-centered task (bottom). In the color DMS task, the monkey had to select as target the dot on the end of the bar that matched in color the cue presented earlier in the trial. In the object-centered task, the monkey had to select the dot on the end of the bar associated with the color of the cue (left for green or right for red). B. Display geometry under twelve conditions in the color DMS task. C. Display geometry under six conditions in the object-centered task.

3.2.4. Stimuli

Geometry. The displays (Fig. 20) were identical for the two monkeys but the distance from the eyes to the monitor was less for M2 by a factor of 0.96. In analyzing saccade trajectories, we scaled up data from M2 by a factor of 1.04 so as to achieve register with data from M1. The values given here are for M1. The fixation spot was a 0.43° x 0.43° white square presented at the center of the screen. The foveal color cue was a 1.7° x 1.7° gray, green, or red square. The bar display consisted of two 1.3° x 1.3° squares centered on the ends of a horizontal gray bar 7.1° long and 0.28° thick. The bar display was centered at one of three locations at an elevation of 11.4°. One location was centered above fixation. The other two points were offset to the right or left by half a bar length. This design allowed analyzing neuronal activity accompanying a saccade to the same dot (at the near left or near right location in Fig. 20B-C) as a function of whether it occupied the left or right end of a bar.

Luminance and hue. The fixation point had a luminance of 83 cd/m^2 and CIE x and y chromaticity coefficients of 0.28 and 0.32. The red cue and target dot had a luminance of 33 cd/m^2 and CIE x and y chromaticity coefficients of 0.33 and 0.17. The green cue and target dot had a luminance of 67 cd/m^2 and CIE x and y chromaticity coefficients of 0.25 and 0.66. The gray bar and target dot had a luminance of 57 cd/m^2 and CIE x and y chromaticity coefficients of 0.27 and 0.31.

3.2.5. Single-neuron recording

At the beginning of each day's session, a varnish-coated tungsten microelectrode with an initial impedance of several megohms at 1 KHz (Frederick Haer & Co., Bowdoinham, ME) was advanced vertically through the dura into the immediately underlying cortex using a hydraulic

microdrive (Narashige, Tokyo, Japan). The electrode could be placed reproducibly at points forming a square grid with 1 mm spacing (Crist et al. 1988). Single neurons were isolated using both online and offline template-matching and principal components analysis sorting (Plexon Inc, Dallas, TX).

3.2.6. Behavioral control and data collection

All aspects of behavioral procedure, including presentation of stimuli, monitoring of eye movements, and delivery of reward, were under the control of a Pentium-based computer running Cortex software (http://www.cortex.salk.edu). Eye position was monitored by means of a scleral search coil system (Riverbend Instruments, Inc., Birmingham, AL). The X and Y coordinates of eye position were stored at 10 ms intervals. Stimuli generated by an active matrix LCD projector were rear-projected on a frontoparallel screen 25.4 cm (M1) and 24.5 (M2) cm from the monkey's eyes. Reward in the form of 0.1 cc of juice was delivered through a spigot under control of a solenoid valve upon successful completion of each trial.

3.2.7. Analysis of behavioral performance

Behavioral data, including percent correct and reaction time, as well saccade velocity, amplitude, and landing points, were calculated for each trial in both tasks. These data were compared across tasks to determine the behavioral effect of changes in task requirements. In all cases, significant differences in behavioral data were assessed using t-tests or Kolmogorov-Smirnov tests ($p < 0.05$).

3.2.8. Analysis of saccade metrics

The aim of this step was to characterize the properties of the saccade executed on each trial. First, the direction of gaze was determined for each 10 ms bin during a 500 ms epoch beginning with offset of the fixation spot. Then the instant of maximal velocity was identified by finding the pair of adjacent 10 ms bins (B_m and B_{m+1}) for which the displacement of the eye in degrees of visual angle (ΔE_m) was maximal. The maximal velocity, in degrees of visual angle per second, was given by $100*\Delta E_m$. The start of the saccade was identified by moving backward in time until encountering a pair of bins, B_s and B_{s+1}, for which $\Delta E_s < \Delta E_m/4$. Saccadic reaction time was taken as the interval between offset of the fixation spot and the beginning of bin B_{s+1}. The finish of the saccade was identified by moving forward in time until encountering a pair of bins, B_f and B_{f+1}, for which $\Delta E_f < \Delta E_m/4$. Saccade amplitude was taken as the distance in degrees of visual angle between eye positions recorded at B_s and B_{f+1}. The final position of the eye was estimated on the basis of B_{f+7} so as to allow time for asymptotic deceleration without exceeding the minimal reaction time for any corrective saccade.

3.2.9. Analysis of neuronal activity

To characterize the dependence of neuronal activity on the retina-centered direction of the saccade and the object-centered location of the target, we carried out a series of ANOVAs as described in the text. Independent analyses were carried out on data from three epochs: a pre-bar-onset epoch (foveal cue onset + 100 ms to bar onset + 100 ms), a post-bar-onset epoch (bar onset + 100 ms to fixation point offset + 100 ms), and a peri-saccadic epoch (saccade initiation +/- 150 ms). The criterion for significance was taken as $p < 0.05$ unless otherwise stated. In

comparing counts of neurons exhibiting significant effects, we used a χ^2 test. In all such cases, if there was only one degree of freedom, we incorporated a Yates correction.

3.2.10. Multiple regression analysis

In order to determine whether firing rate was correlated with object-centered location independently of any effect arising from subtle variations in saccades between bar-left and bar-right trials, we performed a multivariate regression analysis, fitting three models to data collected from each neuron during trials in which the target (the right or left end of a bar) appeared at a given screen location:

1) $Y = \beta_0 + \beta_1 Obj + \beta_2 Lat + \beta_3 Vel + \beta_4 Amp + \beta_5 Xpos + \beta_6 Ypos$

2) $Y = \beta_0 + \beta_1 Lat + \beta_2 Vel + \beta_3 Amp + \beta_4 Xpos + \beta_5 Ypos$

3) $Y = \beta_0 + \beta_1 Obj$

where Y = firing rate measured during the post-bar-onset period (target onset +100 ms to saccade initiation +100 ms), Obj = object-centered location (0 or 1 for bar-left or bar-right), Lat = latency (from fixation spot offset), Vel = peak velocity, Amp = amplitude, and Xpos and Ypos = final x and y landing positions respectively. Having fitted the parameters of each model to a neuron's data, we determined, using an F-test, whether the full model (1), when compared to each of the reduced models (2, 3) accounted for significantly more of the variance in the data than could be explained by its larger number of degrees of freedom. If model 1 provided a significant improvement over model 2, we concluded that neuronal activity depended significantly on object-centered location independently of any tendency for saccade parameters to co-vary with

object-centered location. If model 1 provided a significant improvement over model 3, we concluded, by similar reasoning, that neuronal activity depended significantly on variations in the saccade. We computed F as:

$$F_{k,m-(n+k)} = \frac{\left(\frac{SS_{red} - SS_{full}}{k}\right)}{\left[\frac{SS_{full}}{m-(n+k)}\right]}$$

where k = the difference in degrees of freedom between the two models, m = the number of trials, n = 1 was the number of neurons, and SS_{full} and SS_{red} were the residual sums of squares for the full model and the reduced model.

3.2.11. Characterization of recording sites

The location of the recording sites relative to gross morphological landmarks was assessed by analysis of structural MR images. Scanning was carried out in a Brükker 4.7 T magnet in which the anesthetized monkey was supported by an MR-compatible stereotaxic device. Fiducial marks made visible by means of a contrast agent included the centers of the ear bars and selected locations inside the recording chamber. Frontoparallel and parasagittal slices of 2 mm thickness were collected over the entire extent of the cerebral hemisphere. To determine the location of recording sites relative to functional divisions of cortex, we mapped out regions under each chamber from which oculomotor responses could be elicited at low threshold (≤ 50 μA) by electrical microstimulation (1.65 ms biphasic pulses delivered through the recording microelectrode at a frequency of 300 Hz in trains 200 ms long).

3.3. Results

3.3.1. Overview

The general aim of this experiment was to monitor neuronal activity in the SEF while monkeys executed saccades to targets located at the left or right end of a horizontal bar at two successive stages of training: (1) when they had been trained on and were following a color delayed-match-to-sample (DMS) rule (select the end of the bar with the same color as a sample presented earlier in the trial) and (2) when they had been trained on and were following a color-conditional object-centered rule (select the end of the bar associated with the color presented earlier in the trial). The geometry of the stimuli and saccades was the same during both stages of data collection (Fig. 20). Only during the second stage, however, had the monkeys received training requiring them to select a target on the basis of its object-centered location. The central questions were (1) whether SEF neurons would exhibit object-centered spatial selectivity even during stage 1 when the monkeys were naïve with respect to the use of an object-centered rule and (2) whether object-centered selectivity would be enhanced during stage 2, when the monkeys had learned and were using an object-centered rule.

The first stage of training, in which the monkeys learned the color DMS task, occupied many months (11 and 9 months in M1 and M2 respectively). The first stage of neuronal data collection ensued immediately and occupied several months (3 and 5 months in M1 and M2 respectively). During this stage, we recorded from 259 neurons (99 and 160 in M1 and M2 respectively). Inducing transfer from the color DMS task to the color-conditional object-centered task required merely (1) limiting the color DMS task to conditions in which the green dot was on the left end of the target bar and the red dot on the right end and (2) gradually desaturating the red and green dots until they were a uniform gray. Consequently, the second

stage of training, in which the monkeys learned the color-conditional object-centered task, proceeded swiftly (occupying 7 and 3 days in M1 and M2 respectively). The second stage of neuronal data collection ensued immediately and occupied two months in each monkey. During this stage, we recorded from 217 neurons (118 and 99 in M1 and M2 respectively).

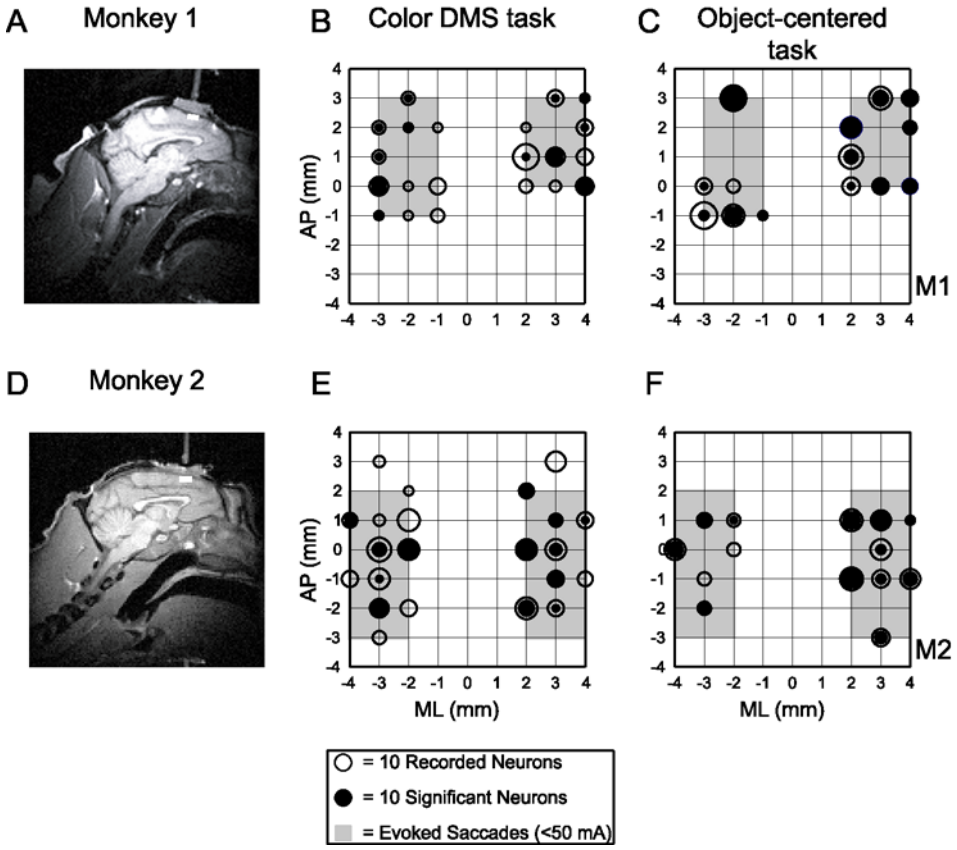

Fig. 21. Recording sites.

A. Parasagittal MR image through the medial face of the right hemisphere of M1. The approximately vertical line above the brain marks AP and ML zero in recording-grid coordinates. The center of the grid in each monkey was located approximately 5 mm rostral to the genu of the arcuate sulcus and over the interhemispheric cleft. The white rectangle superimposed on the gray matter demarcates the region in which recording was carried out. B. Location relative to grid coordinates in M1 of neurons exhibiting significant object-centered spatial selectivity during performance of the color DMS task in stage 1 of the experiment. At each location, the area of the outer (open) bubble indicates the number of recorded neurons and the area of inner (filled) bubble indicates the number exhibiting selectivity. Gray shading demarcates the region within which electrical microstimulation elicited eye movements. C. Neurons in M1 exhibiting significant object-centered selectivity during performance of the object-centered task in stage 2 of the experiment. D-F. As above but for M2.

3.3.2. Recording sites

Recording sites during both stages of data collection (Fig. 21) were within a bilateral region of the frontal lobe identified as the SEF on the basis of electrical microstimulation mapping (saccades could be elicited at currents of less than 50 μA) and on the basis of its location as established through the analysis of MR images (2-8 mm rostral to the genu of the arcuate sulcus and within a few mm of the interhemispheric cleft). In this study, we deviated from standard practice in previous studies of object-centered selectivity in the SEF (Olson 2003; Olson and Gettner 1995, 1999; Olson and Tremblay 2000; Tremblay et al. 2002) by recording from all isolated neurons regardless of whether they appeared to exhibit task-related activity on preliminary testing.

3.3.3. Behavior

Percent Correct. In assessing behavioral performance during the neuronal data collection sessions, we confined our attention to a set of trial conditions across which the retina-centered direction of the saccade and the object-centered location of the target were fully counterbalanced (near left and near right conditions in Fig. 20B-C). We did so because it was under these conditions that subsequent steps of data analysis were based. The score for each session was taken as the number of trials on which the monkey made a saccade to the correct end of the bar expressed as a percentage of all trials on which he responded to fixation spot offset by making a saccade. In both monkeys, the mean percent correct across all data-collection sessions was higher in the color DMS task (95% and 90% in M1 and M2 respectively) than in the object-centered task (89% in each monkey) but only in M1 did the difference achieve significance (Kolmogorov-Smirnov test, $p << 0.0001$).

Reaction time. We first computed the mean of the reaction time (the interval between when the fixation spot was extinguished and when the saccade began) for correct trials in each session, confining attention to trial conditions in which the target was at the near left or near right location. Then we computed the mean across sessions for each task. The mean reaction time was higher in the color DMS task (97 and 188 ms in M1 and M2 respectively) than in the object-centered task (88 and 83 ms in M1 and M2 respectively). From the fact that these values were so low, it is clear that on some trials the monkeys committed to execution of the saccade before offset of the fixation spot. They were not penalized for anticipatory behavior. It was only required that the gaze remain within the central window until extinction of the fixation spot.

Saccadic landing point. The landing points of saccades to targets at the four possible locations (far left, near left, near right and far right) varied somewhat across tasks and conditions (Fig. 22). The variability was small. Nevertheless, it was important to determine whether saccades to the left and right ends of bars had different trajectories because, if they did, then neurons apparently selective for the object-centered location of the target might simply be exhibiting selectivity for the direction of the saccade. On comparing landing points across bar-left and bar-right conditions, we found that differences with respect to the vertical axis were small and inconsistent but that differences with respect to the horizontal axis conformed to a pattern whereby the saccade deviated slightly from the end of the bar toward its center, as reported previously (Olson and Tremblay 2000). Thus, across conditions in which the target dot on the left end of the bar and the target dot on the right end of the bar occupied the same screen location, the gaze consistently landed slightly farther to the right when the left dot on the bar's left end was the target than when the target was the dot on the bar's right end. The mean offset between the two landing points was 0.42 degrees of visual angle in the color DMS task (0.56° in

M1 and 0.27° in M2) and 0.43 degrees of visual angle in the color-conditional object-centered task (0.42° in M1 and 0.43° in M2). We demonstrate below that this small deviation had only a minimal impact on neuronal activity (3.3.8, Ruling out a contribution of saccade metrics).

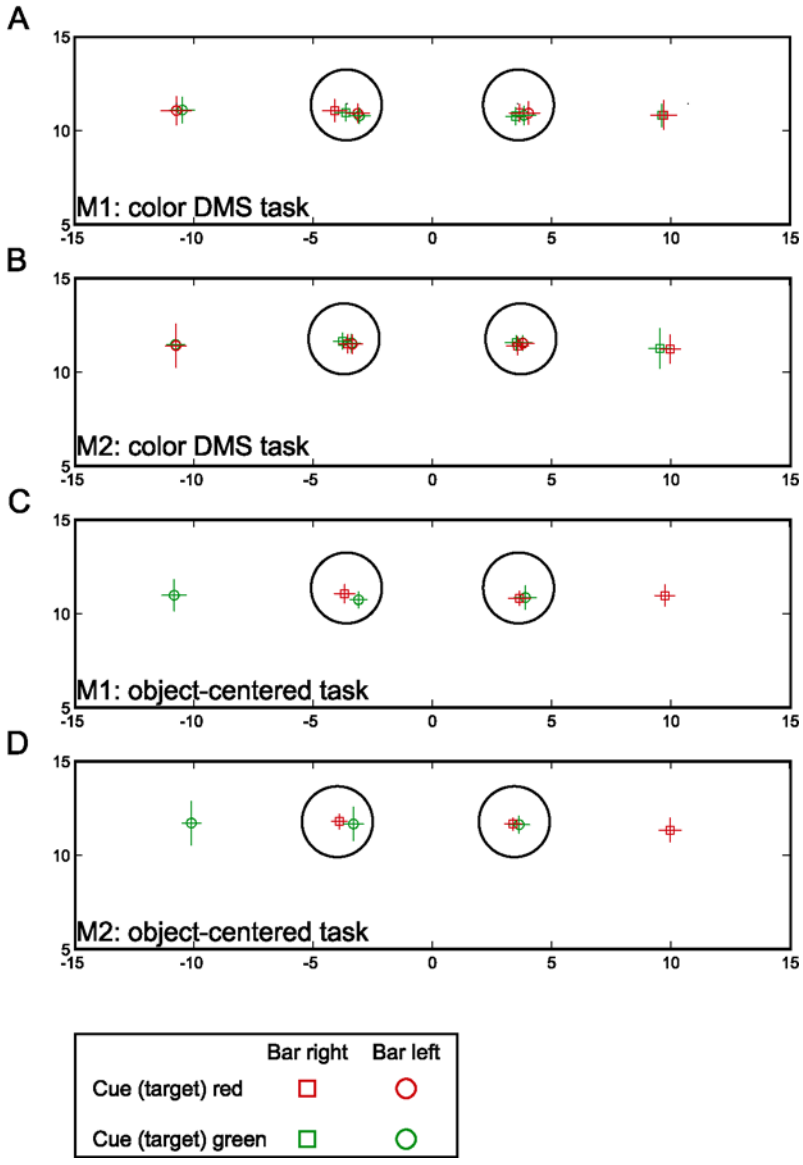

Fig. 22. Saccadic landing positions.

Means and standard deviations of saccadic end-points for each monkey in each task. Circles are centered on the locations of the targets at near left and near right locations. Each of these locations could be occupied by either the left or the right end of a bar. Scale is in degrees of visual angle relative to the initial fixation point.

3.3.4. Moderate incidence of object-centered selectivity in the color DMS task

Neuronal data analysis focused on three periods during the trial: (1) the pre-bar-onset epoch, during which the color of the sample was known but the location of the target was not (cue onset + 100 ms to bar onset + 100 ms), (2) the post-bar-onset epoch, during which both the color of the target and its location were known(bar onset +100 ms to fixation offset + 100 ms), and (3) a peri-saccadic epoch (from 150 ms before to 150 ms after saccade initiation). The first two epochs began and ended at points in time offset by 100 ms from the occurrence of significant visual events so as to take into account the approximate latency at which visual events affect neuronal activity in the SEF. For each neuron, and for each trial epoch independently, a three-factor ANOVA was carried out to assess the dependence of firing rate on (1) the retina-centered location of the target (near left or near right), (2) the object-centered location of the target (bar-left or bar-right) and (3) the color of the target (red or green). The analysis was confined to trials completed successfully under the eight conditions in which the target was at the near left or near right location (Fig. 20B). Across this set of conditions, retina-centered location, object-centered location and color were fully counterbalanced. The results are summarized in Table 4.

Pre-bar-onset epoch. In the pre-bar-onset epoch, the target display had not yet appeared. Accordingly, it would unreasonable to expect to observe object-centered selectivity or retina-centered selectivity during this epoch. Indeed, significant main effects of object-centered and retina-centered direction were no more common than expected by chance (χ^2 test, $p > 0.05$). The colored foveal cue was, however, presented at the beginning of this epoch. Accordingly, neurons might reasonably be expected to exhibit color selectivity. Indeed, the rate of incidence of main effects of color (24/259 = 9% of neurons) exceeded the frequency significantly expected

	Monkey	Color		Object-Centered		Retina-Centered	
		R>G	G>R	C>I	I>C	C>I	I>C
Pre-Bar-Onset Epoch	**M1 (n = 99)**	3 (3%)	7 (7%)	1 (1%)	1 (1%)	3 (3%)	3 (3%)
	M2 (n = 160)	11 (7%)	3 (2%)	2 (1%)	1 (1%)	2 (1%)	4 (3%)
	Total (n = 259)	**14 (5%)**	**10 (4%)**	**3 (1%)**	**2 (1%)**	**5 (2%)**	**7 (3%)**
Post-Bar-Onset Epoch	**M1 (n = 99)**	2 (2%)	2 (2%)	8 (8%)	13 (13%)	28 (28%)	18 (18%)
	M2 (n = 160)	4 (3%)	20 (13%)	26 (16%)	22 (14%)	23 (14%)	16 (10%)
	Total (n = 259)	**6 (2%)**	**22 (8%)**	**34 (13%)**	**35 (14%)**	**51 (20%)**	**34 (13%)**
Peri-Saccadic Epoch	**M1 (n = 99)**	4 (4%)	1 (1%)	12 (12%)	13 (13%)	8 (8%)	16 (16%)
	M2 (n = 160)	4 (3%)	15 (9%)	19 (12%)	16 (10%)	12 (8%)	19 (12%)
	Total (n = 259)	**8 (3%)**	**16 (6%)**	**31 (12%)**	**29 (11%)**	**20 (8%)**	**35 (14%)**

Table 4. Color DMS task: Counts of neurons exhibiting selectivity for color, for object-centered location and for retina-centered location

Results of ANOVAs carried out on data from 259 neurons during stage 1 of the study with firing rate as the dependent variable and with the color of the cue and target (red, green), the object-centered location of the target (bar-left or bar-right) and the retina-centered location of the target (near left, near right) as three factors. Independent analyses were carried out on data from the pre-bar-onset epoch (cue onset + 100 ms to bar onset + 100 ms), the post-bar-onset epoch (bar onset + 100 ms to fixation point offset + 100 ms) and the peri-saccadic epoch (saccade initiation +/- 150 ms). "Color": significant main effect of color. R>G and G>R: Stronger firing for red than for green and vice versa. "Object-centered": significant main effect of object-centered location. "Retina-centered": significant main effect of retina-centered location. C>I: stronger firing when the target was at the end of the bar contralateral to the recording hemisphere (in the case of object-centered selectivity) or in the visual field contralateral to the recording hemisphere (in the case of retina-centered selectivity). I>C: the opposite pattern.

by chance in each monkey (χ^2 test, p = 0.036 in M1 and p = .046 in M2). We conclude that selectivity for the color of the cue, although rare, was genuinely present.

Post-bar-onset epoch. The target display was turned on at the beginning of this epoch. Accordingly, one might reasonably expect to observe selectivity for any of the three factors. Main effects of object-centered location were present in 69/259 = 27% of neurons. Main effects of the retina-centered location were present in 85/259 = 33% of neurons. Main effects of the color of the target were observed in 28/259 = 11% of neurons, with the rate of incidence significantly exceeding the rate expected by chance only in M2 (χ^2 test, p << 0.0001). We

conclude (a) that neurons were selective for spatial factors more commonly than for color and (b) that neurons exhibiting object-centered and retina-centered selectivity were approximately equally common.

Peri-saccadic epoch. Main effects of object-centered location were present in 60/259 = 23% of neurons. Main effects of retina-centered location were present in 55/259 = 21% of neurons. Main effects of color were present in 24/259 = 9% of neurons, with the rate of incidence of such effects significantly exceeded the rate expected by chance only in M2 (χ^2 test, $p = 0.0001$). We conclude (a) that neurons were selective for spatial factors more commonly than for color and (b) that neurons exhibiting object-centered and retina-centered selectivity were approximately equally common.

Summary. The question at the heart of this stage of analysis was whether SEF neurons would exhibit selectivity for the object-centered location of the target in monkeys trained to select targets on the basis of color and never trained in the use of an object-centered rule. The answer is in the affirmative: in more than a quarter of the recorded neurons, the firing rate during the period from appearance of the target display to execution of the saccade depended significantly on the object-centered location of the target.

3.3.5. Increased incidence of object-centered selectivity and reduced incidence of retina-centered selectivity in the object-centered task

During the second stage of data collection, when monkeys were performing the object-centered task, we analyzed neuronal selectivity by a procedure identical to that applied to data from the Color DMS task with the sole exception that the color of the cue was not included as an independent factor. This omission was motivated by the consideration that color and object-

centered location were not dissociable in the object-centered task because each color cued one object-centered location. The results are summarized in Table 5.

	Monkey	Object-Centered		Retina-Centered	
		C>I	I>C	C>I	I>C
Pre-Bar-Onset Epoch	**M1 (n = 118)**	13 (11%)	13 (11%)	1 (1%)	2 (2%)
	M2 (n = 99)	16 (16%)	5 (5%)	1 (1%)	3 (3%)
	Total (n = 217)	**29 (13%)**	**18 (8%)**	**2 (1%)**	**5 (2%)**
Post-Bar-Onset Epoch	**M1 (n = 118)**	30 (25%)	24 (20%)	13 (11%)	18 (15%)
	M2 (n = 99)	26 (26%)	19 (19%)	11 (11%)	8 (8%)
	Total (n = 217)	**56 (26%)**	**43 (20%)**	**24 (11%)**	**26 (12%)**
Peri-Saccadic Epoch	**M1 (n = 118)**	15 (13%)	15 (13%)	6 (5%)	13 (11%)
	M2 (n = 99)	18 (18%)	13 (13%)	7 (7%)	13 (13%)
	Total (n = 217)	**33 (15%)**	**28 (13%)**	**13 (6%)**	**26 (12%)**

Table 5. Object-centered task: Counts of neurons exhibiting selectivity for object-centered location and for retina-centered location.

Results of ANOVAs carried out on data from 217 neurons during stage 2 of the study. Conventions as in Table 4.

Pre-bar-onset epoch. At the outset of the pre-bar-onset epoch, a colored cue conveyed the object-centered instruction. Accordingly, one might expect to observe object-centered selectivity (technically indistinguishable from color selectivity) during this epoch. However, because the bar had not yet appeared, one would not expect retina-centered selectivity. Indeed, significant main effects of object-centered location were present in 47/217 = 22% of neurons, whereas significant main effects of retina-centered location (in 7/217 = 3% of neurons) did not exceed the rate expected by chance (χ^2 test, $p > 0.05$). The rate of incidence of object-centered selectivity in this task (22%) was significantly greater than the rate of incidence of color selectivity (11%) during the corresponding epoch in the color DMS task (χ^2 test, $p = 0.03$ in M1 and $p = 0.008$ in

M2). We conclude that a substantial number of neurons was selective for the object-centered instruction conveyed by the color cue even before onset of the target bar.

Post-bar-onset epoch. Main effects of object-centered location were present in 99/217 = 46% of neurons, while main effects of retina-centered location were present in 50/217 = 23% of neurons. The frequency of object-centered selectivity in this task (46%) was significantly greater than its frequency (27%) during the corresponding epoch in the color DMS task (χ^2 test, $p = 0.0003$ in M1 and $p << 0.0001$in M2) (Fig. 23A). In contrast, the frequency of retina-centered selectivity (23%) was lower than in the previous task (33%). This effect was present in both monkeys and attained significance in M1 (χ^2 test, $p = 0.003$) (Fig. 23B). The fact that retina-centered selectivity was less frequent in the object-centered task than in the color DMS task is noteworthy for two reasons. 1) It indicates that the observed enhancement of object-centered selectivity during the second stage of data collection was not due simply to our having recorded from a population containing more task-related neurons. 2) It suggests that training on the object-centered task actually induced a reduction in the number of neurons exhibiting retina-centered spatial selectivity.

Peri-saccadic epoch. Main effects of object-centered location were present in 61/217 = 28% of neurons, while main effects of retina-centered location were present in 39/217 = 18% of neurons. The rate of object-centered selectivity in this task (28%) was greater than its rate (23%) during the corresponding epoch in the color DMS task but the difference did not attain significance in either monkey or in the combined data (χ^2 test, $p > 0.05$). The rate of retina-centered selectivity (18%) was less than in the previous task (21%), but the effect did not attain significance in either monkey or in the combined data (χ^2 test, $p > 0.05$). Thus effects observed during the post-bar-onset epoch (enhanced object-centered selectivity and reduced retina-

centered selectivity in the object-centered task as compared to the color DMS task) persisted during the peri-saccadic epoch but only as insignificant trends.

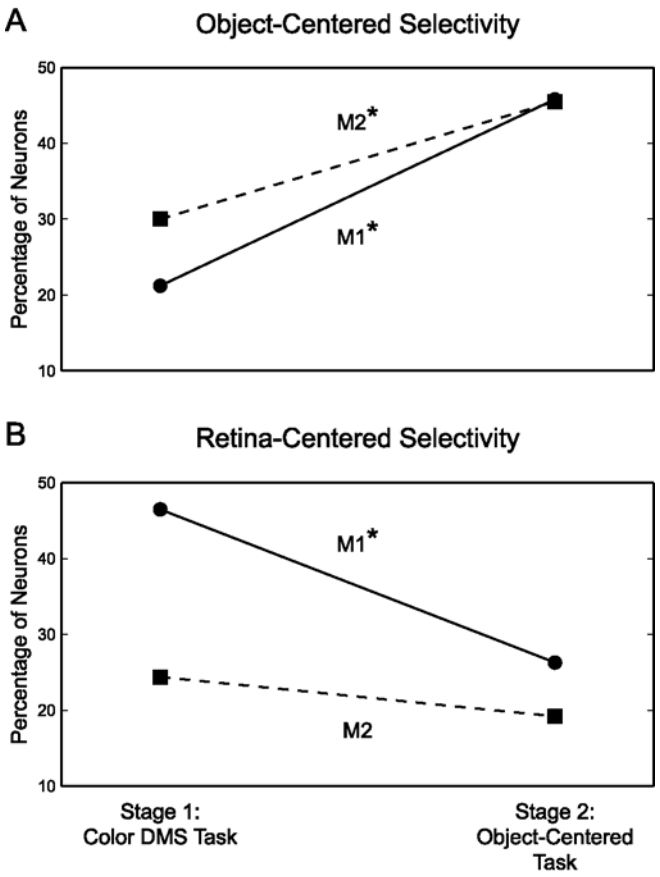

Fig. 23. Statistical comparison of selectivity between stage 1 and stage 2.

The percentage of neurons exhibiting object-centered selectivity was greater (A) and the percentage exhibiting retina-centered selectivity was less (B) during performance of the object-centered task at stage 2 of training than during performance of the color DMS task at stage 1 of training. Counts based on statistically significant selectivity during the post-bar-onset epoch as revealed by an ANOVA. Asterisks indicate instances in which the change in percentage achieved statistical significance. M1 and M2: monkeys 1 and 2.

Consistency across the period of data collection. Because the period of data collection during this stage of the experiment (two months) was markedly longer than immediately preceding training period (approximately a week), it might be supposed that training continued to occur and object-centered selectivity continued to increase over the data collection period. To

assess this possibility, we computed, for each neuron, an index of object-centered spatial selectivity during the post-bar-onset epoch: Abs(R-L)/(R+L)), where R and L represent the mean firing rates on bar-right and bar-left trials. This computation was based on the same subset of trials as the one on which the ANOVA was based. We then asked whether there was a consistent tendency for the values to increase as a function of the neuron's position in the recording sequence. In neither monkey was there a significant trend. Moreover, the slope of the best-fit line was slightly negative in each monkey. We conclude that object-centered selectivity remained at constant strength over the course of the recording period.

Summary. The question at the heart of this stage of analysis was whether more SEF neurons would exhibit selectivity for the object-centered location of the target in the object-centered task than had done so, prior to object-centered training, in the color DMS task. The answer is in the affirmative: the fraction of recorded neurons exhibiting object-centered selectivity during the post-bar-onset epoch rose from around a quarter to around a half and the fraction of neurons exhibiting retina-centered selectivity underwent a complementary decline.

3.3.6. Strength of object-centered selectivity compared between the two tasks

Although neurons in both stages of the experiment exhibited statistically significant object-centered selectivity, it was apparent from casual inspection of firing-rate data that object-centered signals tended to be stronger in the object-centered task than they had been in the color DMS task. This may be seen in histograms representing dramatic instances of object-centered selectivity observed in the two tasks (Fig. 24). In the neuron recorded during performance of the color DMS task, firing was moderately stronger on bar-left than on bar-right trials, with the difference most apparent when the saccade was directed to the near right target (Fig. 24A). In

the neuron recorded during performance of the object-centered task, firing was intense on bar-left trials and nearly absent on bar-right trials regardless of saccade direction (Fig. 24B).

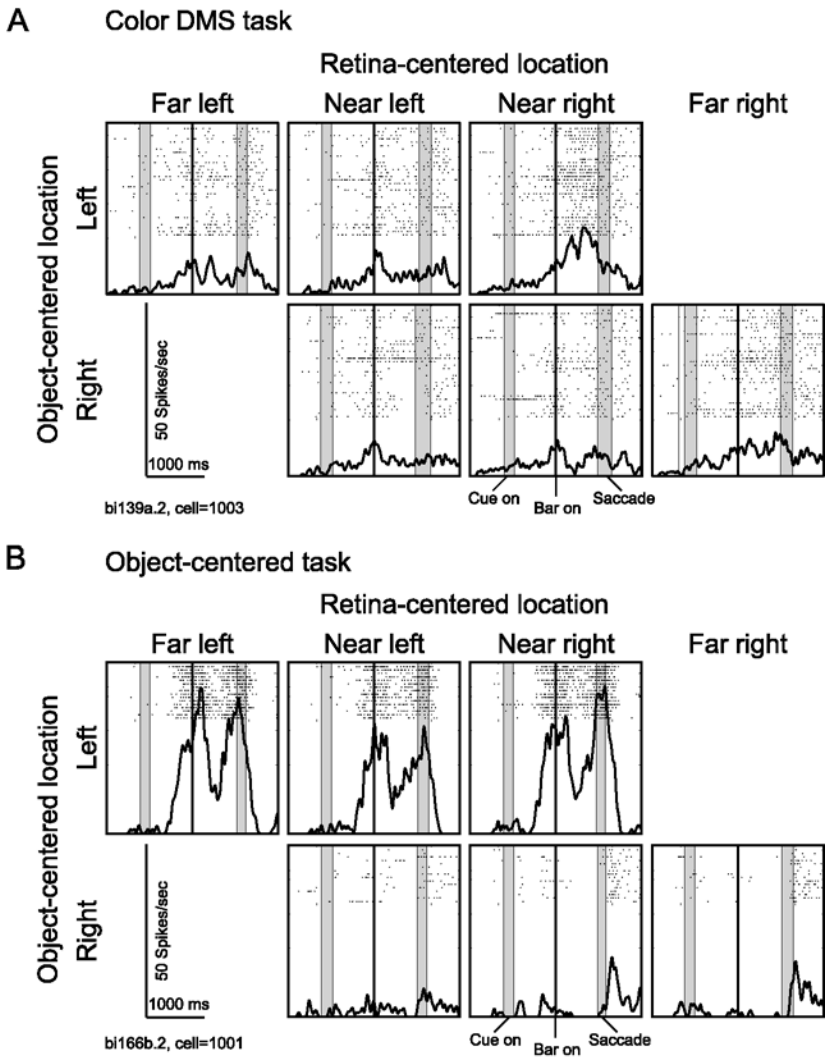

Fig. 24. Activity of two single neurons during performance of the color DMS task (A) and the object-centered task (B).

Object-centered spatial selectivity appeared more robust during stage 2 of the experiment (when monkeys were performing the object-centered task) than during stage 1 (when they were performing the color DMS task). A. Rasters and spike density functions representing the firing of an SEF neuron exhibiting significant object-centered spatial selectivity in the context of the color DMS task during stage 1 of the experiment. Panels in the same column represent conditions in which the target was at the same location on the screen but occupied different ends of a bar. The neuron fired more strongly during bar-left trials. B. Data from a neuron exhibiting significant object-centered spatial selectivity (firing more strongly on bar-left trials) in the context of the object-centered task during stage 2 of the experiment.

As a means for systematically comparing the strength of object-centered activity between tasks, we constructed population histograms representing the average firing rate across the population of recorded neurons on trials when the target was at the neuron's preferred object-centered location and on trials when it was at the opposite location. The preferred object-centered location of each neuron was defined as the one associated with stronger firing during the post-bar-onset epoch. The analysis was based exclusively on successfully completed trials in which the target was at the near left or near right location. Thus the retina-centered direction of the saccade was fully counterbalanced against the object-centered location of the target. The results are shown in Fig. 25. Each panel in this figure contains a pair of histograms, one representing activity on trials when the target was in the preferred object-centered location and the other representing activity when the target was in the opposite location. The degree by which firing on preferred-direction trials exceeded firing on opposite-direction trials is indicated by filling in the space between the two curves from the beginning to the end of the post-bar-onset epoch. In population histograms based on data from all recorded neurons (leftmost panels in Fig. 25) it is evident that the average strength of the object-centered signal (corresponding to the width of the black ribbon) was greater in the object-centered task (Fig. 25B) than in the color DMS task (Fig. 25A) in each monkey. This effect could have been due (a) to the higher incidence of neurons with significant object-centered selectivity or (b) to the presence of weaker signals even among neurons with significant object-centered selectivity. To distinguish between these possibilities, we also constructed population histograms based exclusively on the activity of neurons exhibiting significant main effects of object-centered location during the post-bar-onset epoch (rightmost panels in Fig. 25). Even in these histograms, the average strength of the

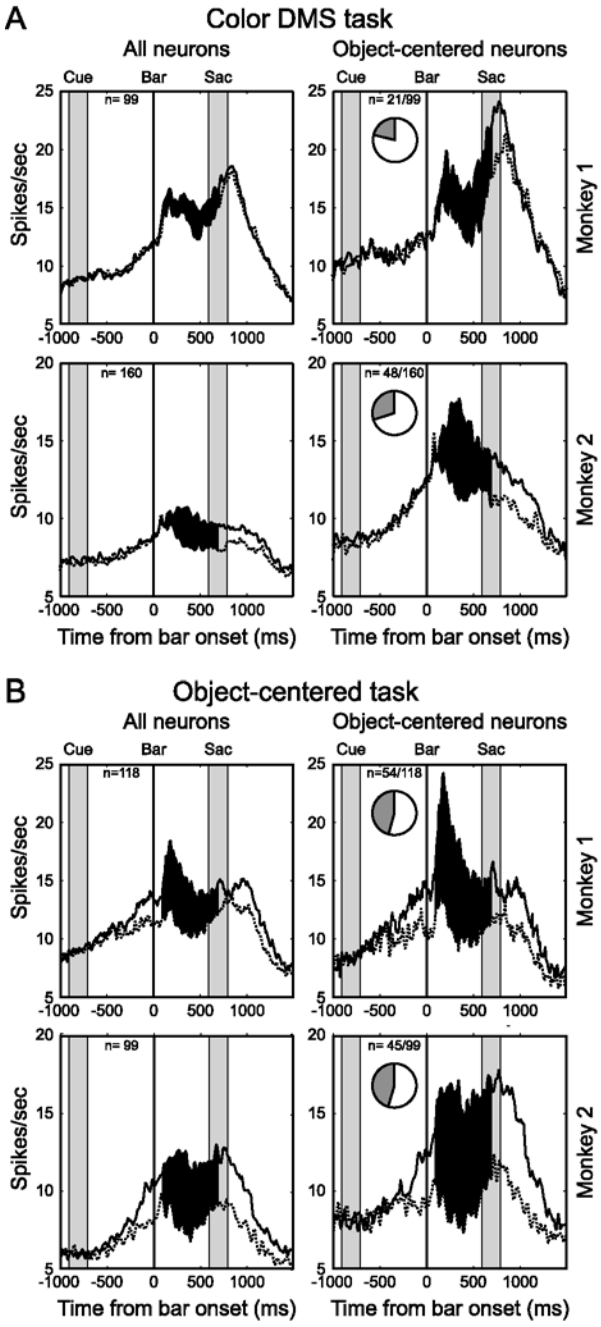

Fig. 25. Population histograms.

The object-centered activity of the neuronal population was more robust in the context of the object-centered task during stage 2 of the experiment than in the context of the color DMS task during stage 1. A. Population histograms from stage 1 (left column: all neurons; right column: neurons with significant object-centered spatial selectivity; top row: M1; bottom row: M2). Solid (or broken) curve represents mean population firing rate on trials in which the target was on the preferred (or non-preferred) end of a bar. The width of the black ribbon interposed between the two curves during the post-bar-onset epoch represents the strength of the object-centered signal. B. Population histograms from stage 2.

object-centered signal (corresponding to the width of the black ribbon) was greater in the object-centered task (Fig. 25B) than in the color DMS task (Fig. 25A) in each monkey.

To test quantitatively the impression that object-centered signals were stronger in the context of the object-centered task than in the context of the color DMS task, we computed for each neuron an index of object-centered selectivity: Abs(R-L)/(R+L), where R and L represent the mean firing rates during the post-bar-onset epoch on bar-left and bar-right trials respectively, with consideration restricted to trials in which the target was at the near left or near right location, so that retina-centered direction was counterbalanced against object-centered location (Fig. 26). With all neurons included in the analysis, the distribution of indices was shifted toward higher values for the object-centered task (mean = 0.22) as compared to the color DMS task (mean = 0.12) and the effect was significant (Kolmogorov-Smirnov test, $p << 0.0001$). With consideration restricted to neurons exhibiting a significant main effect of object-centered location during the post-bar-onset epoch (black bars in Fig. 26), the same trend was present, with the mean value for the object-centered task being 0.31 and the mean value for the color DMS task being 0.24 although for this population the effect did not achieve significance (Kolmogorov-Smirnov test, $p > 0.05$). We conclude that neurons with significant object-centered selectivity tended to carry stronger object-centered signals during the late stage of the experiment, when the monkeys were performing the object-centered task, than during the early stage of the experiment, when they had not yet been trained to use an object-centered rule and were performing the color DMS task.

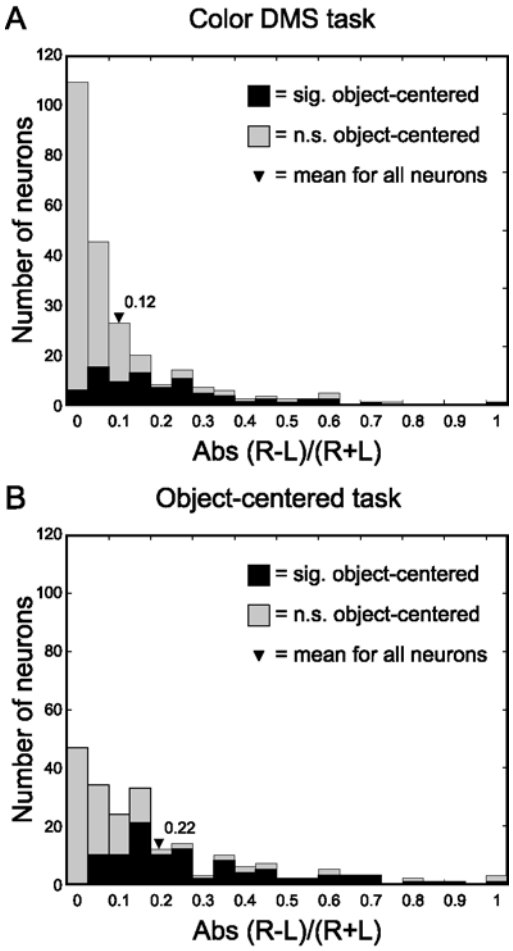

Fig. 26. Indices of object-centered selectivity compared across tasks.

The distribution of indices representing the strength of the neuronal object-centered signal was shifted toward higher values for neurons recorded in the context of the object-centered task during stage 2 of the experiment (B) as compared to neurons recorded in the context of the color DMS task during stage 1 (A). Black bars represent the subset of neurons with significant object-centered spatial selectivity. R (or L) was the mean firing rate on bar-right (or bar-left) trials during the post-bar-onset epoch.

3.3.7. Purity of object-centered selectivity compared between the two tasks

It might be argued that firing dependent on the object-centered location of the target was related not to the location of the target on the bar but rather to the location of the bar on the screen. These factors were partially correlated. Even with consideration restricted to trials requiring saccades to the near left or near right target (a constraint which afforded full counterbalancing of retina-centered direction against object-centered location), the average

location of the bar was to the left on bar-right trials and to the right on bar-left trials (Fig. 27A). Thus a main effect of object-centered location during the post-bar-onset epoch could have arisen from neuronal sensitivity either to the location of the target on the bar (Fig. 27B) or to the location of the bar on the screen (Fig. 27C).

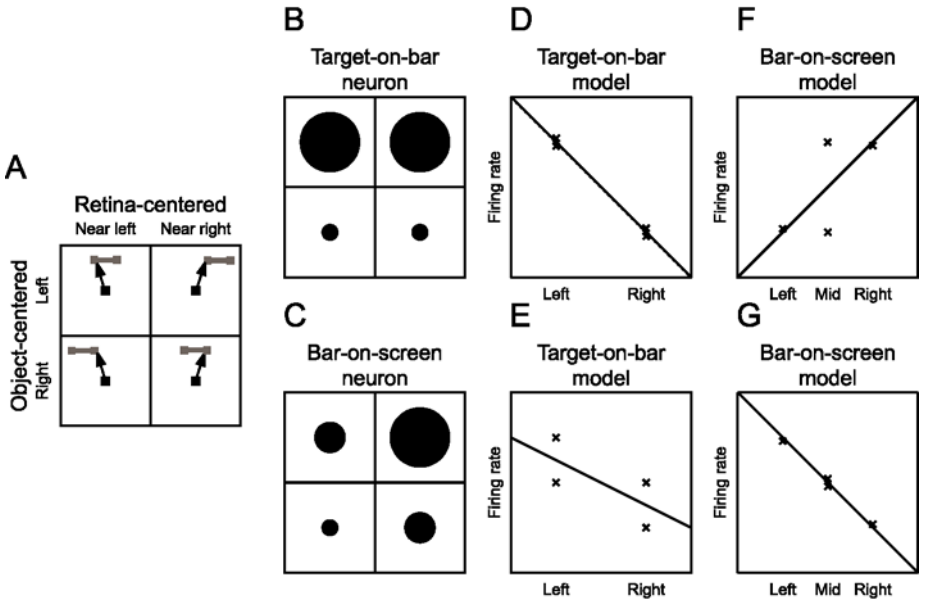

Fig. 27. Schematic of bar-on-screen vs. target-on-bar analysis

A. Across the conditions on which data analysis was based, the object-centered location of the target (bar-left or bar-right) and the location of the bar on the screen (left, middle or right) were partially correlated. The average location of the bar was farther to the left when the target was on its right end and vice versa. Thus neurons with apparent object-centered selectivity could actually have been sensitive to the location of the bar on the screen. B. The pattern of firing across conditions expected if the neuron were genuinely sensitive to the location of the target on the bar. C. The pattern of firing expected if the neuron were actually sensitive to the location of the bar on the screen. D-E. A model in which firing depends solely on the location of the target on the bar accounts for a high percentage of the variance in firing rate across conditions of the target-on-bar neuron (D) but not of the bar-on-screen neuron (E). F-G. For a model in which firing depends solely on the location of the bar on the screen, the situation is reversed.

To assess the degree to which each main effect of object-centered location depended on the location of the target on the bar vs. the location of the bar on the screen, we fit the data from each neuron with two models: a target-on-bar model in which the firing rate was a linear function of the location of the target on the bar and a bar-on-screen model in which the firing rate was a

linear function of the location of the bar on the screen. Having found the best fit for each case, we computed the fraction of the initial variance in the firing rate that was accounted for by the model. In the hypothetical cases of Fig. 27, it is clear that the target-on-bar model accounts for more of the variance in the target-on-bar neuron's firing rate (Fig. 27D vs. 27F) and that the bar-on-screen model accounts for more of the bar-on-screen neuron's variance (Fig. 27E vs. 27G). The results are summarized in Fig. 28, where, for each neuron exhibiting a main effect of object-centered location during the post-bar-onset epoch, the fraction of variance accounted for by the target-on-bar model is plotted against the fraction of variance accounted for by the bar-on-screen model. In a majority of neurons, the target-on-bar model accounted for the data better than the bar-on-screen model, as indicated by the fact that a majority of points lies above the identity diagonal in plots based on data from both the color DMS task (Fig. 28A) and the object-centered task (Fig. 28B). The moderate preponderance of points above the diagonal in the color DMS task (58%) did not achieve significance (χ^2 test, $p > 0.05$); however, the marked preponderance in the object-centered task (78%) was highly significant (χ^2 test, $p << 0.0001$). The difference between the tasks with respect to the distribution of points above and below the diagonal was also significant (χ^2 test, $p = 0.010$). We conclude (a) that many neurons in both tasks possessed the trait of being more sensitive to the location of the target on the bar than to the location of the bar on the screen and (b) that the frequency of neurons with this trait was greater in the object-centered task (after object-centered training) than in the color DMS task (before object-centered training).

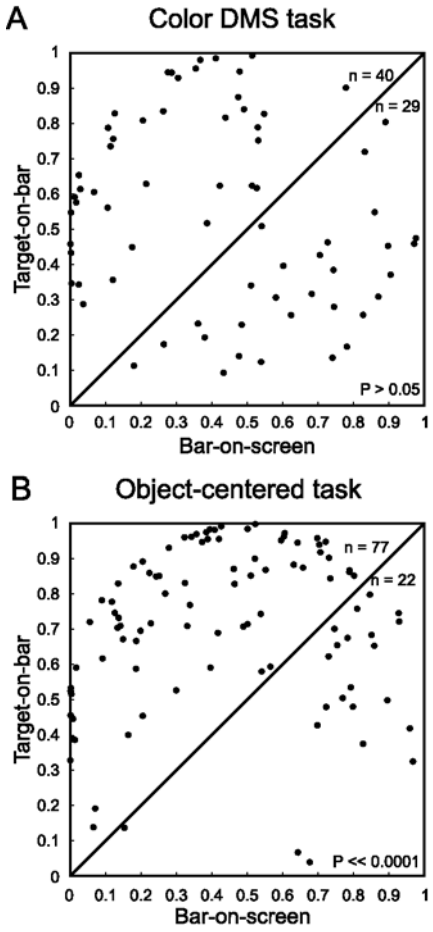

Fig. 28. Neuronal selectivity for the location of the bar-on-screen vs. the location of target-on-bar.

For each neuron with object-centered spatial selectivity, the fraction of firing-rate variance accounted for by the target-on-bar model is plotted against the fraction of variance accounted for by the bar-on-screen model (see Fig. 7). Points above the identity line, representing cases in which the target-on-bar model accounted for a larger fraction of variance, were more markedly preponderant in the context of the object-centered task during stage 2 of the experiment (B) than in the context of the color DMS task during stage 1 (A). The p value in each panel indicates outcome of a χ^2 test assessing whether the distribution of points above and below the identity line deviated significantly from an even distribution.

3.3.8. Ruling out a contribution of saccade metrics

It is conceivable that neurons in either task might have appeared to be selective for object-centered location because they were sensitive to subtle variations in saccades directed to a given location on the screen when that location was occupied by a dot on the left end of a bar vs. a dot on the right end of the bar. To address this issue, we carried out a multivariate regression

analysis, fitting three models to data from each neuron: (1) a reduced model containing only a parameter for object-centered location, (2) a reduced model containing parameters for saccadic latency, velocity, amplitude, horizontal landing position and vertical landing position, and (3) a full model containing both sets of factors (see Methods). Having obtained the fits, we then asked, using an F-test, whether the amount of variance accounted for by the full model was significantly greater than the amount accounted for by the reduced object-centered model (in which case the properties of the saccade contributed significantly to determining the neuronal firing rate) and, conversely, whether the amount of variance accounted for by the full model was significantly greater than the amount accounted for by the reduced saccadic model (in which case the factor of object-centered location contributed significantly to determining the neuronal firing rate). This analysis was carried out independently for two sets of data from each neuron: a set based on trials in which the target was at the near left location and a set based on trials in which the target was at the near right location. Thus it focused on trial-to-trial variations in saccades that occurred despite the fact that the target was, in a formal sense, always at the same location. By this approach, we analyzed data from 69 neurons exhibiting a significant main effect of object-centered location during the post-bar-onset epoch in the color DMS task and 99 neurons doing so in the object-centered task. The analysis focused on the post-bar-onset epoch. The analysis concerned 138 cases (69 neurons x 2 locations) from the color DMS task and 198 cases (99 neurons x 2 locations) from the object-centered task. The general finding was that the neuronal firing rate was much more frequently dependent on object-centered location than on the parameters of the saccade. There was a significant dependence on object-centered location in 47/138 = 34% of cases from the color DMS task and in 94/198 = 47% of cases from the object-centered task. In contrast, there was a significant dependence on the parameters of the saccade in

only 16/138 = 12% of cases from the color DMS task and 21/198 = 11% of cases from the object-centered task. In light of the fact that the neurons selected for analysis had all exhibited a significant main effect of object-centered location in an ANOVA based on the firing rate the post-bar-onset delay period, one might ask why there were cases in this analysis in which the firing rate was not dependent on object-centered location. The answer is that the multiple regression analysis, as described here, was less powerful than the ANOVA, on which the selection of neurons was based, because it concerned subsets of the full data set (in which the saccade was directed either to the near left or to the near right target). We conclude that object-centered spatial selectivity, as observed in both the color DMS task and the object-centered task, was genuine rather than an indirect manifestation of sensitivity to subtle differences between saccades occurring on bar-left and bar-right trials.

3.4. Discussion

3.4.1. Overview

The dual aims of this study were (1) to determine whether neurons in the macaque SEF would exhibit selectivity for the object-centered locations of saccade targets before monkeys were trained to select targets on the basis of their object-centered location and (2) to determine whether training on the use of an object-centered rule would enhance neuronal selectivity for object-centered location. All previous studies of object-centered spatial selectivity in the SEF have been carried out in monkeys trained to select targets on the basis of their object-centered location (Moorman and Olson 2005a; Olson 2003; Olson and Gettner 1995, 1999; Olson and Tremblay 2000; Tremblay et al. 2002) and thus have not addressed these issues. We have found

(1) that there is a moderate level of selectivity for object-centered location prior to training and (2) that object-centered selectivity is markedly enhanced following training. We conclude that object-centered spatial selectivity is present in the SEF in a rudimentary form even in monkeys naïve with respect to the use of object-centered rules but that it is sharpened and strengthened by training on the use of an object-centered rule.

3.4.2. Object-centered selectivity present prior to training

During stage 1 of data collection, when the monkeys had already learned and were performing the color DMS task, we observed statistically significant selectivity for object-centered location in 21/99 neurons in M1 and 48/160 neurons in M2 (Table 4). The counts in each monkey were in excess of counts expected by chance from type I errors at a high level of statistical significance (χ^2 test, $p < 10^{-12}$). It might still be argued that the neurons apparently selective for object-centered location were actually selective for some factor different from but correlated with object-centered location. This cannot have been either the color of the target or its retina-centered location because both were precisely counterbalanced against object-centered location across the conditions used for data analysis. However, it might have been the metrics of the saccade (which varied slightly as a function of whether the target occupied the left or right end of a bar) and the location of the bar on the screen (which was partially correlated with the location of the target on the bar). With respect to the first possibility, we demonstrated by means of a multiple regression analysis that sensitivity to saccade metrics could not account for object-centered selectivity. With respect to the second possibility, we demonstrated that more than half of neurons exhibiting a significant main effect of object-centered location were more sensitive to the location of the target on the bar than to the location of the bar on the screen. We therefore

conclude that SEF neurons were genuinely selective for the object-centered location of the target prior to training on an object-centered rule.

3.4.3. Object-centered selectivity enhanced by training

During stage 2 of data collection, when the monkeys had already learned and were performing the color-conditional object-centered task, the fraction of neurons exhibiting object-centered spatial selectivity during the post-bar-onset epoch (Table 5) was highly significantly greater than the corresponding fraction during stage 1 in each monkey (χ^2 test, $p < 0.0005$). Moreover, neuronal signals reflecting object-centered location were stronger (Fig. 26) and less contaminated by any influence arising from the location of the bar on the screen (Fig. 28). It might be argued that the enhancement was related to the coloring of the ends of the bar (both gray in this task as contrasted to one red and one green in the color DMS task). However, it is known that SEF neurons in monkeys trained to perform an object-centered task exhibit nearly identical levels of object-centered selectivity when the ends of the bar are of distinct colors and when they are uniformly achromatic (Moorman and Olson 2005c, Aim 3; Tremblay et al. 2002). It might be argued that the enhancement was a direct result of the monkeys' using an object-centered rule during the recording sessions and was merely an indirect result of training insofar as training resulted in the use of such a rule. However, it is known that SEF neurons automatically exhibit robust object-centered selectivity even during performance of the color DMS task once monkeys have been trained on the use of an object-centered rule (Moorman and Olson 2005c, Aim 3; Tremblay et al. 2002). We conclude that training on an object-centered rule induces a change somewhere in the brain that is manifest in the SEF as an enhancement in the strength and quality of neuronal object-centered signals.

The change in the SEF induced by training on the object-centered task developed remarkably swiftly. It required only approximately a week of training to induce the monkeys to shift from following a color rule to following a rule based on object-centered location. The stage of electrophysiological data collection, which ensued immediately, was eight times as long as the initial stage of training. One might reasonably expect training-induced effects to develop during this period. Yet the enhancement of object-centered selectivity was present in full strength from the outset of recording, as established by our analysis of the consistency across the data collection period. This indicates that functional changes in the SEF were the product of the quick voluntary shift accompanying mastery of the new strategy rather than of a slow cumulative shift driven by repeated performance. Nevertheless, we must note that SEF neurons, once the monkey has been trained, exhibit robust object-centered selectivity even on trials not requiring use of an object-centered strategy (Moorman and Olson 2005c; Tremblay et al. 2002). Paradoxically, the effects of training develop quickly in concert with task mastery but are not labile and do not depend strongly on task set.

3.4.4. Retina-centered selectivity attenuated by training

Unexpectedly, we observed a trend in both monkeys toward a reduction of retina-centered spatial selectivity after training. Because this trend achieved statistical significance in only one monkey, we must not place too much weight on it. Nevertheless, it is worth asking how best to understand the occurrence of the decrease. As a means for optimizing performance, it is difficult to explain. Even in the object-centered task, the monkeys were required to plan and execute saccades, which, in the end, had to be programmed relative to an eye-centered reference frame. An alternative is to consider that object-centered representations may compete with retina-

centered representations for limited functional resources. If, prior to training, neurons already utilized their full dynamic range for representing retina-centered direction, firing maximally for rightward and minimally for leftward saccades. Then, in order for a signal representing object-centered location to be added to the retina-centered signal without saturation at the floor or ceiling, it would be necessary for the range of the retina-centered signal to be compressed around its mean, with an attendant reduction of gain.

3.4.5. Relationship to previous demonstrations of training effects in SEF

This study adds to a small existing literature on training effects in the SEF. Mann et al. (1988), in a largely anecdotal account, claimed that in monkeys trained for a period of days to make saccades to one or the other of two diametrically opposed targets, electrical stimulation of the SEF during the delay period preceding the imperative cue tended to elicit an eye movement to one target or the other. This might be interpreted as reflecting an enhancement of the representation of learned saccades in the SEF but could equally well have arisen if electrical stimulation of the SEF simply triggered a saccade already prepared and represented by neuronal activity in areas downstream from the stimulation site. Furthermore, Tehovnik and Slocum (2000), in a more rigorous study of this phenomenon, failed to replicate the effect, casting doubt on its validity. Chen and Wise (1995a,b, 1996), monitoring neuronal activity while monkeys learned an arbitrary set of associations between four foveal patterns and four saccade directions, found (a) that some neurons fired at different levels during periods when the associations were being learned and had become familiar and (b) that the neuronal representation of saccade direction became more robust as the associations between the patterns and the saccade directions became more deeply ingrained. Only the second effect can be viewed as a product of training. It

involves a change in the ability of visual patterns to elicit neuronal activity in the SEF representing the saccades that are associated with them. The associations are not necessarily represented in the SEF nor is it necessarily the case that learning the associations is accompanied by any change in the way in which SEF neurons represent saccade direction. The current results are unique in demonstrating that training can induce a shift in the nature of the spatial reference frame with respect to which saccade direction is represented.

3.4.6. Representation of color by SEF neurons

In the color DMS task, the firing of a few neurons was significantly affected by the color of the target. The percentage of neurons with this trait (9%, 11% and 9% during the pre-bar-onset, post-bar-onset and peri-saccadic epochs respectively) was comparable to the percentage observed in an earlier study of monkeys trained on both a color DMS task and an object-centered task (13%, 8% and 8% during three roughly corresponding epochs) (Tremblay et al. 2002). This result is of interest both because the number is so low and because it is not zero. 1) The fact that the number is low tells us that the SEF is specialized for the representation of spatial information. Color-selective neurons were less common than neurons with object-centered selectivity even though were monkeys were selecting the target by color and had never even been trained to use an object-centered rule. If neurons in the SEF were simply sensitive to whatever attributes of stimuli, spatial or non-spatial, guided their selection as targets, then this would not be so. 2) The fact that the number is not zero seems to indicate that SEF neurons are not completely insensitive to color. We must qualify this conclusion by noting that the green cue was approximately twice as bright as the red cue (Methods: Stimuli) and that brightness as opposed to hue therefore cannot be absolutely ruled out as a determinant of neuronal firing rate.

If we assume that a few neurons were indeed sensitive to color, then a question follows: is this an innate property of SEF neurons or is it a result of training or of the behavioral set (attention to color) induced by training? It has been reported that training on tasks requiring the selection of targets by color can induce color sensitivity in neurons of the frontal eye field (Bichot et al. 1996) and parietal area LIP (Toth and Assad 2002). Perhaps color selectivity in the SEF, modest as it is, is the result of training on or performance of the color DMS task. To ascertain whether this is so would require testing for color selectivity in monkeys trained on and performing tasks in which target selection is based solely on spatial rules.

4. Automatic encoding of object-centered space in SEF neurons

4.1. Introduction

The macaque SEF, an area on the dorsomedial shoulder of the frontal lobe, is involved in spatial representation related to the generation of saccadic eye movements. This is indicated by the fact that intracortical microstimulation at levels of current elicits eye movements (Fujii et al. 1995; Lee and Tehovnik 1995; Mann et al. 1988; Martinez-Trujillo et al. 2003a; Martinez-Trujillo et al. 2004; Martinez-Trujillo et al. 2003b; Missal and Heinen 2001, 2004; Mitz and Godschalk 1989; Russo and Bruce 1993; Schall 1991a; Schlag and Schlag-Rey 1985, 1987a, b; Tehovnik and Lee 1993; Tehovnik et al. 1994; Tehovnik and Slocum 2000; Tehovnik et al. 1999; Tehovnik et al. 1998; Tehovnik and Sommer 1996, 1997; Tian and Lynch 1995). It is also indicated by the fact that single neurons are active during the planning and execution of eye movements toward targets in restricted response fields (Bon and Lucchetti 1991, 1992; Chen and Wise 1995a, b, 1996, 1997; Coe et al. 2002; Fujii et al. 2002; Hanes et al. 1995; Lee and Tehovnik 1995; Mushiake et al. 1996; Olson and Gettner 1995, 1999, 2002; Olson et al. 2000; Olson and Tremblay 2000; Russo and Bruce 1996, 2000; Schall 1991a, b; Schlag and Schlag-Rey 1985, 1987b; Schlag et al. 1992; Schlag-Rey et al. 1997; Tremblay et al. 2002).

Around half of SEF neurons that fire in conjunction with the planning and executing saccades are sensitive to the object-centered location of the saccade target. These neurons fire at different rates before saccades to the left or right end of a horizontal bar even when the properties of the saccade are held constant (Olson 2003; Olson and Gettner 1995). Object-centered signals in the SEF represent the location of the target relative to the object

independently of concrete factors such as the nature of the cue conveying the instruction (Olson and Gettner 1999) or the physical properties of the object (Olson and Tremblay 2000). Many SEF neurons represent object-centered location over a wide or even unlimited range of saccade directions (Moorman and Olson 2005a).

It was shown in a previous study that SEF neurons represent the object-centered location of a saccade target automatically even when the target has not been selected by an object-centered rule (Tremblay et al. 2002). The monkeys in that study, already strongly experienced at tasks in which one cue or another instructed them to select as target the left or right end of a bar, were introduced to a new task in which, on interleaved trials, they had to perform according to the old object-centered rule or, alternatively, in response to a red (or green) cue, had to select as target the red (or green) end of a bar. Even on trials in which the target was selected on the basis of its color, neuronal activity in the SEF reflected the target's object-centered location. From these results it would be premature to conclude that neurons in the SEF automatically encode object-centered location under all conditions. Two features of the experiment may have favored this outcome: (1) the monkeys had been trained first and for a much longer period of time on the object-centered than on the color-based version of the task and (2) they were required to select a target by an object-centered rule during trials randomly interleaved with (and just as frequent as) the color-based trials.

The aim of the present experiment was to test the limits of the conditions under which SEF neurons automatically exhibit object-centered spatial selectivity by recording from neurons in two monkeys (1) trained first and most extensively on a color-based task and (2) performing whole sessions of color-based trials without any interleaving of trials requiring the selection of targets by an object-based rule. The results indicate that even under these conditions, SEF

neurons robustly encode the object-centered locations of saccade targets and do so with a strength that does not decline over the course of at least a hundred trials. Thus the automatic encoding of object-centered location by SEF neurons does not depend either on excessive training in or on the very recent use of object-centered rules.

4.2. Methods

4.2.1. Subjects

Two adult male rhesus monkeys were used (Macaca mulatta; laboratory designations Bi and Ro hereafter referred to as M1 and M2). Experimental procedures were approved by the Carnegie Mellon University Animal Care and Use Committee and were in compliance with the guidelines set forth in the United States Public Health Service Guide for the Care and Use of Laboratory Animals.

4.2.2. Preparatory surgery

At the outset of the training period, each monkey underwent sterile surgery under general anesthesia maintained with isofluorane inhalation. The top of the skull was exposed, bone screws were inserted around the perimeter of the exposed area, a continuous cap of rapidly hardening acrylic was laid down so as to cover the skull and embed the heads of the screws, a head-restraint bar was embedded in the cap, and scleral search coils were implanted on the eyes, with the leads directed subcutaneously to plugs on the acrylic cap (Robinson 1963). Following initial training, a 2-cm-diameter disk of acrylic and skull, centered on the midline of the brain approximately at anterior 21 mm (Horsley-Clarke coordinates), was removed and a cylindrical recording chamber was cemented into the hole with its base just above the exposed dural

membrane.

4.2.3. Tasks

Each monkey was first (over the course of 14 months) trained on and tested in the color DMS task and then (over the course of two months) trained on and tested in the color-conditional object-centered task. Only after that stage was the practice adopted of having each monkey perform the two tasks in alternation during the same recording session. Which task was run first and which was run second varied in rough alternation from neuron to neuron.

The tasks were identical with respect to the timing of events and the geometry of the stimuli (Fig. 29). They differed only with respect (1) to the coloring of the target bar (red on one end and green on the other in the color DMS task vs. uniformly gray in the object-centered task) and (2) the rule by which the monkey selected one end of the bar as the target for a saccade (the end of the same color as the cue in the color DMS task vs. the end associated with the color of the cue – left for green and right for red – in the color-conditional object-centered task).

Each trial began with presentation of a central fixation spot and attainment of fixation in an approximately 5° x 5° fixation window. After a series of intervening events, including presentation of a foveal instructional cue and onset of an eccentric target display, the fixation spot was turned off, whereupon the monkey was required to make a saccade to the target (the left or right end of a horizontal bar), landing within a 5° x 5° window centered on it and maintaining gaze on it for an interval that varied randomly across trials in the range 0-300 ms. Upon termination of this interval, the display was extinguished and juice reward was delivered. The twelve conditions in the color DMS task (Fig. 1B) or the six conditions in the object-centered task (Fig. 1C) were interleaved randomly subject to the constraint that one trial conforming to

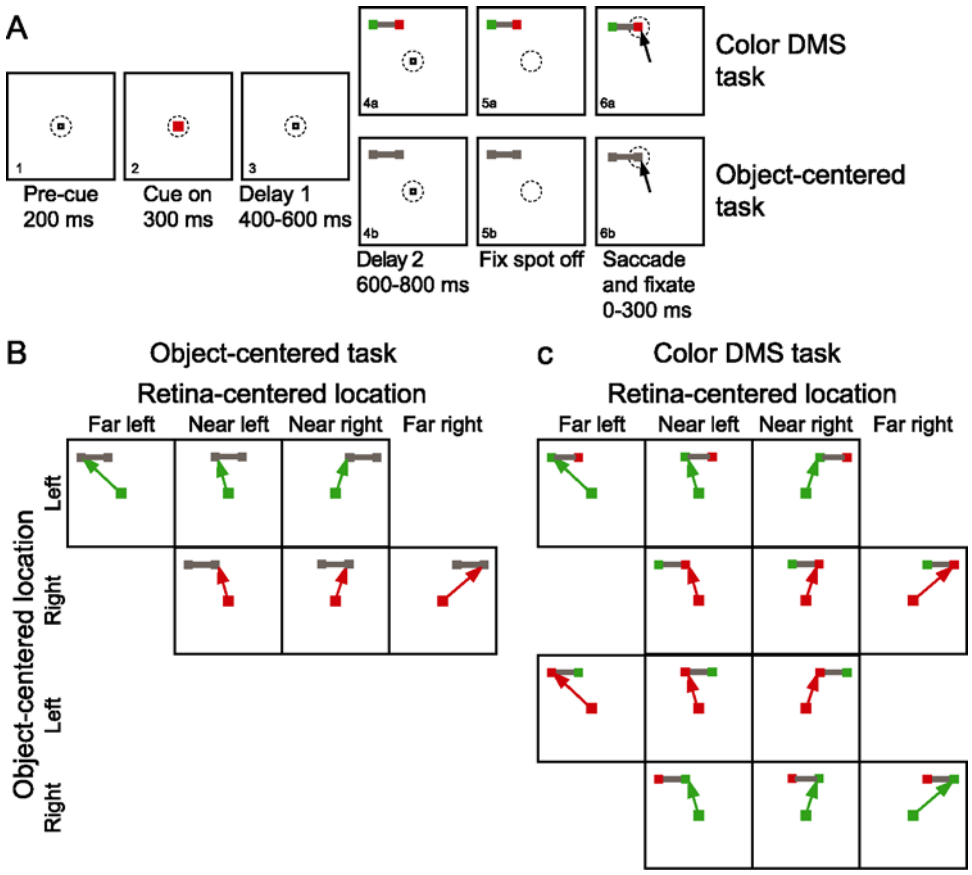

Fig. 29. Task design.

A. Sequence of events in the color-conditional object-centered task and the color delayed match-to-sample task. In the object-centered task, the monkey had to select the dot on the end of the bar associated with the color of the cue (left for green or right for red). In the color DMS task, the monkey had to select as target the dot on the end of the bar that matched in color the cue presented earlier in the trial. B. Display geometry under six conditions in the object-centered task. C. Display geometry under twelve conditions in the color DMS task.

each condition had to be completed successfully before the beginning of the next block of twelve or six trials. Data collection continued until 16 trials had been completed under each condition unless the neuron was lost. In the event of the neuron's being lost, the data were retained and included in the database for subsequent analysis if at least eight trials had been completed successfully under each condition.

4.2.4. Stimuli

Geometry. The displays (Fig. 29) were identical for the two monkeys but the distance from the eyes to the monitor was less for M2 by a factor of 0.96. In analyzing saccade trajectories, we scaled up data from M2 by a factor of 1.04 so as to achieve register with data from M1. The values given here are for M1. The fixation spot was a 0.43° x 0.43° white square presented at the center of the screen. The foveal color cue was a 1.7° x 1.7° gray, green, or red square. The bar display consisted of two 1.3° x 1.3° squares centered on the ends of a horizontal gray bar 7.1° long and 0.28° thick. The bar display was centered at one of three locations at an elevation of 11.4°. One location was centered above fixation. The other two points were offset to the right or left by half a bar length. This design allowed analyzing neuronal activity accompanying a saccade to the same dot (at the near left or near right location in Fig. 29B-C) as a function of whether it occupied the left or right end of a bar.

Luminance and hue. The fixation point had a luminance of 83 cd/m^2 and CIE x and y chromaticity coefficients of 0.28 and 0.32. The red cue and target dot had a luminance of 33 cd/m^2 and CIE x and y chromaticity coefficients of 0.33 and 0.17. The green cue and target dot had a luminance of 67 cd/m^2 and CIE x and y chromaticity coefficients of 0.25 and 0.66. The gray bar and target dot had a luminance of 57 cd/m^2 and CIE x and y chromaticity coefficients of 0.27 and 0.31.

4.2.5. Single-neuron recording

At the beginning of each day's session, a varnish-coated tungsten microelectrode with an initial impedance of several megohms at 1 KHz (Frederick Haer & Co., Bowdoinham, ME) was advanced vertically through the dura into the immediately underlying cortex using a hydraulic

microdrive (Narashige, Tokyo, Japan). The electrode could be placed reproducibly at points forming a square grid with 1 mm spacing (Crist et al. 1988). Single neurons were isolated using both online and offline template-matching and principal components analysis sorting (Plexon Inc, Dallas, TX).

4.2.6. Behavioral control and data collection

All aspects of behavioral procedure, including presentation of stimuli, monitoring of eye movements, and delivery of reward, were under the control of a Pentium-based computer running Cortex software (http://www.cortex.salk.edu). Eye position was monitored by means of a scleral search coil system (Riverbend Instruments, Inc., Birmingham, AL). The X and Y coordinates of eye position were stored at 10 ms intervals. Stimuli generated by an active matrix LCD projector were rear-projected on a frontoparallel screen 25.4 cm (M1) and 24.5 (M2) cm from the monkey's eyes. Reward in the form of 0.1 cc of juice was delivered through a spigot under control of a solenoid valve upon successful completion of each trial.

4.2.7. Analysis of behavioral performance

Behavioral data, including percent correct and reaction time, as well saccade velocity, amplitude, and landing points, were calculated for each trial in both tasks. These data were compared across tasks to determine the behavioral effect of changes in task requirements. In all cases, significant differences in behavioral data were assessed using t-tests or Kolmogorov-Smirnov tests ($p < 0.05$).

4.2.8. Analysis of saccade metrics

The aim of this step was to characterize the properties of the saccade executed on each trial. First, the direction of gaze was determined for each 10 ms bin during a 500 ms epoch beginning with offset of the fixation spot. Then the instant of maximal velocity was identified by finding the pair of adjacent 10 ms bins (B_m and B_{m+1}) for which the displacement of the eye in degrees of visual angle (ΔE_m) was maximal. The maximal velocity, in degrees of visual angle per second, was given by $100*\Delta E_m$. The start of the saccade was identified by moving backward in time until encountering a pair of bins, B_s and B_{s+1}, for which $\Delta E_s < \Delta E_m/4$. Saccadic reaction time was taken as the interval between offset of the fixation spot and the beginning of bin B_{s+1}. The finish of the saccade was identified by moving forward in time until encountering a pair of bins, B_f and B_{f+1}, for which $\Delta E_f < \Delta E_m/4$. Saccade amplitude was taken as the distance in degrees of visual angle between eye positions recorded at B_s and B_{f+1}. The final position of the eye was estimated on the basis of B_{f+7} so as to allow time for asymptotic deceleration without exceeding the minimal reaction time for any corrective saccade.

4.2.9. Analysis of neuronal activity

To characterize the dependence of neuronal activity on the retina-centered direction of the saccade and the object-centered location of the target, we carried out a series of ANOVAs as described in the text. Independent analyses were carried out on data from three epochs: a pre-bar-onset epoch (foveal cue onset + 100 ms to bar onset + 100 ms), a post-bar-onset epoch (bar onset + 100 ms to fixation point offset + 100 ms), and a peri-saccadic epoch (saccade initiation +/- 150 ms). The criterion for significance was taken as $p < 0.05$ unless otherwise stated. In

comparing counts of neurons exhibiting significant effects, we used a χ^2 test. In all such cases, if there was only one degree of freedom, we incorporated a Yates correction.

4.2.10. Multiple regression analysis

In order to determine whether firing rate was correlated with object-centered location independently of any effect arising from subtle variations in saccades between bar-left and bar-right trials, we performed a multivariate regression analysis, fitting three models to data collected from each neuron during trials in which the target (the right or left end of a bar) appeared at a given screen location:

1) $Y = \beta_0 + \beta_1 Obj + \beta_2 Lat + \beta_3 Vel + \beta_4 Amp + \beta_5 Xpos + \beta_6 Ypos$

2) $Y = \beta_0 + \beta_1 Lat + \beta_2 Vel + \beta_3 Amp + \beta_4 Xpos + \beta_5 Ypos$

3) $Y = \beta_0 + \beta_1 Obj$

where Y = firing rate measured during the post-target-onset period (target onset +100 ms to saccade initiation +100 ms), Obj = object-centered location (0 or 1 for bar-left or bar-right), Lat = latency (from fixation spot offset), Vel = peak velocity, Amp = amplitude, and Xpos and Ypos = final x and y landing positions respectively. Having fitted the parameters of each model to a neuron's data, we determined, using an F-test, whether the full model (1), when compared to each of the reduced models (2, 3) accounted for significantly more of the variance in the data than could be explained by its larger number of degrees of freedom. If model 1 provided a significant improvement over model 2, we concluded that neuronal activity depended significantly on object-centered location independently of any tendency for saccade parameters

to co-vary with object-centered location. If model 1 provided a significant improvement over model 3, we concluded, by similar reasoning, that neuronal activity depended significantly on variations in the saccade. We computed F as:

$$F_{k,m-(n+k)} = \frac{\left(\frac{SS_{red} - SS_{full}}{k}\right)}{\left[\frac{SS_{full}}{m-(n+k)}\right]}$$

where k = the difference in degrees of freedom between the two models, m = the number of trials, n = 1 was the number of neurons, and SS_{full} and SS_{red} were the residual sums of squares for the full model and the reduced model.

4.2.11. Characterization of recording sites

The location of the recording sites (Fig. 30) relative to gross morphological landmarks was assessed by analysis of structural MR images. Scanning was carried out in a Brükker 4.7 T magnet in which the anesthetized monkey was supported by an MR-compatible stereotaxic device. Fiducial marks made visible by means of a contrast agent included the centers of the ear bars and selected locations inside the recording chamber. Frontoparallel and parasagittal slices of 2 mm thickness were collected over the entire extent of the cerebral hemisphere. To determine the location of recording sites relative to functional divisions of cortex, we mapped out regions under each chamber from which oculomotor responses could be elicited at low threshold (≤ 50 μA) by electrical microstimulation (1.65 ms biphasic pulses delivered through the recording microelectrode at a frequency of 300 Hz in trains 200 ms long).

4.3. Results

4.3.1. Overview

The general aim of this experiment was to determine whether SEF neurons exhibiting object-centered selectivity in a task requiring the monkey to select a saccade target by an object-centered rule (the color-conditional object-centered task) would also exhibit object-centered selectivity in a task requiring the monkey to select a target by a color-based rule (the color DMS task). The geometry of the stimuli and saccades was the same in both tasks (Fig. 30). The approach was to collect a full data set from a given neuron in the context of one task and then, if possible, to do so in the context of the other task. The order of the tasks was varied from neuron to neuron.

We recorded from 127 neurons in the color DMS task (84 and 43 in M1 and M2 respectively) and 134 neurons in the object-centered task (93 and 41 in M1 and M2 respectively). Of these, 116 were characterized in both tasks (82 and 34 in M1 and M2 respectively). The color DMS task and object-centered task were run first in 59 and 57 neurons respectively.
The recording sites were within a bilateral region of the frontal lobe identified as the SEF on the basis of electrical microstimulation mapping (all recording sites were within 1 mm of a location at which saccades could be elicited at currents of less than 50 μA) and on the basis of its location as established through the analysis of MR images (4-8 mm rostral to the genu of the arcuate sulcus and within a few mm of the interhemispheric cleft).

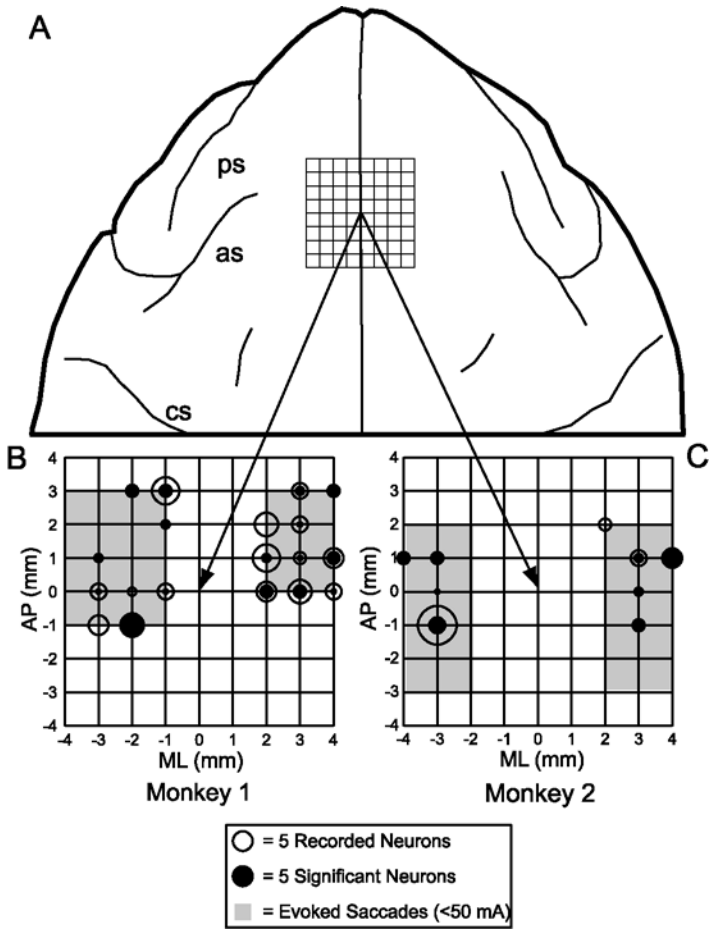

Fig. 30. Recording sites.

A. Recording grid superimposed on a schematic dorsal view of the frontal lobes. The center of the grid in each monkey was located approximately 5 mm rostral to the genu of the arcuate sulcus and over the interhemispheric cleft. B. Location relative to grid coordinates in M1 of neurons exhibiting significant object-centered spatial selectivity during performance of either task. At each location, the area of the outer (open) bubble indicates the number of recorded neurons and the area of inner (filled) bubble indicates the number exhibiting selectivity. Gray shading demarcates the region within which electrical microstimulation elicited eye movements. C. Same for M2.

4.3.2. Behavior

Percent Correct. In assessing behavioral performance during the neuronal data collection sessions, we confined our attention to a set of trial conditions across which retina-centered direction of the saccade and the object-centered location of the target were fully counterbalanced (near left and near right conditions in Fig. 29B-C). It was on these conditions that subsequent steps of data analysis were based. The percent correct score for each session was taken as the

number of trials on which the monkey made a saccade to the correct end of the bar expressed as a percentage of all trials on which he made a saccade to either end of the bar. The mean percent correct across all data-collection sessions was 88% in the object-centered task (90% and 85% in M1 and M2 respectively) and 90% in the color DMS task (90% and 89% in M1 and M2 respectively). The tendency for M2 to perform better on the color DMS task than on the object-centered task achieved significance (Kolmogorov-Smirnov test, $p = 0.04$).

Reaction time. We first computed the mean of the reaction time (the interval between when the fixation spot was extinguished and initiation of the saccade) for correct trials in each session, confining attention to trial conditions in which the target was at the near left or near right location. Then we computed the mean across sessions for each task. The mean reaction time was longer in the color DMS task (133 and 178 ms in M1 and M2 respectively) than in the object-centered task (125 and 111 ms in M1 and M2 respectively). This effect achieved significance in M2 (Kolmogorov-Smirnov test, $p << 0.0001$).

Impact of color-location incongruence. In the color DMS task, the two targets (red and green) appeared with equal frequency on the two ends of the bar (left and right). However, in the color-conditional object-centered task, each color instructed the monkey to select one end of the bar as a target (green being associated with left and red with right). To determine whether associations formed in the context of the object-centered task affected performance in the color DMS task, we carried out an analysis on data broken into halves according to whether the colored targets were at locations congruent with their associations (green dot on the left and red dot on the right) or incongruent with their associations (red dot on the left and green dot on the right). In M1, the percent correct scores on congruent trials (91%) incongruent trials (89%) were significantly different (Wilcoxon signed rank test, $p = 0.02$) although the reaction times (132 and

134 ms under congruent and incongruent conditions respectively) were not (paired t-test). In M2, the reaction times under congruent (175 ms) and incongruent (181 ms) conditions were significantly different (paired t-test, $p = 0.02$) although the percent correct scores (at 89% under both conditions) were not. We conclude that color-location associations formed in the color-conditional object-centered task persisted in the color DMS task, hindering the generation of correct responses on incongruent trials by inducing wrong choices in M1 and slowing correct choices in M2.

Saccadic landing point. On comparing landing points across bar-left and bar-right conditions (Fig. 31), we found that differences with respect to the vertical axis were small and inconsistent but that differences with respect to the horizontal axis conformed to a pattern whereby the saccade deviated slightly toward the center of the bar as reported previously (Olson and Tremblay 2000). Across conditions in which the left end of the bar and the right end of the bar occupied the same screen location, the gaze consistently landed slightly farther to the right when the left end of the bar was the target than when the right end was the target. The mean offset between the two landing points was 0.44 degrees of visual angle in the object-centered task (0.51° in M1 and 0.37° in M2) and 0.39 degrees of visual angle in the color-conditional color DMS task (0.54° in M1 and 0.23° in M2). We demonstrate below that this small deviation exerted only a minimal effect on neuronal activity (4.3.7, Ruling Out an Effect Based on Saccade Metrics).

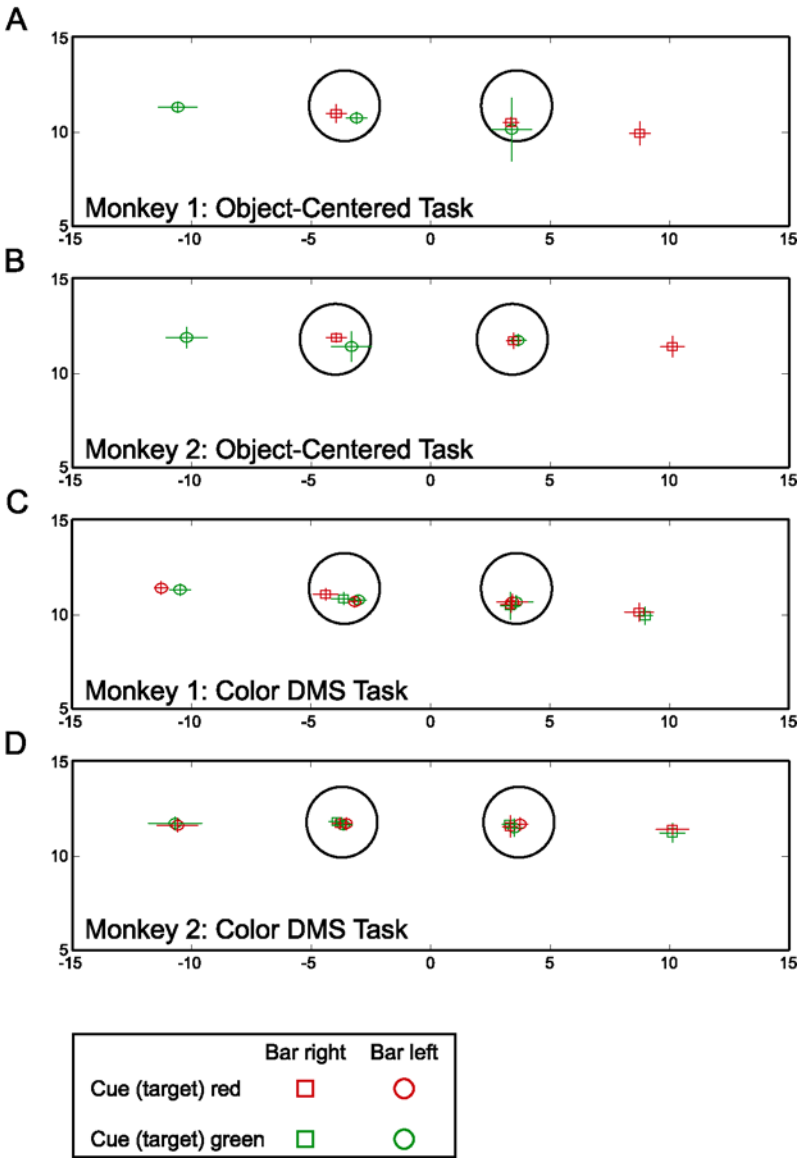

Fig. 31. Saccadic landing positions.

Means and standard deviations of saccadic end-points for each monkey in each task. Circles are centered on the locations of the targets at near left and near right locations. Each of these locations could be occupied by either the left or the right end of a bar. Scale is in degrees of visual angle relative to the initial fixation point.

4.3.3. Spatial selectivity in the object-centered task

Neuronal data analysis focused on three epochs during the trial: (1) a pre-bar-onset epoch, during which the color of the sample was known but the location of the target was not (cue-onset

+ 100 ms to bar-onset + 100 ms), (2) a post-bar-onset epoch, during which both the color of the target and its location were known (bar onset +100 ms to fixation offset + 100 ms), and (3) a peri-saccadic epoch (from 150 ms before to 150 ms after saccade onset). The first two epochs began and ended at points in time offset by 100 ms from the occurrence of significant visual events so as to take into account the approximate latency of effects exerted by visual events on neuronal activity in SEF. For each neuron, and for each trial epoch independently, a two-factor ANOVA was carried out to assess the dependence of firing rate on (1) the retina-centered location of the target (near left or near right) and (2) the object-centered location of the target (bar-left or bar-right). The analysis was confined to trials completed successfully under the four conditions in which the target was at the near left or near right location (Fig. 29B) so as to counterbalance retina-centered location against object-centered location. The results are summarized in Table 6.

Pre-bar-onset epoch. At the outset of the pre-bar-onset epoch, a colored cue conveyed the object-centered instruction. Accordingly, one might expect to observe object-centered selectivity during this epoch. However, because the bar had not yet appeared, one would not expect retina-centered selectivity. Indeed, significant main effects of object-centered location were present in 24/134 = 18% of neurons, whereas significant main effects of retina-centered location (in 7/134 = 5% of neurons) did not exceed the rate expected by chance (χ^2 test, $p > 0.05$). We conclude that some neurons were selective for object-centered location prior to onset of the target array. It is theoretically possible that these neurons might have been selective for the color of the cue. However, in a previous study involving a variant of this task, that explanation was ruled out (Olson and Gettner 1999).

	Monkey	Object-Centered		Retina-Centered	
		C>I	I>C	C>I	I>C
Pre-Bar-Onset Epoch	M1 (N=93)	14 (15%)	5 (5%)	4 (4%)	2 (2%)
	M2 (n=41)	4 (10%)	1 (2%)	1 (2%)	0 (0%)
	Total (n=134)	**18 (13%)**	**6 (4%)**	**5 (4%)**	**2 (1%)**
Post-Bar-Onset Epoch	M1 (N=93)	16 (17%)	7 (8%)	14 (15%)	5 (5%)
	M2 (n=41)	7 (17%)	11 (27%)	4 (10%)	5 (12%)
	Total (n=134)	**23 (17%)**	**18 (13%)**	**18 (13%)**	**10 (7%)**
Peri-Saccadic Epoch	M1 (N=93)	6 (6%)	14 (15%)	5 (5%)	2 (2%)
	M2 (n=41)	3 (7%)	4 (10%)	2 (5%)	3 (7%)
	Total (n=134)	**9 (6%)**	**18 (13%)**	**7 (5%)**	**5 (4%)**

Table 6. Object-centered task: Counts of neurons exhibiting selectivity for object-centered location and for retina-centered location.

Results of ANOVAs carried out on data from 134 neurons recorded in the context of the object-centered task, with firing rate as the dependent variable and with the object-centered location of the target (bar-left or bar-right) and the retina-centered location of the target (near left, near right) as two factors. Independent analyses were carried out on data from the pre-bar-onset epoch (cue onset + 100 ms to bar onset + 100 ms), the post-bar-onset epoch (bar onset + 100 ms to fixation point offset + 100 ms) and the peri-saccadic epoch (saccade initiation +/- 150 ms). "Object-centered": significant main effect of object-centered location. "Retina-centered": significant main effect of retina-centered location. C>I: stronger firing when the target was at the end of the bar contralateral to the recording hemisphere (in the case of object-centered selectivity) or in the visual field contralateral to the recording hemisphere (in the case of retina-centered selectivity). I>C: the opposite pattern.

Post-bar-onset epoch. The target display was turned on at the beginning of this epoch. Accordingly, one might reasonably expect to observe selectivity for either of the factors. Main effects of object-centered location were present in 41/134 = 31% of neurons. Main effects of the retina-centered location were present in 28/134 = 21% of neurons. We conclude that neurons exhibiting object-centered selectivity were somewhat more common than those exhibiting retina-centered selectivity.

Peri-saccadic epoch. Main effects of object-centered location were present in 27/134 = 20% of neurons. Main effects of retina-centered location were present in 12/134 = 9% of neurons. We conclude that neurons exhibiting object-centered selectivity were somewhat more common than those exhibiting retina-centered selectivity.

Summary. The aim of this step of analysis was to replicate previous observations to the effect that some SEF neurons exhibit object-centered spatial selectivity in monkeys performing a task that requires selection of a saccade target on the basis of its object-centered location (Olson 2003; Olson and Gettner 1995, 1999; Olson and Tremblay 2000; Tremblay et al. 2002). This finding was indeed replicated. In around a third of the recorded neurons, the firing rate during the period from appearance of the target display to execution of the saccade depended significantly on the object-centered location of the target.

4.3.4. Spatial and color selectivity in the color DMS task

For each neuron, and for each trial epoch independently, a three-factor ANOVA was carried out to assess the dependence of firing rate on (1) the retina-centered location of the target (near left or near right), (2) the object-centered location of the target (bar-left or bar-right) and (3) the color of the target (red or green). The analysis was confined to trials completed successfully under the eight conditions in which the target was at the near left or near right location (Fig. 1C). Across this set of conditions, retina-centered location, object-centered location and color were fully counterbalanced. The results are summarized in Table 7.

Pre-bar-onset epoch. In the pre-bar-onset epoch, the target display had not yet appeared. Accordingly, it would unreasonable to expect to observe object-centered selectivity or retina-centered selectivity during this epoch. Indeed, significant main effects of object-centered and

	Monkey	Color		Object-Centered		Retina-Centered	
		R>G	G>R	C>I	I>C	C>I	I>C
Pre-Bar-Onset Epoch	M1 (N=84)	7 (8%)	2 (2%)	3 (4%)	0 (0%)	0 (0%)	1 (1%)
	M2 (N=43)	4 (9%)	3 (7%)	3 (7%)	1 (2%)	1 (2%)	1 (2%)
	Total (N=127)	**11 (9%)**	**5 (4%)**	**6 (5%)**	**1 (1%)**	**1 (1%)**	**2 (2%)**
Post-Bar-Onset Epoch	M1 (N=84)	3 (4%)	2 (2%)	17 (20%)	11 (13%)	12 (14%)	4 (5%)
	M2 (N=43)	2 (5%)	7 (16%)	8 (19%)	8 (19%)	2 (5%)	7 (16%)
	Total (N=127)	**5 (4%)**	**9 (7%)**	**25 (20%)**	**19 (15%)**	**14 (11%)**	**11 (9%)**
Peri-Saccadic Epoch	M1 (N=84)	2 (2%)	4 (5%)	12 (14%)	3 (4%)	5 (6%)	8 (10%)
	M2 (N=43)	4 (9%)	4 (9%)	2 (5%)	7 (16%)	0 (0%)	6 (14%)
	Total (N=127)	**6 (5%)**	**8 (6%)**	**14 (11%)**	**10 (8%)**	**5 (4%)**	**14 (11%)**

Table 7. Color DMS task: Counts of neurons exhibiting selectivity for color, for object-centered location and for retina-centered location.

Results of ANOVAs carried out on data from 127 neurons recorded in the context of the color DMS task, with firing rate as the dependent variable and with the color of the cue and target (red, green), the object-centered location of the target (bar-left or bar-right) and the retina-centered location of the target (near left, near right) as three factors. "Color": significant main effect of color. R>G and G>R: Stronger firing for red than for green and vice versa. Other conventions as in Table 1.

retina-centered direction were no more common than expected by chance (χ^2 test, $p > 0.05$). The colored foveal cue was, however, presented at the beginning of this epoch. Accordingly, neurons might reasonably be expected to exhibit color selectivity. Indeed, the rate of incidence of main effects of color (16/127 = 13% of neurons) exceeded the frequency expected by chance in each monkey (χ^2 test, $p = 0.03$ in M1 and $p = 0.002$ in M2). We conclude that some neurons fired at different rates in response to cues of different colors. However, these neurons may well have been selective for the location that the monkey had learned to associate with the color (in the object-centered task) rather than for the color itself. This issue will be taken up in a later section (4.3.10, Relation of color selectivity to spatial selectivity in the color DMS task).

Post-bar-onset epoch. The target display was turned on at the beginning of this epoch. Accordingly, one might reasonably expect to observe selectivity for any of the three factors. Main effects of object-centered location were present in 44/127 = 35% of neurons. Main effects of the retina-centered location were present in 25/127 = 20% of neurons. Main effects of the color of the target were observed in 14/127 = 11% of neurons, with the rate of incidence significantly exceeding the rate expected by chance only in M2 (χ^2 test, $p << 0.0001$). We conclude (a) that neurons were selective for spatial factors more commonly than for color and (b) that neurons exhibiting object-centered selectivity were somewhat more common than those exhibiting retina-centered selectivity.

Peri-saccadic epoch. Main effects of object-centered location were present in 24/127 = 19% of neurons. Main effects of retina-centered location were present in 19/127 = 15% of neurons. Main effects of color were present in 14/127 = 11% of neurons. However, the rate of incidence of these effects exceeded the rate expected by chance only in M2 (χ^2 test, $p = 0.0002$). We conclude (a) that neurons were selective for spatial factors more commonly than for color and (b) that neurons exhibiting object-centered selectivity were somewhat more common than those exhibiting retina-centered selectivity.

Summary. The question at the heart of this phase of analysis was whether SEF neurons would exhibit selectivity for the object-centered location of the target in monkeys performing a task that required targets to be selected on the basis of color and that did not require the use of an object-centered rule. The answer is in the affirmative: in more than a third of the recorded neurons, the firing rate during the period from appearance of the target display to execution of the saccade depended significantly on the object-centered location of the target.

4.3.5. Relative frequency of selectivity in the two tasks

No form of selectivity during any epoch occurred at a significantly different rate in the object-centered task than in the color DMS task (χ^2 test, $p > 0.05$) despite the fact that the prospects for a weak effect's emerging as significant were enhanced in the color DMS task because, with twelve conditions instead of six, the number of trials run was twice as great on average. During the pre-bar-onset epoch, the rate of object-centered selectivity in the object-centered task was not significantly different from the rate of color selectivity in the color DMS task (these rates are comparable if, as will be considered in a later section, color selectivity in the DMS task was a manifestation of neuronal selectivity for the object-centered location associated with the color). During the post-bar-onset epoch, neither the rate of object-centered nor of retina-centered selectivity differed significantly between tasks. During the peri-saccadic epoch, the same was true. We conclude that, so far as statistical measures are concerned, the tendency for SEF neurons to exhibit object-centered and retina-centered spatial selectivity was unaffected by task context.

4.3.6. Comparison of spatial selectivity in the two tasks

To investigate whether a given neuron tended to exhibit the same pattern of spatial selectivity in both tasks, we carried out further steps of analysis confined to the 116 neurons from which data were collected in both contexts. On casual observation of histograms, it was apparent that neuronal spatial selectivity tended to be conserved across tasks. For example, the neuron of Fig. 32 fired more strongly on bar-right than on bar-left trials. In order to characterize the degree to which neurons behaved consistently across tasks, we employed both statistics-based and index-based measures.

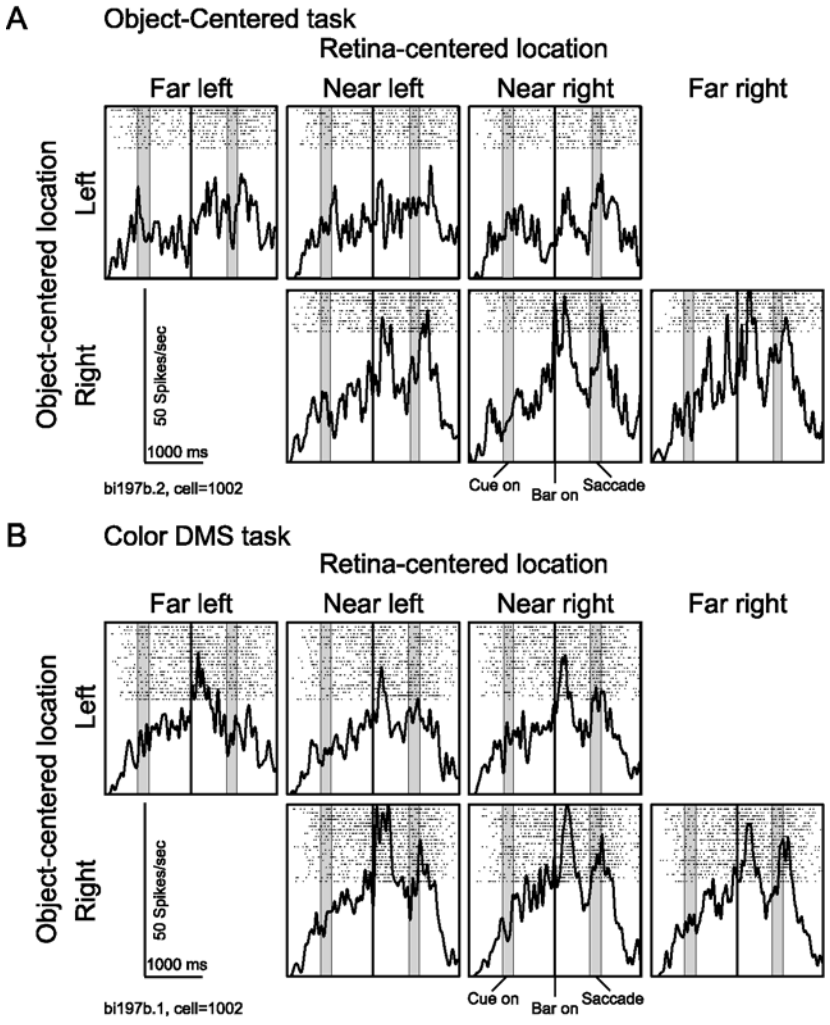

Fig. 32. Data from a neuron more active on bar-right than on bar-left trials in both tasks.

A. Rasters and spike density functions representing activity in the context of the object-centered task. Panels in the same column represent conditions in which the target was at the same location on the screen. Panels in the same row represent cases in which the target was at the same end of the bar. B. Activity of the same neuron in the context of the color DMS task.

First, we asked whether a neuron exhibiting significant selectivity for a particular factor during a particular epoch in one task tended to do so in the other task as well. The results, summarized in Fig. 33, demonstrate a significant degree of concordance. During the pre-bar-onset epoch, neurons exhibiting color selectivity in the color DMS task tended to exhibit object-centered selectivity in the object-centered task as indicated by the fact that the number of counts

in the match diagonal (Fig. 33A) exceeded the number expected on the basis of the null hypothesis that the two traits were distributed independently. This effect approached significance (χ^2 test, $p = 0.051$). Because the monkeys had learned to associate color and location, this effect could have arisen from the expression in both task contexts either of selectivity for color or of selectivity for object-centered location, as discussed in a later section. During both the post-bar-onset epoch (Fig. 33C) and the peri-saccadic epoch (Fig. 33E), the tendency for neurons exhibiting object-centered selectivity in one task to do so in the other achieved significance (χ^2 test, $p << 0.0001$ and $p = 0.021$).

Next, we asked whether the signed magnitude of the signal carried in one task was correlated with the signed magnitude of the signal carried in the other task. The results, summarized in Fig. 33, again demonstrate a high degree of concordance between tasks. During the pre-bar-onset epoch (Fig. 33B), there was a significant ($p = 0.02$) positive correlation between (1) the index of color selectivity in the color DMS task, $(R - G)/(R + G)$, where R and G were the firing rates on trials in which the cue was red or green, and (2) the index of object-centered selectivity in the object-centered task, $(R – L)/(R + L)$ where R and L were the firing rates on bar-right trials (introduced by a green cue) and bar-left trials (introduced by a red cue) respectively. During both the post-bar-onset epoch (Fig. 33D) and the peri-saccadic epoch (Fig. 33F), there was a significant ($p << 0.0001$ and $p = 0.01$) positive correlation between indices of object-centered selectivity computed identically in the two tasks as $(R - L)/(R + L)$. We conclude that neurons preferring a given object-centered location in the object-centered task tended to prefer the same object-centered location in the color DMS task.

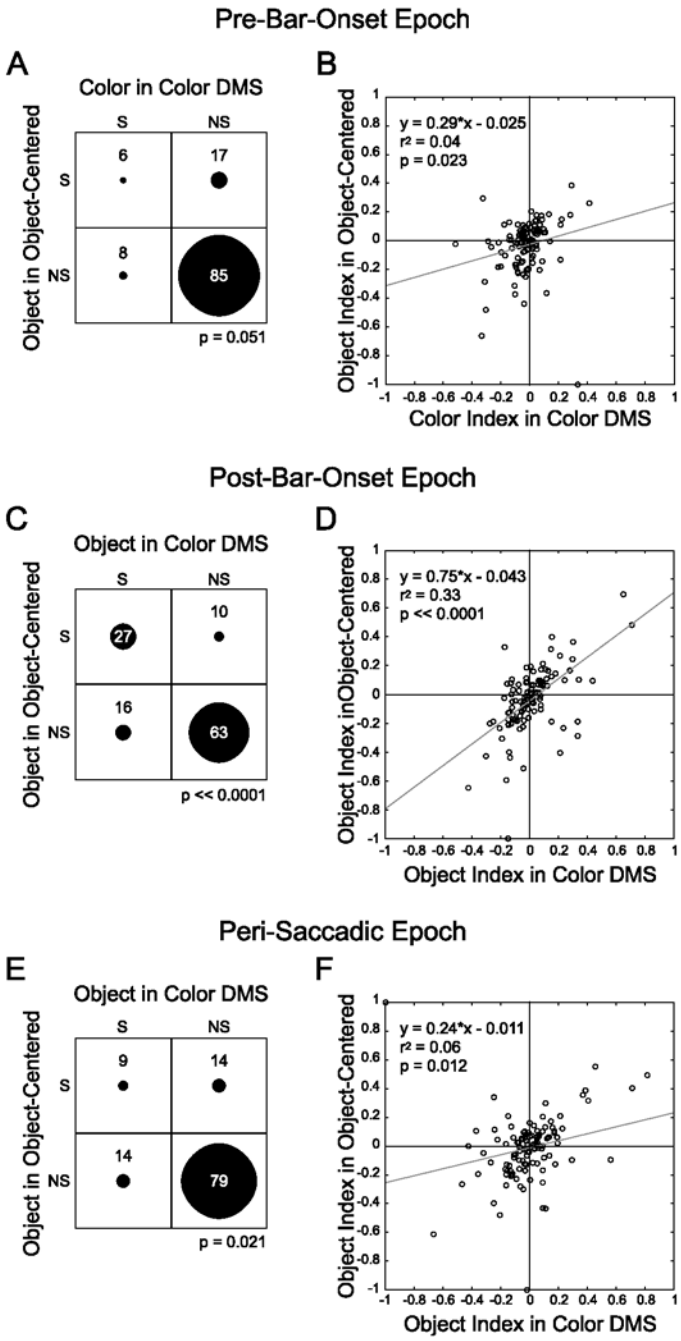

Fig. 33. Neurons exhibiting object-centered selectivity in one task tended to do so in the other task as well.

A. Cross-plot of counts of neurons exhibiting (S) or not exhibiting (NS) significant object-centered selectivity during the pre-bar-onset epoch in the two tasks. Counts in the match column exceeded the number expected if object-centered selectivity in one task was unrelated to object-centered selectivity in the other task. The effect approaches significance (χ^2 test, p = 0.051). B. Cross-plot of indices of object-centered selectivity measured in the two tasks during the pre-bar-onset epoch. The index was computed as (R - L)/(R + L) where R and L were firing rates on bar-right and bar-left trials respectively. The correlation was significant (p = 0.023). C-D. Same for post-bar-onset epoch. E-F. Same for peri-saccadic epoch.

The fact that the indices were positively correlated does not indicate that they were of equal magnitude. To determine whether the index of object-centered selectivity tended to be greater in one task than in the other, we considered all cases in which the sign of the index was the same in both tasks. During the pre-bar-onset epoch, there was an excess of cases (51/84 = 61%) in which the index was larger in the object-centered task. This effect approached significance (χ^2 test, p = 0.06). During the post-bar-onset epoch, cases in which the index of object-centered selectivity was higher in the object-centered task were preponderant (62/97 = 64%) and the preponderance was significant (χ^2 test, p = 0.008). During the peri-saccadic epoch, there was no consistent effect: the object-centered index was stronger in the object-centered task in only 38/77 = 49% of cases. We conclude that object-centered signals were stronger in the object-centered task than in the color DMS task during the period of the trial leading up to execution of the saccade.

To confirm this conclusion qualitatively, we constructed population histograms representing the average firing rate of the 116 neurons studied in the context of both tasks. First, each neuron's preferred object-centered location was identified: the location, bar-left or bar-right, associated with stronger firing during the post-bar-onset epoch, with consideration restricted to trials in which the target was at the near left or near right location on the screen. Then the results from all neurons were combined in population histograms representing the average firing rate on trials in which the target was at the preferred or non-preferred location. The results are shown in Fig. 34. Each panel in this figure contains a pair of histograms representing activity on trials in which the target was at the preferred and non-preferred locations. The degree by which firing on preferred-direction trials exceeded firing on opposite-direction trials is indicated by filling in the space between the two curves from the beginning to the end of the post-bar-onset epoch. In population histograms based on data from all recorded

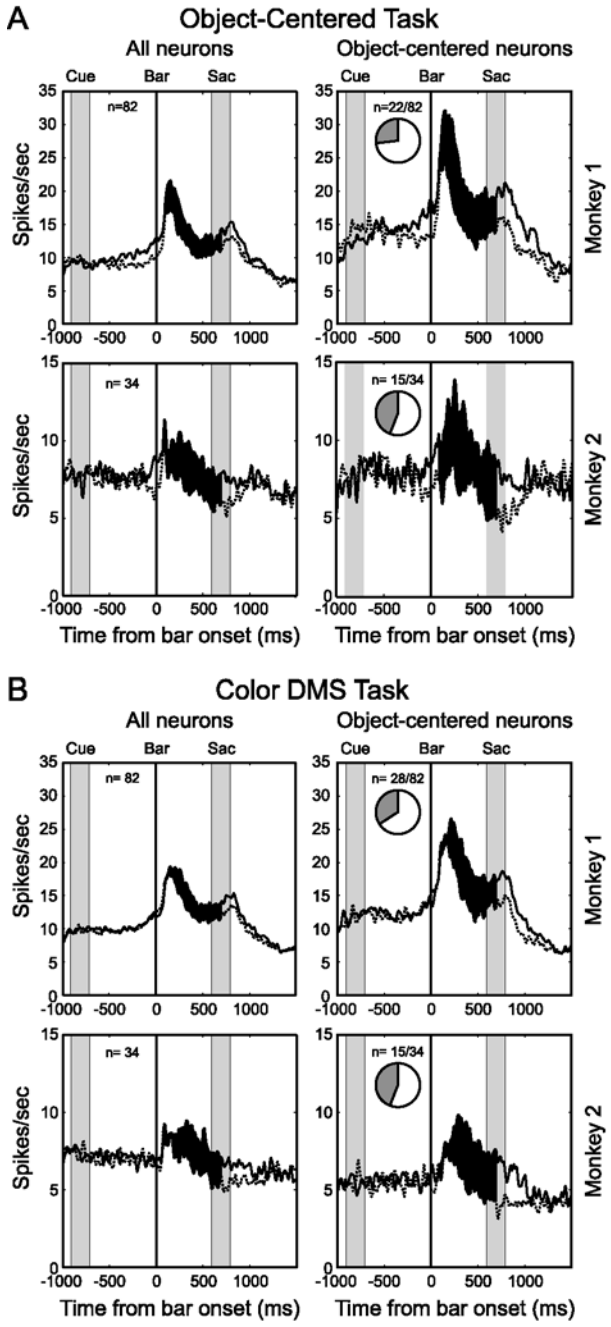

Fig. 34. Population histograms.

The object-centered activity of the neuronal population was moderately more robust in the context of the object-centered task (A) than in the context of the color DMS task (B). A. Population histograms representing activity during the object-centered task (left column: all neurons; right column: neurons with significant object-centered spatial selectivity during the post-bar-onset epoch; top row: M1; bottom row: M2). Solid (or broken) curve represents mean population firing rate on trials in which the target was on the preferred (or non-preferred) end of a bar. The width of the black ribbon interposed between the two curves during the post-bar-onset epoch represents the strength of the object-centered signal. B. Population histograms for the color DMS task. A and B represent the activity of the same population of neurons (116 neurons studied in the context of both tasks).

neurons (leftmost panels in Fig. 34) and on data from neurons with significant object-centered selectivity (rightmost panels in Fig. 34), it appears that the average strength of the object-centered signal (corresponding to the width of the black ribbon) was slightly greater in the object-centered task (Fig. 34A) than in the color DMS task (Fig. 34B) in both M1 (top row of each tetrad of panels) and M2 (bottom row of each tetrad of panels).

4.3.7. Ruling out an effect based on bar location

Across the conditions on which have based the analysis of the data, there was a partial correlation between the location of the target on the bar and the location of the bar on the screen. The average location of the bar was to the left on bar-right trials and to the right on bar-left trials (Fig. 29B-C, near left and near right locations). In principle, a main effect of object-centered location during the post-bar-onset epoch, when the bar was visible, could have arisen from neuronal sensitivity either to the object-centered location of the target or to the location of the bar on the screen. We have shown an example of a neuron in which firing was clearly dependent on object-centered location and not on the location of the bar on the screen (Fig. 32). It remains, however, to address the issue of whether this pattern was characteristic of the population as a whole. Toward this end, we fit the data from each neuron with two models: a target-on-bar model in which the firing rate was a linear function of the location of the target on the bar (left or right) and a bar-on-screen model in which the firing rate was a linear function of the location of the bar on the screen (left, middle or right). The conditions on which this analysis was based were the standard ones in which the target was at the near left or near right location on the screen. Having found the best fit for each case, we computed the fraction of the initial variance in the firing rate that was accounted for by the model. The results, summarized in Fig. 35, make

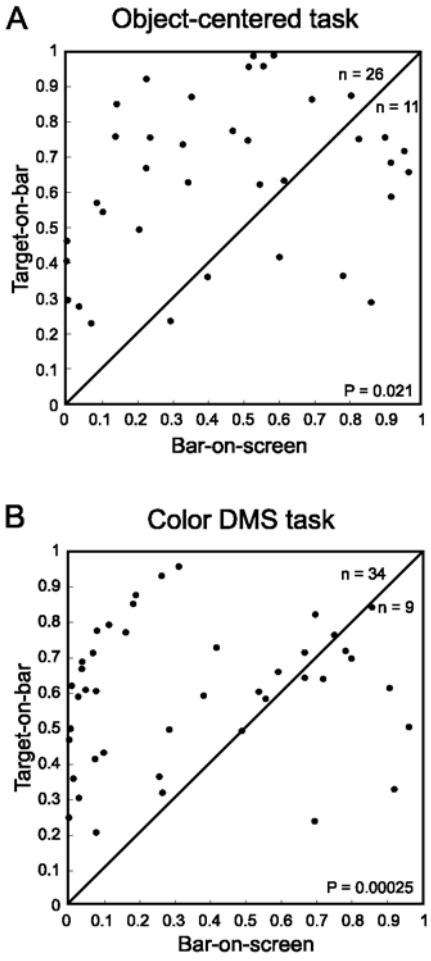

Fig. 35. Neuronal selectivity for the location of the bar-on-screen vs. the location of target-on-bar.

For each neuron with object-centered spatial selectivity, the fraction of firing-rate variance accounted for on the assumption that firing depends on the object-centered location of the target is plotted against the fraction of variance accounted for on the assumption that firing depends on the location of the bar on the screen. This analysis was necessary because the two factors were partially correlated. Points above the identity line, representing cases in which the data were better accounted for by the assumption that firing depended on object-centered location, were more significantly preponderant in the context of both the (A) object-centered task (χ^2 test, $p < 0.05$) and (B) the color DMS task ($p < 0.0005$).

clear that a majority of neurons were more sensitive to the object-centered location of the target than to the location of the bar on the screen. In the object-centered task, the fraction of variance accounted for by the object-centered model was greater than the fraction accounted for by the bar-on-screen model in 26/37 = 70% neurons and the preponderance of neurons for which this was true was significant (χ^2 test, $p = 0.02$). In the color DMS task, the fraction was even higher

(34/43 = 79% of neurons) and the effect even more significant (χ^2 test, p = 0.0003). We conclude that most neurons in both tasks were more sensitive to the location of the target on the bar than to the location of the bar on the screen.

4.3.8. Ruling out an effect based on saccade metrics

There was a partial correlation between the object-centered location of the target and the trajectory of the saccade. Even when the target dot was at an identical location on the screen, the eyes deviated slightly to the right if it occupied the left end of a bar and slightly to the left if it occupied the right end of a bar (see 4.3.2, Behavior). In other words, the eyes deviated toward the center of the bar. In principle, a main effect of object-centered location during the post-bar-onset epoch, when the bar was visible and the eye movement was being planned, could have arisen from neuronal sensitivity either to the object-centered location of the target or to the direction of the planned saccade. We have shown an example of a neuron in which firing was clearly dependent on object-centered location independently saccade direction, as evidenced by the fact that even across conditions in which the target occupied widely different locations on the screen the firing rate depended exclusively on object-centered location (Fig. 32). However, it remains to ask whether the population as a whole was sensitive to object-centered location as distinct from the properties of the saccade. To answer this question, we carried out a multivariate regression analysis, fitting three models to data from each neuron: (1) a reduced model containing only a parameter for object-centered location, (2) a reduced model containing parameters for saccadic latency, velocity, amplitude, horizontal landing position and vertical landing position, and (3) a full model containing both sets of factors (see 4.2, Methods). Having obtained the fits, we then asked, using an F-test, whether the amount of variance accounted for

by the full model was significantly greater than the amount accounted for by the reduced object-centered model (in which case the properties of the saccade contributed significantly to determining the neuronal firing rate) and, conversely, whether the amount of variance accounted for by the full model was significantly greater than the amount accounted for by the reduced saccadic model (in which case the factor of object-centered location contributed significantly to determining the neuronal firing rate). This analysis was carried out independently for two sets of data from each neuron: a set based on trials in which the target was at the near left location and a set based on trials in which the target was at the near right location. Thus it focused on trial-to-trial variations in saccades that occurred despite the fact that the target was, in a formal sense, always at the same location.

By this approach, we analyzed activity during the post-bar-onset epoch in all 41 neurons exhibiting a significant main effect of object-centered location in the object-centered task and all 44 neurons doing so in the color DMS task. We carried out separate analyses for instances in which the target was at the near left and near right location on the screen (Fig. 29B-C). Thus the full series concerned 82 cases (41 neurons x 2 locations) from the object-centered task and 88 cases (44 neurons x 2 locations) from the color DMS task. The general finding was that the neuronal firing rate was much more frequently dependent on object-centered location than on the parameters of the saccade. There was a significant dependence on object-centered location in 38/82 = 46% of cases from the object-centered task and in 50/88 = 57% of cases from the color DMS task. In contrast, there was a significant dependence on the parameters of the saccade (not necessarily excluding dependence on object-centered location) in only 6/82 = 7% of cases from the object-centered task and 7/88 = 8% of cases from the color DMS task, values barely above the rate of 5% expected from type I errors in light of the criterion for significance ($p < 0.05$).

The fact that there were instances in which the regression analysis failed to reveal significant dependence on object-centered location (although neurons had been selected for this trait) can be explained by the fact that this analysis was statistically less powerful (concerning subsets of the full data set) and that there may have been neurons in which the firing rate genuinely depended on object-centered location at one of the screen locations and not the other. We conclude that object-centered spatial selectivity, as observed in both tasks, was genuine rather than an indirect manifestation of sensitivity to subtle differences between saccades occurring on bar-left and bar-right trials.

4.3.9. Constancy of object-centered selectivity over the course of the color DMS session

It might have been the case that neurons exhibited object-centered selectivity early in any given color DMS session but lost it as the session progressed. To investigate this possibility, we plotted the average value of the index of object-centered spatial selectivity, Abs(R - L)/(R + L), where R and L were firing rates on bar-left and bar-right trials, as a function of time during the session for the color DMS task and, independently, for the object-centered task. The approach involved (a) confining attention to neurons studied in both tasks and (b) computing the average across those neurons of the index computed for each successive block of trials during the recording session. In the color DMS (or object-centered) task, each block consisted of twelve (or six) contiguous trials, one trial conforming to each of the twelve (or six) possible conditions (Fig. 29B-C). There was a trade-off between the number of blocks (out of the 16 that were completed when possible) and the number of neurons (out of 116 studied in both tasks) that could be included in the analysis. As the number of blocks increased, more neurons had to be excluded

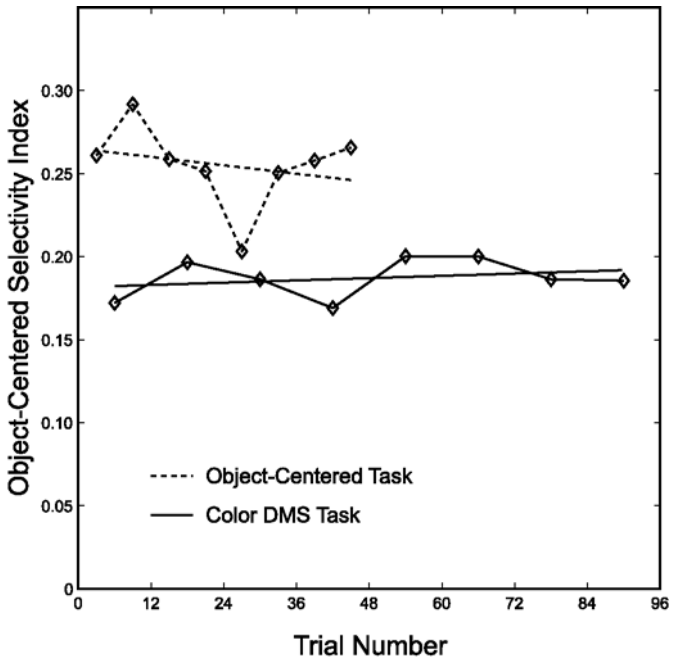

Fig. 36. No change in strength of object-centered selectivity across trials.

The strength of the object-centered signal remained constant over the course of the recording session. For each successive block of trials (containing six trials in the object-centered task and twelve in the color DMS task), the object-centered index was computed as Abs(R – L)/(R + L) where R and L were the firing rates during the post-bar-onset delay period on bar-right and bar-left trials respectively. The plots for the object-centered task and color DMS task are based on data from the same 94 neurons. The slopes of the best-fit lines were not significantly different from zero.

because (a) they had not been studied for the requisite number of blocks in both tasks or (b) the index could not be computed for one of the blocks in one of the tasks due to the absence of firing. In Fig. 36 are shown the results for 94 neurons during the first eight blocks of trials (encompassing 96 trials in the color DMS task and 48 trials in the object-centered task). In neither task was there a significant trend over time (the slopes of the best-fit lines are not significantly different from zero). Moreover, in the color DMS task, the observed minor trend involved an increase over time. These results were unaltered by repeating the analysis for larger numbers of blocks (12 or 16) and smaller numbers of neurons. They were also not altered by confining the analysis to neurons exhibiting significant object-centered selectivity in one task or

the other. We conclude that there was no decline in object-centered spatial selectivity over the course of a color DMS session.

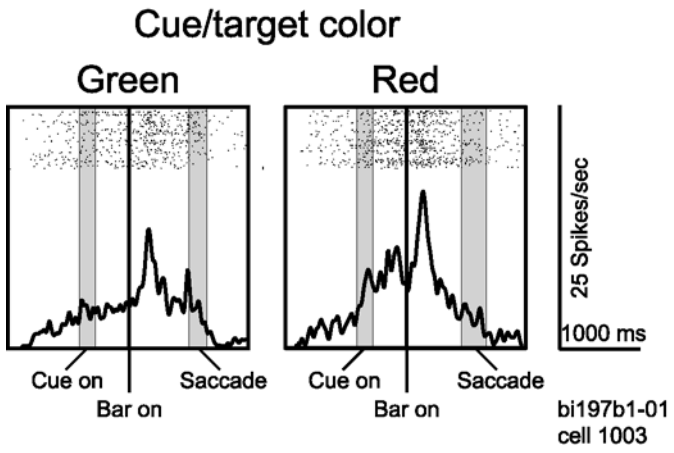

Fig. 37. Single neuron exhibiting significant selectivity for color.

Data from a neuron more active, in the color DMS task, on trials involving a red cue and target than on those involving a green cue and target.

4.3.10. Relation of color selectivity to spatial selectivity in the color DMS task

Some neurons exhibited unmistakable selectivity for the color of the cue and target (red or green) in the context of the color DMS task. An example of a neuron selective for red is shown in Fig. 9. The existence of a few such neurons is not surprising because it has been shown previously that a few neurons fire at significantly different rates on trials in which saccade targets are different colors (Tremblay et al. 2002). However, the rate of incidence of color selectivity was relatively high in the present study, especially during the pre-bar-onset epoch (13%). We wondered if this might be related to the fact that the monkeys had learned to associate the colors used in the color DMS task with particular object-centered locations. To explore this issue, we constructed population histograms representing the average firing rate of 44 neurons exhibiting significant object-centered selectivity during the post-bar-onset epoch of

the color DMS task. We subdivided trials into four groups formed by crossing the color of the target (red or green) with its object-centered location (bar-left or bar-right). The results are shown in Fig. 38. It is clear in this figure that the population fired more strongly, during the post-bar-onset epoch, when the target was at the preferred object-centered location (thick curves). This is a predictable result of the way in which the trials were categorized. However, two other effects, not predictable and therefore informative, are apparent in the figure. 1) During the pre-bar-onset epoch, the population fired more strongly when the cue was of the color associated with the preferred direction (blue curves) than when it was of the color associated with the non-preferred direction (red curves). In other words, neurons preferring a given object-centered direction fired more strongly in response to the color associated with that direction. Thus associations formed in the context of the color-conditional object-centered task affected neuronal activity in the color DMS task. 2) Following onset of the bar, there was a period of several hundred milliseconds when the population fired more strongly if the color and location of the target were incongruent (not associated with each other) than if they were congruent (associated with each other) (each broken curve is higher than the continuous curve of corresponding thickness). In other words, under conditions of conflict, there was an enhancement of neuronal activity. This phenomenon, although quite different from the previous one, also provides evidence that color-location associations formed in the context of the color conditional object-centered task affected neuronal activity in the color DMS task.

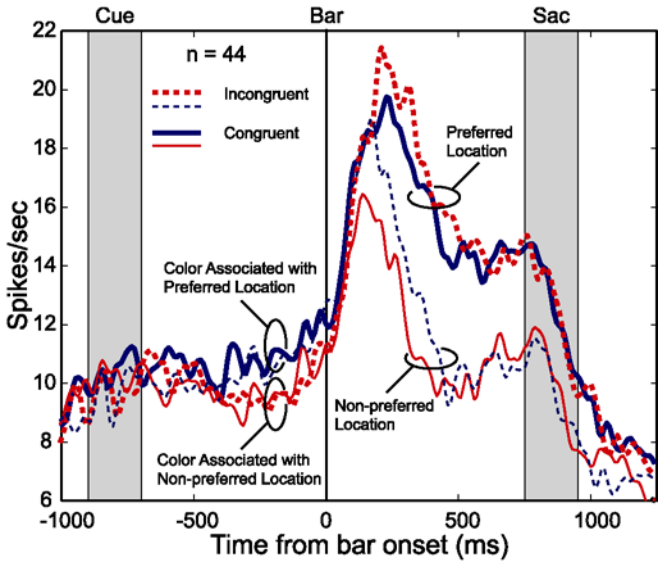

Fig. 38. Population histograms.

Population histograms representing the activity of all 44 neurons that exhibited significant object-centered selectivity during the post-bar-onset epoch in the color DMS task. Firing was stronger when the target was at the preferred object-centered location (thick curves are higher than thin curves following bar onset) as guaranteed by the way in which conditions were sorted. However, two other effects emerged that were not predictable from the sorting procedure. 1) Neuronal activity during the pre-bar-onset epoch was stronger when the cue was of the color associated (in the object-centered task) with the neuron's preferred object-centered direction (blue curves) than when it was of the color associated with the non-preferred object-centered direction (red curves). 2) Neuronal activity during the post-bar-onset epoch was stronger when the color and location of the target were incongruent (according to the association established in the object-centered task) than when they were congruent (the broken thick curve is above the continuous thick curve and the broken thin curve is above the continuous thin curve).

4.4. Discussion

4.4.1. Automatic expression of object-centered selectivity in color DMS task

The motivation for this study arose from an earlier observation that neurons automatically expressed object-centered spatial selectivity during performance of a color delayed match to sample task, signaling the object-centered location of the target even when the monkey was required only to process color and was free to ignore object-centered location (Tremblay et al. 2002). This finding clearly established that the occurrence of object-centered selectivity did not

depend on active use of an object-centered rule. However, it was obtained under circumstances that may have strongly favored the representation of object-centered space. The monkeys had been trained first and for the longest time on an object-centered task. Furthermore, during data collection, trials requiring that the target be selected on the basis of color were randomly interleaved with trials requiring that it be selected on the basis of object-centered location, so that the habit need not persist long for the effect to be robust. The aim of the present study was to ascertain whether, with these conditions removed, the tendency for SEF neurons automatically to represent the object-centered location of the target would persist. The essential finding is that neurons continued to represent object-centered location robustly in monkeys performing a color DMS task even though the monkeys had been trained later and more briefly on the object-centered task and even though data were collected during sessions in which monkeys had to select targets only by a color-based rule. There was not even any apparent diminution over the course of the data collection session in the strength of object-centered activity (Fig. 36). We conclude that the tendency for SEF neurons to represent the object-centered locations of targets is genuinely independent not only of the current but of the recent use of an object-centered rule for target selection.

4.4.2. Object-centered selectivity in color DMS task: innate or learned?

In an earlier study, we recorded from SEF neurons at two stages of training (Moorman and Olson 2005b, Aim 2). In stage 1, we trained monkeys to perform the color DMS task and then demonstrated that SEF neurons exhibited a moderate degree of object-centered selectivity during its performance. In stage 2, we trained them to perform the object-centered task and demonstrated that neurons recorded in its context exhibited enhanced object-centered selectivity.

The conclusion of that study was that object-centered selectivity is an innate property of SEF neurons that can be markedly enhanced through training on the use of an object-centered rule. In the present study, conducted subsequently on the same monkeys, we found that neurons in the SEF automatically exhibited object-centered spatial selectivity in the context of the color DMS task. This observation leads to the question: did they simply exhibit the rudimentary level of selectivity that was present innately, prior to training on the use of an object-centered rule, or, alternatively, did they exhibit an enhanced level of selectivity, as would be expected if training had induced a change that persisted even outside the context of the object-centered task?

To answer this question, we compared, across this study and the previous one, key measures of object-centered selectivity. The results, presented in Fig. 39, reveal that the pattern of neuronal spatial selectivity observed in the context of the color DMS task in the current study (a) was different from the pattern observed in the context of the color DMS task during stage 1 of training and (b) resembled the pattern observed in the context of the object-centered task during stage 2 of training and in the present study. This is true of comparisons based on three measures. 1) The incidence, among spatially selective neurons, of object-centered selectivity was uniformly high during the three stages of data collection following training on the object-centered task (Fig. 11A). In particular, the incidence in the context of the color DMS task in this study (44/55 = 80%) was significantly higher than in the context of the same task during stage 1 of training (69/119 = 58%) (χ^2 test, $p = 0.0078$). 2) The incidence, among spatially selective neurons, of retina-centered selectivity was uniformly low during the three stages of data collection following training on the object-centered task (Fig. 39A). In particular, the incidence in the context of the color DMS task in this study (25/55 = 46%) was significantly lower than in the context of the

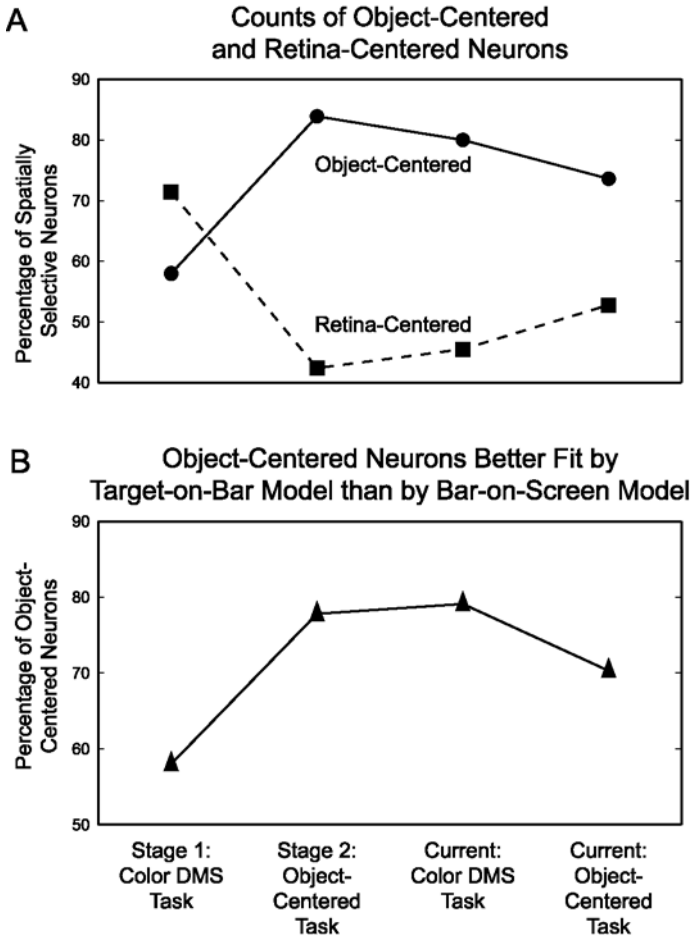

Fig. 39. Spatial selectivity compared across stages of task performance.

Measures of spatial selectivity obtained in this study compared to measures obtained during stage 1 of training (when the monkeys had learned and were exclusively performing the color DMS task) and stage 2 of training (when they had learned and were exclusively performing the color-conditional object-centered task) as described in a previous study (Moorman and Olson 2005b, Aim 2). A. Percentage of spatially selective neurons exhibiting selectivity for object-centered location (circles) and retina-centered location (squares). Spatially selective neurons were defined as those exhibiting either object-centered or retina-centered selectivity or both. Object-centered and retina-centered selectivity genuinely varied in complementary fashion over the course of study. They were not constrained to do so because neurons selective for retina-centered location at the outset of training could simply have remained selective for it while developing a superadded selectivity for object-centered location. B. Percentage of neurons exhibiting object-centered selectivity for which it was the case that the data were better fit by a model in which firing depended on the location of the target on the bar than by a model in which firing depended on the location of the bar on the screen (cf. Fig. 35). All measures were based on firing during the post-bar-onset epoch.

same task during stage 1 of training (85/119 = 71%) (χ^2 test, p = 0.0017). 3) The incidence, among neurons selective for object-centered location, of cases in which the data were better fit by a model in which firing depended on the location of the target on the bar than by a model in

which firing depended on the location of the bar on the screen was uniformly high during the three stages of data collection following training on the object-centered task (Fig. 39B). In particular, the incidence in the context of the color DMS task in this study (34/43 = 79%) was significantly higher than in the context of the same task during stage 1 of training (40/69 = 58%) (χ^2 test, p = 0.037). We conclude that SEF neurons manifested, in the context of the color DMS task in this study, a degree of object-centered spatial selectivity that reflected the monkeys' having been trained to follow an object-centered rule and that exceeded the degree present innately before training.

4.4.3. Conflict induced by color-location associations

In order to perform the color-conditional object-centered task, the monkeys had to have mastered a strict association between colors (green or red) and object-centered locations (the left or right end of the bar). In the color DMS task, the pairing of color with location was congruent with the learned associations on one half of trials (those in which the green and red targets appeared on the left and right respectively) and incongruent on the other half. The monkeys' behavior was subtly but systematically impaired on incongruent trials: M1 was less accurate and M2 was slower to respond. Thus associations formed in the context of the object-centered task carried over to affect behavior in the color DMS task. The same was true of neuronal activity during color DMS performance, as indicated by two measures discussed below.

During the pre-bar-onset epoch, when the colored cue had been presented but the object-centered location of the target was not yet known because the bar had not yet appeared, neurons fired more vigorously when the color was the one associated with their preferred object-centered direction than when it was not (Fig. 38). This phenomenon is reminiscent of others described in

the literature whereby learned associations affect neuronal activity even when irrelevant to task performance. For instance, neurons in the monkey superior colliculus respond selectively to visual motion displays that the monkey has learned to associate with saccades into their response fields even when the monkey is merely passively fixating (Horwitz et al. 2004a) and neurons in the frontal eye field fire more strongly when images that have been saccade targets on a previous day are in their response field even when the monkey is searching for a different image (Bichot and Schall 1999). Likewise, prefrontal neurons selective for a go or a no-go response fire more strongly if that response is associated with the shape or color of an instructional cue even when the monkey has been instructed to ignore that stimulus dimension (Lauwereyns et al. 2001).

During a period of several hundred ms following onset of the bar, neurons fired more strongly on average if the target was at a location incongruent with its color than if it was at a congruent location (Fig. 38). This constituted a replication of a phenomenon made previously in different monkeys performing a slightly different version of the color DMS task (Tremblay et al. 2002). It fits with the general observation that population activity in the SEF tends to be strong under conditions of conflict, including countermanding a planned saccade (Stuphorn et al. 2000b), preparing to make an antisaccade (Amador et al. 2004; Schlag-Rey et al. 1997) and making a saccade away from the location of the pattern cue (Olson et al. 2000) or color cue (Olson and Gettner 2002) that has instructed it.

5. General Discussion

5.1. Overview

The goal of the research reported here was to understand how SEF neurons are capable of representing object-centered locations. We focused our investigations on three main issues. Aim 1 addressed the mechanism by which SEF neurons represent locations using both a retina-centered spatial reference frame and an object-centered spatial reference frame (Moorman and Olson 2005a). The results from this study show that SEF neurons are capable of exhibiting selectivity for locations in retina-centered reference frames only, in object-centered reference frames only, or in both, combining in additive, multiplicative, or purely transformative ways. Aim 2 investigated whether object-centered selectivity is inherent to SEF neurons, and whether learning to perform an object-centered task affects this selectivity (Moorman and Olson 2005b). In this study, we showed that some neurons exhibit object-centered spatial selectivity before learning an object-centered rule, but that more neurons show stronger selectivity following learning. Aim 3 examined whether the high degree of object-centered selectivity observed in SEF neurons could be up- or down-regulated by having monkeys perform multiple blocks of either object-centered or non-object-centered tasks (Moorman and Olson 2005c). The results of this study showed that an approximately equal number of neurons encoded locations in object-centered coordinates during performance of the color DMS task and during performance of the object-centered task, but that the strength of object-centered selectivity was heightened during performance of the explicitly object-centered task. The remainder of the discussion will focus on the relevance of the results presented here, and will consider them in the context of previous studies.

5.2. Aim 1: Interaction of retina-centered and object-centered signals in SEF neurons

5.2.1. Summary of results

5.2.1.1. New results concerning retina-centered selectivity

Retina-centered selectivity is broadly tuned. We determined that the retina-centered response fields of SEF neurons are relatively broad, encompassing approximately 45 degrees in their angular extent. Previous studies of the response fields of SEF neurons have shown that SEF neurons exhibit invariance for saccade eccentricity (Russo and Bruce 1996, 2000), but no study to date, has characterized how broad a range of variations in saccade direction result in maximal activation of SEF neurons. This result shows that the retina-centered selectivity of SEF neurons can be well characterized using relatively few locations and that SEF neurons may be only coarsely tuned for retina-centered locations.

Retina-centered selectivity is similar in both the dot task and the bar task. While selectivity was similar across the two tasks, more neurons displayed significant retina-centered selectivity during the bar task than the dot task. As noted, this may be a genuine feature of SEF neurons, or may be an artifact of having more conditions factored into the statistical analysis of bar trials. The strength and direction of retina-centered selectivity was extremely similar in both tasks, supporting the hypothesis that retina-centered encoding is for the most part, the same in both tasks. While some work from our laboratory has compared retina-centered spatial selectivity in a dot task to object-centered selectivity in a bar task (Olson and Gettner 1995; Olson and Tremblay 2000), this is the first study to characterize retina-centered response properties for the same neuron in both tasks across the entire visual field.

5.2.1.2. New results concerning object-centered selectivity

SEF neurons can encode the object-centered location of a saccade. Studies from our laboratory have come to this conclusion based activity related to saccades directed to objects located in the upper hemifield only (Olson and Gettner 1995, 1999; Olson and Tremblay 2000; Tremblay et al. 2002). The results of the current study confirm those of the previous studies from our laboratory and extend them by showing that SEF neurons can exhibit object-centered selectivity when saccades are directed to locations in either the upper or lower visual hemifield. The invariance of object-centered selectivity to retina-centered location, while often extensive, is not always complete, as shown in section 5.2.1.3 below.

Neurons that display object-centered selectivity in one temporal epoch tend to display object-centered selectivity in other epochs. This result was found to be true using both a statistical analysis during prefabricated epochs as well as using an index-based correlation analysis that characterized selectivity over time independent of any epoch selection. We also found, however, that there are multiple smaller epochs within the trial in which neurons exhibit heightened object-centered selectivity. These smaller epochs suggest that there are different populations of SEF neurons that exhibit significant object-centered selectivity at different times over the course of the trial: following the onset of the cue, surrounding the onset of the bar target, and following the onset of the bar target. The details of the response properties that discriminate these populations of neurons, and what function each population may play in task performance require further analysis. What we have shown, however, is the initial characterization of different SEF neurons that might signal different aspects of the performance of an object-centered task

SEF neurons encode object-centered space metrically. More than 50% of our significantly object-centered neurons were metric and not categorical in their encoding of object-centered space, with firing rate on dot trials being intermediate between the firing rates on preferred and anti-preferred object-centered location. This was not conserved across the population as a whole, however, suggesting that the metric representation of object-centered space may specific to neurons with object-centered response fields. These results suggest that the object-centered selectivity observed in SEF neurons is not, for the most part, a result of neurons showing preference for one arbitrary category as compared to another, as has been seen in prefrontal cortex (Freedman et al. 2001, 2002, 2003). Rather, our results support the claim that many SEF neurons represent a specific location in space that is defined in relation to an object. Other neurons in the SEF may additionally encode locations categorically, which would not be surprising given that Kosslyn and colleagues found activation of the human SEF while subjects performed both categorical and metric spatial tasks (Kosslyn et al. 1998). An adequate comparison would require studies designed explicitly to address this question.

5.2.1.3. New results concerning the interaction of retina-centered spatial selectivity and object-centered spatial selectivity

The main focus of Aim 1 was to determine if and how object-centered signals and retina-centered signals interact in the same neurons. We addressed this issue both at the level of the population of neurons from which we recorded, and on an individual neuron-by-neuron basis, producing the following results.

Different neurons show different combinations of spatial selectivity. Our statistical analysis described many neurons that exhibited a combination, in the same neuron, of both

retina-centered and object-centered selectivity. An equally large proportion of neurons showed retina-centered selectivity in the absence of object-centered selectivity, and a small proportion of neurons showed object-centered selectivity in the absence of retina-centered selectivity. All of these types of selectivity have been demonstrated before though, as noted above, only for saccade targets in the upper hemifield (Olson and Tremblay 2000). Particularly notable about the results of the previous and current studies are the observations that some neurons exhibit object-centered selectivity in the absence of retina-centered selectivity. While this proportion of neurons was relatively low, their existence informs us that object-centered selectivity in the SEF is not necessarily dependent on retina-centered selectivity.

Retina-centered selectivity is stronger than object-centered selectivity. Given that the results of our statistical analyses above described the majority of SEF neurons as being either significantly selective for retina-centered locations or for both retina-centered and object-centered locations, this bias towards stronger retina-centered is not surprising. This bias could be a reflection of the inherent response properties of SEF neurons. It is also possible that the heightened strength could be a result of characterizing retina-centered selectivity with four locations and object-centered selectivity with only two locations. Further tests with more object-centered target locations should be performed to settle this issue. Regardless, this effect has not been described before and is useful in characterizing the response properties of SEF neurons.

Preferred retina-centered directions tend to align with preferred object-centered directions. This correlation has been demonstrated before (Olson and Tremblay 2000), though only for a limited number of targets in the upper hemifield. Again, we might expect to see a higher degree of correlation if more object-centered targets were used so as to bring the number of retina-centered and object-centered targets into register.

SEF neurons show significant object-centered selectivity at multiple locations. We addressed this issue using a statistical analysis and an index-based analysis. Statistical analysis demonstrated that neurons that show object-centered selectivity at one retina-centered location tend to show it at least at one other location and, in some cases, all retina-centered locations. In other cases, object-centered selectivity was not displayed at all retina-centered locations. Index analysis similarly showed that the strength of object-centered selectivity is not uniform at each of the retina-centered locations at which we analyze object-centered selectivity, but that object-centered spatial selectivity is largely preserved across retina-centered locations. We can conclude from these results that object-centered selectivity, while modulated by retina-centered position in some cases, is largely preserved across a broad extent of retina-centered space. This conclusion is important, as noted earlier, for showing that neurons can exhibit object-centered selectivity outside the extent of their retina-centered response field.

The results reported to this point describe how combinations of object-centered and retina-centered selectivity is manifested across the population of neurons. The following section addresses how the interaction between object-centered and retina-centered selectivity occurs within individual neurons.

Retina-centered selectivity and object-centered selectivity interact in multiple ways at the level of the single neuron. Focusing this analysis only on neurons that displayed both retina-centered selectivity in the dot task and object-centered selectivity in the bar task, we compared, for each neuron, the firing rate related to saccades directed to four locations in the dot task to firing rate related to saccades directed to the same four locations in the bar task. The relationship between the firing rate in these two tasks was assessed by how well they corresponded to a

number of linear models, schematized in Figs. 15 and 16. Of those neurons exhibiting a difference in the two tasks, we found that the relationship between the firing rates in the two tasks was accurately described by one of the explanatory three models (pure, additive, multiplicative), with a bias for multiplicative and additive interactions (and a combination of the two). We conclude from these results that different SEF neurons combine retina-centered and object-centered signals in different ways. In some cases, the signals combine in a multiplicative fashion, as has been seen in the integration of multiple egocentric reference frames in neurons of other areas (see section 5.3). However, we characterized an almost equal number of neurons as exhibiting additive interactions. Only a few groups have acknowledged the existence of additive interactions prior to this report. We also characterized a small number of neurons as being best fit by a pure model. This pure interaction, whereby the retina-centered signal disappears during performance of the bar task, has not been described before. These findings are important for understanding 1) how individual SEF neurons represent locations, 2) what role SEF plays in spatial representation and sensorimotor integration, and 3) how sensorimotor neurons in general integrate signals related to different spatial reference frames, as will be discussed below.

5.2.2. Relationship of Aim 1 to studies of object-centered selectivity

The section above describes the majority of the novel findings of the study. We focus here on two broad aspects of this new information. First, previous studies of object-centered processing by our laboratory have focused on targets located in the upper hemifield (Olson and Gettner 1995, 1999; Olson and Tremblay 2000; Tremblay et al. 2002). It could be argued that object-centered selectivity is a phenomenon unique to the upper hemifield, thus diminishing the interpretation that object-centered selectivity is a general phenomenon. In this study we have

shown that object-centered selectivity can exist at multiple locations in both the upper and lower hemifields, confirming that it is a spatially ubiquitous phenomenon.

The second major informative aspect of our study is the fact that selectivity for object-centered space tends to co-exist with retina-centered selectivity, both across the population of SEF neurons, and within a subset of individual SEF neurons. This study, by using saccade target locations in multiple regions in visual space, was able to characterize both the retina-centered selectivity and the object-centered selectivity of SEF neurons, something that has not been done before. The results of the study show that some neurons exhibit exclusively object-centered selectivity, many neurons exhibit exclusively retina-centered selectivity, and a large proportion of neurons exhibit an interaction between the two, suggesting that neurons in the SEF play many roles in the representation of object-centered and retina-centered space, and the conversion between the two. A discussion of the relevance of how these signals combine is presented below.

5.2.3. Relationship of Aim 1 to studies of reference frame interactions

The work presented in Aim 1 is one of the first studies to address the neuronal basis of the interaction between retina-centered reference frames and object-centered reference frames. However, the means by which single neurons combine different egocentric reference frames have been described in significant detail. The fact that these relationships have been so well characterized has allowed a number of groups to propose computational theories about how this combination occurs. The results of Aim 1 allow us to determine whether these theories, based on the interaction of multiple egocentric reference frames, also apply to interactions between an egocentric (retina-centered) and an allocentric (object-centered) reference frame. We first

provide an overview of two of the more prominent of these theories: gain field models and basis function models. Basis function models are particularly relevant as one group of investigators has proposed a mechanism whereby object-centered signals in SEF neurons can be explained in egocentric terms using a basis function framework. Following this overview, we will discuss how our data describing the interaction of reference frames in SEF neurons relate to the types of interactions described in the models

5.2.3.1. Models of reference frame interactions: gain fields and basis functions

The conceptualization of gain field and basis function models as a mechanism for reference frame interactions were originally based on data obtained from the recording of neurons in parietal cortex. Studies of sensorimotor integration in the parietal cortex have shown that neurons in areas 7a and LIP display retina-centered selectivity for visual stimuli that is modulated by the varying direction of gaze or the orientation of the body (Andersen et al. 1990b; Andersen et al. 1985; Andersen and Mountcastle 1983; Brotchie et al. 1995; Sakata et al. 1980; Snyder et al. 1998). The location of the visual response field of the neuron maintains its position with respect to the retina, but the magnitude of the response is different for different gaze positions. The modulation of visual activity by gaze is called gain field modulation, as the change in gaze affects the gain of the visual signal. The combination is largely considered to be multiplicative in nature: the activity of each single neuron is usually described as the nonlinear interaction (typically multiplication) between a visual receptive field and a signal representing the effect of changing gaze position (Andersen 1989; Andersen et al. 1990b; Andersen et al. 1985; Brotchie et al. 1995). Gain fields have also been used to describe gaze modulation of memory-related and saccade related activity (Andersen et al. 1990b), suggesting that the gain field mechanism may be a general way of integrating many different types of signals for

sensorimotor transformation. Supporting this idea, many other laboratories have described gain field modulation by neurons in parietal cortex (Bremmer et al. 1997a; Galletti et al. 1995; Nakamura et al. 1999; Read and Siegel 1997), and similar types of gain field interactions have been seen in V1 (Guo and Li 1997; Trotter and Celebrini 1999), V3a (Galletti and Battaglini 1989), and V4 (Bremmer 2000), areas MT and MST (Ben Hamed et al. 2003; Bremmer et al. 1997b; Shenoy et al. 1999; Squatrito and Maioli 1997), ventral and dorsal premotor cortex (Boussaoud 1995; Boussaoud et al. 1993; Boussaoud et al. 1998; Graziano et al. 1997; Graziano et al. 1994; Mushiake et al. 1997), and the superior colliculus (Stuphorn et al. 2000a; Van Opstal et al. 1995).

Based on these data, investigators have developed computational models to describe the mechanism by which signals from the two reference frames interact. Of particular interest is the mathematical function used to combine these signals, because this function is an assumption about how the two signals, represented by two neurons or sets of neurons, actually combine in the brain. Initially, Zipser and Andersen formalized the interaction between a retina-centered visual signal and a head-centered gaze signal by combining them using a sigmoidal logistic function (Andersen and Zipser 1988; Zipser and Andersen 1988). The authors proposed that the initial ascending slope of the sigmoid well characterized the multiplicative interactions seen in parietal neurons, while the more linear aspect of the sigmoid better characterized the additive interaction between visual signal and gaze angle seen in other parietal neurons (Andersen et al. 1997). Most models since then have tended to emphasize the nonlinear (multiplicative) aspect of the integration. Indeed, it has been stated that, while gain fields need not operate in an exclusively multiplicative fashion, they must, in order to be gain fields, operate in a nonlinear (and most likely multiplicative) fashion (Salinas and Abbott 2001; Salinas and Sejnowski 2001;

Salinas and Thier 2000). Consequently, much of the research community interested in visuomotor transformations has focused on the nonlinear interaction of reference frames (see Salinas and Thier 2000 for examples). This is not universally true: some models of reference frame interaction do combine visual signals and gaze signals in a linear fashion (Goodman and Andersen 1990; Van Gisbergen et al. 1996). Furthermore, at least one group (White and Snyder 2004) has proposed, based on computational modeling, that gain fields may be used for the integration of certain signals (e.g., visual signals and gaze position signals), but not for the integration of others (e.g., visual signals and gaze change velocity signals). Explanations of reference frame integration that do not use gain fields, however, are in the minority, as seen in the prominent role that basis function models have played in describing this process.

Recently, investigators have created basis function models to explain the combination of signals from different reference frames. Basis function models are similar to gain field models in that they describe this interaction as nonlinear (Ben Hamed et al. 2003; Deneve et al. 2001; Deneve and Pouget 2003; Pouget et al. 2002; Pouget et al. 1999; Pouget and Sejnowski 1994, 1997a, b, 2001; Pouget and Snyder 2000). In basis function models, inputs such as retina-centered visual receptive fields and head-centered gaze fields are combined in an exclusively nonlinear fashion to create an intermediate layer of basis function units (Pouget et al. 2002; Pouget and Sejnowski 1997b; Pouget and Snyder 2000). These units are capable of simultaneously representing locations using multiple reference frames (such as retina-centered, head-centered, etc.) and can combine these representations in a linear fashion to generate a behaviorally-relevant output in one of multiple reference frames (such as eye-centered, arm-centered, etc.). Basis functions are particularly useful in describing reference frame interactions for at least two reasons. First, the use of basis functions for computations allows complex

nonlinear transformations (such as from retina-centered space to arm-centered space in the case of a visually-guided reach) to be reduced to a linear function, which is a simpler computation, thus making the system more efficient. Second, because basis function units represent locations in multiple reference frames, the model is flexible and can program a number of behavioral responses to sensory input. These characteristics of the basis function model allow for an efficient and comprehensive way of encoding multiple stages of sensorimotor transformations (Deneve and Pouget 2003; Pouget et al. 2002; Pouget et al. 1999; Pouget and Sejnowski 1997b, 2001; Pouget and Snyder 2000).

Because of the way that basis functions encode signals of various reference frames, it has been hypothesized that this type of representation is commonly used by neurons in multiple areas of cortex (Deneve and Pouget 2003; Pouget et al. 2002; Pouget et al. 1999; Pouget and Sejnowski 1997b, 2001; Pouget and Snyder 2000). Basis function models have frequently been used to characterize neuronal reference frame interactions in parietal cortex (Ben Hamed et al. 2003; Pouget et al. 1999; Pouget and Sejnowski 1994, 1997a, b, 2001). Individual neurons have been described as acting like basis function units (Ben Hamed et al. 2003; Pouget et al. 2002; Pouget et al. 1999; Pouget and Sejnowski 1997b, 2001). Further, "lesioned" basis function models of parietal cortex (in which certain basis function units have been inactivated) show examples of neglect that are extremely similar to those observed in patients who have sustained damage to the parietal cortex (Deneve and Pouget 2003; Pouget et al. 1999; Pouget and Sejnowski 2001). Because of the ability of basis function models to represent multiple reference frames simultaneously, these models have even been able to produce neglect-like behavior in both egocentric and object-centered reference frames.

Deneve and Pouget recently created a basis function model designed to explain the object-centered selectivity seen in SEF neurons during performance of the bar task (Deneve and Pouget 2003). SEF neurons were represented as basis function units that combined a number of signals from input units. The input units represented a visual stimulus in retina-centered coordinates (a bar such as the type we use in our studies that could be located at multiple locations and could, in addition, rotate) and an object-centered command signal (essentially a signal telling the model to execute a saccade to the right or left end of the bar). In combining the input signals in a nonlinear fashion, the basis function units developed representations that could be used by the next stage of the model, the output or saccade layer, to generate virtual eye movements to object-centered locations on the virtual bar. The authors found that the representations used by the SEF basis function units were qualitatively similar to the object-centered selectivity seen in real SEF neurons. Of note, the authors state that the model never received an explicit signal representing the object-centered target location on the bar. Instead, the model had received retina-centered signals that had been gain modulated (i.e., multiplied) by stimulus features (such as the object orientation) and by the object-centered command. Despite the absence of an explicit object-centered spatial input signal, the basis function units (the SEF layer) developed response properties that looked object-centered. This observation led the authors to conclude that what has been described in SEF neurons as an object-centered representation is, in reality, a retina-centered signal that is nonlinearly gain modulated by extra-retinal factors, as described by their model. The model does an impressive job of describing a situation in which apparent object-centered reference frames can be observed, but does it accurately model the data? The answer is yes and no. The basis function model, like other types of gain field models, accurately describes

the response properties of the neurons described in this study as multiplicative in their interactions, while failing to account for the other types of neurons that we observed.

5.2.3.2. Do SEF neurons use nonlinear mechanisms to encode object-centered space?

Our current results allow us to address how well the interactions that we observe in SEF neurons fit with the nonlinear models discussed above. We observed multiple types of interactions between retina-centered signals and object-centered signals, as characterized by our linear regression model analysis. In some but not all cases we found multiplicative gain field-type interactions between the two reference frames. An example of a multiplicative neuron is shown in Fig. 8C. Neurons of this type are correctly predicted by both gain field models and basis function models. Given that a large proportion of the neurons that we studied show multiplicative interactions, we agree with the predictions of the models that many neurons in the SEF combine retina-centered signals and object-centered signals in a nonlinear fashion (Fig. 17). However, we also observed linear interactions of the type not predicted by these models. We observed an almost equal number of additive cases as multiplicative (Fig. 17). This proportion of neurons is not predicted by the use of an exclusively multiplicative gain field type of interaction. We must conclude, then, that gain field and basis function models only partially predict the mechanism by which SEF neurons combine retina-centered and object-centered signals.

We are not alone in describing linear reference frame combinations in the activity of neurons. As noted earlier, research from the Andersen laboratory, in which neurons were recorded from areas 7a and LIP, has described interactions between retina-centered signals and gaze signals that are multiplicative, additive, and a combination of the two, much in the same

way that we have (Andersen et al. 1990b; Andersen et al. 1997). Additionally, Sabes and colleagues, in studying the activity of LIP neurons during performance of an object-aligned task, found that many individual neurons displayed activity that was a linear combination of the retina-centered location of the target and the orientation of the target object (Andersen et al. 2004; Sabes et al. 2002). This linear result was verified using a model based analysis in which an additive model was compared to a multiplicative model and found to be a better fit to the data (Breznen and Andersen 2000). Furthermore, as noted in section 2.4.4, some studies reporting multiplicative interactions may actually be overlooking valid additive interactions in their data. Often studies investigating the neural basis of reference frame interactions do not account for gaze-related changes in baseline activity in the absence of visual signals, which can often look extremely similar to gain field modulation of visually-evoked responses (Andersen et al. 1990b; Bremmer 2000; Bremmer et al. 1997a; Bremmer et al. 1999; Bremmer et al. 1997b; Galletti et al. 1995; Read and Siegel 1997; Squatrito and Maioli 1996, 1997). When considering how extra-retinal signals such as gaze influence visually-evoked signals, it is critical to incorporate how these signals affect baseline activity into the equation. The logic behind this necessity is simple: if changes in gaze in the absence of retinal stimulation affect neuronal firing rate in a multiplicative way, the observed multiplicative interaction between visual signals and gaze signals could actually be an additive interaction whereby the visual response is simply added to the gaze-related response, producing a multiplicative-appearing interaction. Some studies do take changes in background activity into consideration when quantitatively assessing signal interaction (Andersen et al. 1990b; Andersen et al. 1985; Andersen and Zipser 1988; Galletti and Battaglini 1989; Read and Siegel 1997; Zipser and Andersen 1988), providing a solid foundation for the existence of multiplicative signals. However, some of these studies have noted that,

following background subtraction, some neurons no longer exhibit gain fields, suggesting that gaze-related signals and visual signals also combine in a linear fashion (Andersen et al. 1990b; Andersen and Zipser 1988). As such, it seems fair to state that at least some neurons combine gaze signals and visually-evoked signals in a multiplicative manner whereas some neurons combine signals using alternate strategies such as addition. Our data support these conclusions, and emphasize the fact that linear interactions can be used by real neurons in combining reference frames.

A second result of ours that contradicts the basis function model of SEF function is our description of neurons exhibiting explicit object-centered spatial selectivity. One of the strengths of the basis function modeling framework is the fact that multiple reference frame signals are represented simultaneously. We observed a number of instances in which object-centered selectivity in the bar task was unaccompanied by retina-centered selectivity in the same task. These neurons were described through statistical analysis (Fig. 18G-J) and through modeling analysis (Fig. 18E-F). A neuron that exhibited retina-centered selectivity in the dot task, but only object-centered selectivity in the bar task is shown in Fig. 8A. If SEF neurons encoded object-centered locations as basis function interactions of other signals, we would expect not to observe the explicit object-centered neurons that we have. This type of reference frame interaction contradicts the mechanism of interaction used in Deneve and Pouget's basis function model of the SEF. In fact, the neuron shown in our Fig. 8A displays a striking similarity to the theoretical neuron shown in Deneve and Pouget (2003)'s Figs. 4B and 4D that should not exist based on the predictions of the basis function model. Admittedly, these neurons did not make up the majority of the cases that we observed in the modeling portion of the study. Their existence, however, challenges the idea the all neurons in the SEF encode object-centered spatial locations only by

using gain field modulation of retina-centered locations. Instead, at least a small population of SEF neurons seem to exhibit selectivity for object-centered locations at the expense of retina-centered spatial selectivity.

Additional factors make interpretation of object-centered selectivity in the context of a basis function framework difficult. One issue that has not been addressed by most computational models, but is critical to the interpretation of physiological experiments, is that of changes in selectivity over the course of each trial. Most basis function (and gain field) models of parietal and/or frontal cortex are static: a single value for each condition is used to represent the response properties of a single neuron (Deneve and Pouget 2003; Pouget and Sejnowski 1997b; Salinas and Abbott 1996; Xing and Andersen 2000b; Zipser and Andersen 1988), but see (Xing and Andersen 2000a). In reality the response properties of neurons in the SEF change over the course of the trial, depending on what information is known to the monkey. Many SEF neurons display object-centered encoding in the early stages of the bar task trials, when only the object-centered location is known. During this epoch, neurons are displaying explicit object-centered encoding in that no retina-centered target information has been provided to the monkey and, as such, SEF neurons have no retina-centered spatial information to encode. Despite this absence of retina-centered information, approximately one third of the SEF neurons from which we recorded express object-centered spatial selectivity. This large proportion of neurons provides further support for the conclusion that the object-centered selectivity expressed by SEF neurons is not necessarily a gain-modulated retina-centered spatial signal.

Another problematic assumption that Deneve and Pouget's basis function model makes is that the SEF output must be in a retina-centered (or eye-centered) reference frame. The authors constrain the output of the model to represent locations in retina-centered coordinates, as this is

considered to be the reference frame used by downstream oculomotor areas such as the superior colliculus (Klier et al. 2001). This assumption is problematic because it presumes that SEF neurons are involved solely in programming saccades in an eye-centered reference frame and that transformations in the SEF have, as their ultimate goal, the representation in retina-centered coordinates. As noted in the introduction, neurons in the SEF project to many other areas that are not necessarily downstream in the oculomotor pathway (Huerta and Kaas 1990), individual neurons in the SEF have been described whose activity has little to do with explicitly programming retina-centered eye movements (Amador et al. 2000, 2004; Chen and Wise 1995a, b, 1996, 1997; Coe et al. 2002; Fujii et al. 2002; Horwitz et al. 2004b; Lu et al. 2002; Mann et al. 1988; Mushiake et al. 1996; Nakamura et al. 2004; Olson and Gettner 1995, 1999, 2002; Olson et al. 2000; Olson and Tremblay 2000; Schlag-Rey et al. 1997; Stuphorn et al. 2000b; Tremblay et al. 2002), and inactivation of the SEF produces only minor deficits in programming saccades to locations in retina-centered space (Schiller and Chou 2000a, b; Schiller and Chou 1998; Sommer and Tehovnik 1999). This compilation of studies strongly suggests that not all SEF neurons send retina-centered oculomotor signals to downstream areas. Even if we limit ourselves to neurons that project downstream in the eye movement system it is unlikely that all of the remaining neurons that project to oculomotor control areas display retina-centered signals. The recent study by Horowitz and colleagues showing that object-centered selectivity is seen in both the SEF and in the superior colliculus provides indirect evidence that the SEF may send object-centered signals to the superior colliculus (Horwitz et al. 2004b). The implication of this observation is that the SEF may output signals that are not strictly retina-centered in nature, relieving the SEF of the requirement that its neurons represent locations in retina-centered space.

5.2.3.3. Aim 1: Conclusions

Ultimately, our data point to the conclusion that the SEF contains neurons that perform many functions in representing locations in different reference frames. Neurons represent only retina-centered locations, only object-centered locations, and multiple types of combinations of the two. In some cases, these combinations are nonlinear. In these cases, we provide experimental support for the numerous computational models of nonlinear reference frame interactions. In other cases these combinations are linear, and the existence of this type of interaction challenges the assumptions made by the majority of these models. In other cases, we find that there is no interaction but, instead, neurons only represent object-centered locations. These neurons also challenge the assumptions of the computational models. We propose that, rather than using a single function to explain the response properties of all neurons in the SEF in the same way, it is far more valuable to examine neurons as members of separate, interrelated circuits, each with different, though possibly overlapping, functions.

5.3. Aim 2: The effect of learning on object-centered signals in SEF neurons

5.3.1. Summary of results

5.3.1.1. New results concerning innate selectivity for object-centered location

Few neurons are selective for color during performance of the color DMS task. Approximately 10% of the recorded neurons were selective for color. This small percentage of color selective neurons is similar to that observed in previous work from our laboratory

(Tremblay et al. 2002), and suggests that, even when monkeys only perform a task in which color is the factor that must be attended to for correct performance, few SEF neurons encode color.

More neurons are selective for retina-centered target location. Approximately 30% of the recorded neurons were selective for the retina-centered location of the target. This finding is expected, given the results from Aim 1 as well as from numerous other studies investigating the retina-centered selectivity of SEF neurons.

A significant number of neurons are selective for object-centered target location. Approximately 25% of the recorded neurons were selective for the object-centered location of the target. This finding supports the hypothesis that SEF neurons exhibit, to some degree, innate object-centered selectivity before monkeys learn to follow an object-centered rule. This percentage of significantly object-centered neurons, while in line with the results of those by Tremblay et al. (2002), is quantitatively different: Tremblay and colleagues found that closer to 50% of the neurons recorded during performance of the color DMS task showed object-centered selectivity, almost double the proportion that we observed. Comparing the results from the two studies, therefore, we are in a position to state that some SEF neurons inherently display object-centered selectivity before any type of object-centered training, but that this proportion of neurons is lower that those seen in previous studies studying monkeys trained on the object-centered task.

5.3.1.2. Results concerning the effect of training on object-centered selectivity

Training induces a dramatic increase in the incidence of object-centered selectivity. Up to 46% of the recorded neurons showed object-centered selectivity after training. This proportion is

more similar to that observed by Tremblay et al. (2002), supporting the conclusion that the high degree of object-centered selectivity observed in their tasks was a product of having trained the monkeys to perform object-centered tasks.

Training induces a decrease in the incidence of retina-centered selectivity. Along with an increase in object-centered selectivity, we simultaneously saw a decrease in proportion of neurons selective for retina-centered selectivity to approximately 20%, as seen in Fig. 23. This decrease in retina-centered selectivity is interesting for two reasons. First it supports the fact that our observation of an increase in object-centered selectivity following training was valid and not simply a product of recording from more task-related neurons in this stage. If the latter explanation was the case, we would expect to see more neurons selective for retina-centered locations as well. Second, the decrease is a new finding relating to the capacity for neurons to represent locations in multiple reference frames. The increase in object-centered representation in SEF neurons appears to come at the expense of retina-centered selectivity, suggesting that there are limited resources for representing locations and that when the use of one reference frame is emphasized, the neural representation of other reference frames is diminished.

5.3.1.3. Results comparing selectivity before and after training

Object-centered selectivity is stronger following training. Using an index-based measure of object-centered strength for each neuron, we observed a significant increase in the strength of object-centered selectivity following training on an object-centered task. These results are in line with the observation of an increased number of neurons showing significant object-centered selectivity following training.

More neurons show selectivity for the location of the target on the bar following training. Using a regression analysis designed to dissociate true object-centered selectivity from selectivity for the location of the bar on the screen, we found that an approximately equal number of neurons showed selectivity for the target location on the bar and for the bar location on the screen before learning, whereas after learning the distribution was significantly biased towards representing the location of the target on the bar. This is the first time that a comparison of this nature has been performed, and the results of this analysis imply that some of the neurons that our statistics describe as exhibiting significant object-centered selectivity before training may be, in reality, showing retina-centered selectivity for the location of the bar on the screen.

5.3.2. Relationship of Aim 2 to studies of object-centered selectivity

The results of the main three measurements reported in this study all point to the same conclusions. Some SEF neurons exhibit significant selectivity for object-centered locations before any type of training on an object-centered task. These neurons may have an innate tendency towards representing space in an object-centered reference frame, whether as a product of neural architecture or as a product of previous experience. However, neurons exhibiting object-centered selectivity following training on an object-centered task are more numerous, show a higher degree of selectivity, and tend to show object-centered selectivity that is less tainted by a signal representing the location of the bar in retina-centered coordinates. Previous studies of object-centered selectivity have not been able to address this issue given that, in all cases, neurons were recorded following extensive training on an object-centered task (Olson and Gettner 1995, 1999; Olson and Tremblay 2000; Tremblay et al. 2002). Not surprisingly given our results, all of these studies found a preponderance of object-centered-coding neurons in the

SEF upon recording from the trained animals. Does this finding mean that instances of object-centered encoding by SEF neurons observed in these previous studies was simply a training effect, and that SEF neurons could conceivably acquire selectivity for any task-relevant dimension? Two arguments suggest that the answer to these questions is no. First, we observed an small but significant proportion of neurons selective for object-centered locations before training, suggesting that there is some inherent tendency for SEF neurons to represent space in this reference frame. Second, as will be discussed below, SEF neurons do not acquire selectivity for any task-relevant dimension, most notably color. The results of our study have shown, therefore, that the learning-induced plasticity in SEF neurons is specific to specific types of task parameters, in particular, spatial reference frames.

As a related point that is not specific to object-centered reference frames per se, these results suggest a mechanism to potentially explain how multiple groups have observed neuronal activity related to different egocentric reference frames in SEF neurons (see section 1.6.3). If training on a task using a specific reference frame can induce selectivity for that particular reference frame, it is possible that previous observations of exclusively head-centered or eye-centered selectivity in SEF neurons may have been a product of extensive training on the use of one reference frame or another. This hypothesis, of course, would require further testing to validate.

5.3.3. Relationship of Aim 2 to studies of sensorimotor learning

5.3.3.1. Learning-related signals in the dorsomedial frontal cortex

That we observed learning-related changes in our study makes our findings similar to previous reports of learning-induced changes in SEF neurons, with a number of important

differences. A series of studies by Chen and Wise found that the activity (Chen and Wise 1995a, b), and directional selectivity (Chen and Wise 1996, 1997) of SEF neurons changed over the course of learning to associate visual stimulus patterns with saccade directions. Critically, our results differ from those observed by Chen and Wise in a fundamental way. As noted in section 3.4.6, the changes in neuronal activity and spatial selectivity described by Chen and Wise to be associated with learning do not actually reflect any learned parameter of the task, that is, their neurons did not develop selectivity for visual patterns independent of saccades. While these signals may have some function in or as a reflection of the learning process, they could also reflect something as simple as changes in arousal over the course of learning. Similarly, the changes in the strength of directional selectivity in these neurons can be described as a basic enhancement of the directional signals that are correlated with the monkeys decision to make saccades in certain directions: as the monkey learns in which direction to make a saccade, saccade related neurons selective for that direction are activated, as would be expected from saccade-controlling neurons in the SEF. We can conclude from the results of Chen and Wise that signals exist in the SEF that may contribute towards task learning, or may reflect the process of task learning. Our data, on the other hand, are the first to show that SEF neurons acquire a novel representation, specifically that of locations in an object-centered reference frame, or at least massively enhance it, as a direct consequence of learning.

Other studies have further emphasized the plastic nature of SEF neurons. A report by Mann and colleagues showed that the activity of neurons in the broadly-defined dorsomedial frontal cortex (DMFC), which contains the SEF, exhibit a high degree of context-dependency (Mann et al. 1988). Following extensive training of monkeys to direct saccades to specific target locations, microstimulation of the DMFC resulted in a preponderance of saccades directed to

those specific locations, as though the response fields of DMFC neurons had gravitated towards those learned locations. These results are subject to a certain degree of scrutiny, however, as Tehovnik and Slocum failed to replicate them in a more rigorous study (Tehovnik and Slocum 2000). Mann and colleagues also reported that single neurons changed their response properties depending on task requirements. For example, many neurons initially fired before monkeys made a saccade to receive reward. When a second saccade was added to the task, the neurons reduced their firing preceding the first saccade and increased their firing immediately before the execution of the second saccade. Some saccade-related neurons even lost their saccade-related activity and developed selectivity for arm-reaches when arm-reaches were introduced as rewarded components of the task. These results differ from ours in that they do not show an induction of new responses with learning. SEF neurons have been shown to respond during arm movements (Fujii et al. 2002; Mushiake et al. 1996), and exhibit activity related to the receipt of reward (Amador et al. 2000; Stuphorn et al. 2000b). While the results of this study reveal the innate diversity of the response properties of DMFC neurons, they do not show, as we have shown, that SEF neurons acquire new response properties as a consequence of training.

Learning to perform new tasks has also been reported to elicit modulation of the activity of neurons in areas of the DMFC outside the SEF. Studies of the supplementary and presupplementary motor areas have shown that neurons either increase or decrease task-related activity during the learning of a motor sequence task (Nakamura et al. 1998). Neurons of the supplementary motor area have also been shown to exhibit less task-related activity following extensive training on a motor task (Aizawa et al. 1991). These results are different from our results in that they do not show the development of selectivity for a learned task parameter, such as a spatial reference frame. They are more similar to the results of Chen and Wise, in that they

show increases or decreases in neuronal activity that signal whether tasks are novel or familiar, thus reflecting the process of learning. However, considering our results along with those described before, it does seem clear that the SEF, and quite possibly supplementary motor areas in general, are clearly affected by and are likely involved in the learning of new behavioral tasks.

Exactly how the activity of SEF neurons may acquire new response properties through learning is not entirely clear at this point. A number of lines of evidence imply that the SEF may receive an important conjunction of learning-related signals that may contribute to learning-related changes seen in individual neurons. In a study of response inhibition by Stuphorn and colleagues, different SEF neurons were shown to fire when monkeys correctly inhibited a saccade, when monkeys erroneously failed to inhibit a saccade, and when monkeys received reward for correct performance (Stuphorn et al. 2000b). Other laboratories have reported the existence of reward-signaling neurons in the SEF (Amador et al. 2000; Mann et al. 1988). Furthermore, the anterior cingulate cortex, an area with strong connectivity to the SEF (Huerta and Kaas 1990; Luppino et al. 2003), has been shown to contain a significant number of neurons exhibiting error-and reinforcement-related signals during performance of the countermanding task (Ito et al. 2003). Additionally, it has been shown that there are strong projections from the brainstem areas A8-A10 to regions of the DMFC including the SEF (Berger et al. 1988; Gaspar et al. 1992; Lewis et al. 1987; Williams and Goldman-Rakic 1993, 1998), the dopaminergic signal of which has been proposed to be critical in the learning process (e.g., Schultz 2002). These different types of signals (correct performance, incorrect performance, and reward) could conceivably sculpt the response properties of SEF neurons that control different types of behavior. So over the course of learning to perform an object-centered task, for example, a conjunction of these signals that signal correct object-centered performance could strengthen

circuits related to object-centered processing and weaken circuits related to retina-centered processing, resulting in the increases and decreases of these types of signals that we have observed in individual neurons. This hypothesis, however, is highly speculative and would require considerably more examination to verify.

5.3.3.2. Learning-induced task parameter representations in single neurons

Learning-induced changes more similar to the type that we have observed in the SEF have been reported in neurons of many areas outside of the supplementary motor areas. In contrast to the majority of studies in supplementary motor areas described above, there are a number of reports of instances in which neurons acquire, through training, response properties that are not innately present in neurons of these areas, similar to what we have observed with object-centered signals. For example, Toth and Assad showed that, by training monkeys to perform a color-conditional saccade task, neurons in LIP develop a selectivity for color that is independent of the associated saccade direction (Toth and Assad 2002). A similar degree of color selectivity was observed by Bichot and colleagues in recording from the FEFs of monkeys performing a task in which targets must be selected on the basis of their color (Bichot et al. 1996). Horwitz et al. found that, following training on a task pairing a motions stimuli with saccades, neurons in the superior colliculus developed selectivity for the motion stimuli even while the monkeys passively fixated (Horwitz et al. 2004a). Induction of response properties related to different stimulus modalities have even been observed. Grunewald and colleagues reported a significant increase in the number of LIP neurons responsive to auditory stimuli during passive fixation following training on a task in which auditory stimuli were associated with saccades (Grunewald et al. 1999).

These examples might lead one to the conclusion that sensorimotor neurons are generally malleable, able to develop selectivity for any important task stimuli. The results of the current study, however, argue against this claim. During the color DMS task, we found that a relatively small proportion of our neurons displayed selectivity for color. If SEF neurons developed selectivity for any relevant task parameter, we would expect to see a considerably higher degree of color representation during the color DMS task, in which color was critical for task performance. Instead, this small proportion of color-selective neurons was drastically outweighed by the proportion of neurons showing increased object-centered selectivity and decreased retina-centered selectivity following object-centered training. Thus, SEF neurons are not generally plastic, acquiring selectivity for any task relevant parameter. Instead, they seem to be specifically receptive to learning-induced changes that are related to the use of a particular spatial reference frame. Based on our results and those of others, we are confident in asserting that neurons of the SEF exhibit a high degree of learning-related plasticity, but that this plasticity is biased towards spatially- or behaviorally- related task components such as spatial reference frame.

5.4. Aim 3: Automatic encoding of object-centered space in SEF neurons

5.4.1. Summary of results

Neurons show equal object-centered selectivity in both tasks. Approximately one-third of the recorded neurons exhibited object-centered selectivity in both the object-centered task and in the color DMS task. These results are similar to those observed by Tremblay and colleagues while monkeys performed interleaved trials of both tasks (Tremblay et al. 2002). This finding

shows that the presence of object-centered selectivity on non-object-centered tasks is not a result of some kind of object-centered hysteresis effect whereby the object-centered signal seen during performance of the color DMS task is due to its temporal proximity to the object-centered task. Rather, the existence of object-centered selectivity is strong in any task in which targets are located on an object, and this selectivity persists whether or not the acquisition of these targets require the use of an object-centered rule.

Neurons show less retina-centered selectivity than object-centered selectivity. Approximately 20% of the neurons showed significant retina-centered selectivity on both tasks. This result, unreported in the study of Tremblay et al., confirms the observation, made in Aim 2, that a increase in object-centered spatial selectivity appears to coexist with a decrease in retina-centered spatial selectivity.

Neurons show an equal degree of bias for signaling the location of the target on the bar. In both tasks, neurons tended to show stronger selectivity for the object-centered location of the target on the bar as opposed to the retina-centered location of the bar on the screen. While this analysis was not performed in the study of Tremblay et al., it is in accord with the conclusions of the study. Furthermore, the selectivity bias for both tasks is more akin to that shown following learning in Aim 2. We conclude that, following object-centered training, SEF neurons reliably signal object-centered location, even during performance of the color DMS task.

Object-centered selectivity is correlated across tasks, but is stronger in the object-centered task. There was a significant correlation in the strength of object-centered selectivity between the two tasks, based on statistical and index measures. The strength of object-centered selectivity was significantly higher during performance of the object-centered task than during performance of the color DMS task, however. Similar results were reported in the study of

Tremblay et al, but the difference in strength across tasks was somewhat less than what we observed. We can conclude from the results of both studies that, once monkeys learn to perform an object-centered task, object-centered selectivity is largely preserved in tasks in which objects are present but object-centered rules need not be followed. However, this conclusion is not absolute and is subject to the caveat that performance on an object-centered task tends to upregulate the strength of object-centered selectivity.

Object-centered selectivity strength does not change gradually over the course task performance. We analyzed whether the strength of object-centered selectivity changed gradually over the course of a series of trials or whether the change was instantaneous between tasks. Our results suggest the latter mechanism: during performance of one task or the other, the strength of object-centered selectivity maintained a consistently high (in the object-centered task) or low (in the color DMS task) level until the end of the task, at which point it shifted almost immediately. This issue could not be addressed directly by the use of interleaved task types in the study of Tremblay et al. However, the fact that the authors saw slightly higher object-centered selectivity during the performance of object-centered tasks that were interleaved with color DMS tasks is in agreement with our results in that they imply that the transition from high to low object-centered selectivity strength may have occurred on a rapid, trial-to-trial time basis.

Color selectivity results from the association between color and object-centered location. We asked whether the neurons selective for object-centered location also showed selectivity for the color associated with that object-centered location, as defined in the object-centered task. We found two examples of this persistence of association. First, we found a trend whereby neurons showing significant object-centered selectivity during the pre-bar-onset delay epoch of the object-centered task tended to show significant color selectivity during the pre-bar-onset

epoch of the color DMS task. Second, we found a significant and positive correlation between the strength of object-centered selectivity during the pre-bar-onset epoch of the object-centered task and the strength of color selectivity during the pre-bar-onset epoch of the color DMS task. These two results provide quantitative evidence that neurons exhibiting object-centered spatial selectivity also display color selectivity, presumably for the color associated with the neuron's preferred object-centered location in the object-centered task.

We validated that the selectivity for color was, indeed, largely due to an association between color and object-centered location by constructing a population histogram consisting of the activity of all neurons showing significant object-centered selectivity during performance of the color DMS task. Data were sorted by color and object-centered location (Fig. 38). Focusing on the pre-bar-onset epoch, we observed an increased degree of selectivity whereby neurons that fired more strongly for a particular object-centered location also fired more strongly for the color associated with that object-centered location.. Of note is the fact that this occurs 1) during performance of the color DMS task in which there is no connection between color and object-centered location and 2) during the pre-target-onset epoch, before the monkey knows where the target will appear (either in object-centered or retina-centered coordinates). The signals that we observe, therefore, are clearly the neural representation of the abstract association between color and object-centered location, persisting despite the requirement for this association, and even in the absence of a spatial target. This effect was not reported in the study by Tremblay et al. (2002) as, in this study, the color of the cue was never correlated with object-centered location. A previous study from our laboratory did show that object-centered selectivity could be elicited by the presentation of a color cue (Olson and Gettner 1999), but in this study color and object-centered location were never uncorrelated as they were in our color DMS task. Thus we have

shown, for the first time, a signal related to the association between color and object-centered location that persists outside of the task in which the association has been made.

Incongruity between color and object-centered location increases activity. We found a second manifestation of the neural basis of the association between color and object-centered location. As can be seen in Fig. 38, following the onset of the bar in the color DMS task, trials in which the color associated with one object-centered location was placed at the other end of the bar (incongruent trials) elicited a greater response than did cases where the color and object-centered locations were aligned (congruent trials). This effect is similar to that observed in the report by Tremblay et al. (2002). In addition to being another example of the neuronal encoding of abstract color-location associations (as above), this result also shows that SEF neurons fire more robustly under conditions in which this association is broken, resulting in conflict or increased task difficulty. This interpretation fits well within much of the literature suggesting that SEF neurons are more active during difficult or conflicting task conditions (Nakamura et al. 2004; Olson and Gettner 2002; Schlag-Rey et al. 1997; Stuphorn et al. 2000b) and extends the observations of these studies to apply to more abstract associations such as those made between a color and a location in object-centered space.

5.4.2. Comparison of the results in Aim 3 with the results in Aim 2: Task learning and task exposure affect reference frame representation

By comparing the results from Aim 2 with Aim 3, we can address the question of whether learning an object-centered rule results in a permanent induction of object-centered neuronal selectivity or whether the strength of this selectivity can vary based on duration of exposure to an object-centered task. The results shown in Fig. 39 suggest that both parameters

influence the degree of object-centered and retina-centered spatial representation in SEF neurons. In Fig. 39, the proportion of neurons exhibiting significant object-centered selectivity is highest following learning the object-centered task (stage 2), and declines slightly during performance of the current task. During stage 2, the monkeys had learned to perform the object-centered task and, in doing so, spent multiple days performing only the object-centered task. Both of these aspects of stage 2 contributed to the observation of a large number of neurons exhibiting significant object-centered selectivity. In comparison, during performance of the current tasks, the monkeys, having previously learned to perform the object-centered task, now performed multiple blocks of first the color DMS task and then the object-centered task (or vice versa) each day, diluting the constant requirement of the use of an object-centered rule. Consequently, the total proportion of object-centered neurons stays high, as a result of learning, but dips slightly during performance of the current task. We can conclude that object-centered selectivity is a learning-induced phenomenon, as shown by the increase from stage 1 to stage 2, but is also subtly modulated by prolonged exposure to the use of an object-centered rule, as shown by the decrease from stage 2 to the current task. Similar effects are seen when comparing the strength of the object-centered signal across neurons and when comparing the proportion of neurons signaling the location of the target on the bar as compared to the location of the target on the screen.

Fig. 39 also shows the decrease in selectivity of neurons exhibiting retina-centered selectivity across the different stages of recording. In this case, we see an effect opposite to that of object-centered selectivity: as the proportion of neurons selective for object-centered location increases as a result of learning, the proportion of neurons showing selectivity for retina-centered location decreases. Furthermore, as the proportion of neurons selective for object-centered

selectivity dips during performance of the current tasks, the proportion of neurons selective for retina-centered selectivity rises slightly. We can conclude from these results that SEF neurons may exhibit a balanced degree of signaling in particular reference frames: when more neurons encode locations in one particular reference frame, fewer neurons encode locations in the other. At first glance, this result seems at odds with the results from Aim 1, in which many neurons were shown to exhibit strong retina-centered selectivity during performance of the bar task. However, it must be remembered that, during the performance of the bar task in Aim 1, monkeys performed interleaved trials of the dot task, necessitating the intermingled use of both retina-centered and object-centered reference frames. In stage 2 of Aim 2 and in Aim 3, the monkeys performed the bar tasks (color DMS or object-centered) in the absence of performance of any kind of dot task. As such, we are not surprised to see a repression of retina-centered selectivity, since the use of this reference frame was not required for successful task completion. This decrease in retina-centered selectivity has been, until now, unreported, and is potentially an important correlate to the rise in object-centered selectivity with training. We propose, based on these results, that when monkeys perform tasks requiring the exclusive use of a particular reference frame, SEF neurons display a heightened representation of locations in that reference frame at the expense of representation of locations in other reference frames. Since our study was not designed to test this hypothesis, we can not say exactly why or how this occurs. However, the changes observed are dramatic, and suggest that the rules governing spatial representation in the SEF are more complicated than a simple simultaneous representation in multiple reference frames.

5.4.3. Why do SEF neurons encode object-centered location when it is not task-relevant?

In the current study, we found that object-centered selectivity persists in the activity of SEF neurons for extensive periods of time even during the color DMS task, in which object-centered selectivity is not relevant for correct task performance. This can be seen in the relatively large proportion of neurons showing significant object-centered selectivity following the onset of the target bar. We are now faced with the question of why SEF neurons would encode object-centered locations in the color DMS task. During performance of the object-centered task, object-centered spatial representation is critical, as no other information is available to guide the saccadic response. During performance of the color DMS task, however, there is no need for object-centered representations: the brain could simply calculate the retina-centered location of the colored target and direct a saccade to that location. Given the lack of need for an object-centered representation, we are left with two possible explanations for its presence. During performance of the color DMS task, 1) a bar was present in the display, and 2) the monkeys directed saccades to the targets located on this bar. One possible explanation for object-centered activity in the color DMS task is that SEF neurons are involved in planning saccades to object-centered locations even when the use of an object-centered reference frame is not required. Under this explanation, saccades directed to objects automatically encode the behavior in an object-centered reference frame. Another possible explanation is that the object-centered representation seen in SEF neurons has less to do with the programming of a saccade to object-centered locations and more to do with the awareness of, or direction of attention to, object-centered locations. Under this explanation, each time an object is displayed, multiple neurons representing multiple object-centered locations would automatically become active

creating, in essence, a reference map of object-centered space that could be used in directing behavior, but is independent of any particular behavioral response. To some degree, the results from Aim 2 support the second explanation: following training, the monkeys performed the same types of eye movements, but we saw an increase in object-centered neural representation. However, this conclusion is still somewhat speculative, given that a) some neurons showed object-centered selectivity when saccades were directed to bar targets before training and b) some other aspect of behavior that we did not measure could have produced the change in spatial selectivity. To truly distinguish between the two possibilities, one would like to test for object-centered selectivity using non-oculomotor tasks. However, our data do show that the presence of an object on the screen automatically triggers an object-centered spatial representation in SEF neurons, even when this representation is not necessary to guide behavior. Whether this representation is dependent on the execution of an object-centered behavior remains to be seen.

5.5. Separate circuits for egocentric and object-centered spatial reference frames?

The studies presented here have shown that SEF neurons represent spatial locations using both egocentric and object-centered coordinate systems. As noted in the introduction, neurons exhibiting forms of object-centered selectivity have been seen in multiple areas throughout the brain, suggesting that there may be distinct neural circuits through which information related to object-centered spatial representations may be generated, propagated, and employed for guiding behavior. Surveying the neuronal data, we find that a number of visual cortical areas contain neurons that show object-centered selectivity for object-parts (V1, V2, V4), or show selective activity for particular objects irrespective of a number of retina-centered changes to the object, such as changes in retina-centered location or scale (IT, STS). Populations of neurons whose

representations of an object are invariant to retina-centered changes could form the foundation of an object-centered map to which neurons in the SEF may refer so as to compute precise locations related to the object. While neurons in IT are not directly connected to the SEF, neurons in the superior temporal cortical areas are, most notably anterior areas in the superior temporal sulcus (Luppino et al. 2001), in which neurons exhibit complex response properties related to object-stimuli (Ashbridge et al. 2000; Bruce et al. 1981; Eifuku et al. 2004; Hasselmo et al. 1989; Perrett et al. 1989; Perrett et al. 1991). Additionally, neurons in IT project both to the FEF (Bullier et al. 1996) and to areas in the prefrontal cortex (Webster et al. 1994), both of which have been shown to exhibit a high degree of connectivity with the SEF (Huerta and Kaas 1990; Schall et al. 1993). SEF also displays retina-centered response properties, the information about which could be acquired from a number of visuomotor areas such as LIP or FEF, both of which contain neurons that encode locations in (sometimes gain-modulated) eye-centered coordinates (Andersen et al. 1990a; Brotchie et al. 1995; Colby et al. 1995; Duhamel et al. 1992; Goldberg and Bruce 1990; Schall 1991a; Snyder et al. 1998). Furthermore, given that neurons in parietal area 7a appear to exhibit object-centered selectivity (Chafee et al. 2005), we might propose that a conjunction of retina-centered and object-centered signals are sent from the parietal cortex to the SEF. It is not surprising, therefore, that an area such as the SEF, with such a high degree of connectivity to visuomotor structures, could be centrally situated to integrate both egocentric and object-centered signals. As noted in section 5.2.3.2, this integration may not simply be a transformation from an object-centered input to a retina-centered output, as it has been observed that superior colliculus neurons, to which the SEF sends projections, also exhibit object-centered selectivity (Horwitz et al. 2004b). Judging from a relatively simple overview of the neuronal data alone, we see that the SEF may be the site of conjunction of a two widespread networks:

one involved in representing locations in object-centered coordinates and one involved in representing locations in egocentric coordinates.

The idea that SEF receives separate object-centered and retina-centered information from parietal and occipital cortex aligns well with the idea that damage to different cortical areas produces either egocentric or object-centered visuospatial neglect. The recent results of Hillis and colleagues are particularly informative in this regard (Hillis et al. 2005). The finding of Hillis et al. that object-centered neglect tends to stem from more ventral structures such as the superior temporal cortex, while egocentric neglect stems from damage to the inferior parietal lobule strongly suggests that these two reference frames may be separable based on anatomical grounds. Consequently, it is not surprising that damage to both ventral structures such as the superior temporal cortex (e.g., Karnath et al. 2004; Karnath et al. 2001) and dorsal structures such as parietal cortex (e.g., Behrmann et al. 2004; Vallar et al. 2003) results in neglect. A simple correlation between these neglect results and the results of single unit data in monkeys, however, is complicated by interpretations of homology between monkey and human neuroanatomy. For example, lesions to the monkey superior temporal sulcus produced instances of egocentric neglect (Watson et al. 1994), leading Hillis and colleagues to propose that the angular gyrus in humans (where damage produced egocentric neglect) is analogous to the superior temporal sulcus in monkeys. Further study is required to determine whether the dichotomy seen by Hillis et al (2005) can be reproduced in single unit or lesion studies in monkeys.

Finally, the idea of different circuits for different reference frames may support the finding that neurons in LIP rarely encode locations in object-aligned or object-centered space (Sabes et al. 2002). It is possible that the SEF may receive object-related signals from ventral

visual areas (and area 7a) and retina-centered signals from intraparietal visuomotor areas, relieving areas such as LIP from the requirement of object-centered representation. An obvious next step is to search for object-centered signals in ventral areas such as the STS, using similar tasks to those employed in studies of the SEF.

5.6. Conclusion: The role of the SEF in spatial cognition

Virtually every study of how SEF neurons encode locations in space has used eye movements as the means of reporting the spatial location. This applies equally to studies investigating object-centered and egocentric spatial representation. An obvious question arises as to whether the spatial selectivity observed in SEF neurons a strictly a component of oculomotor control. There appear to be lines of evidence supporting the role of the SEF in oculomotor behavior (such as anatomical connectivity with oculomotor structures and the reliable ability to elicit saccades with low threshold microstimulation) and in extra-oculomotor behavior (such as the ineffectiveness of SEF inactivation to compromise saccade generation and the numerous studies showing single cell responses completely unrelated to the programming of eye movements). We believe that the SEF plays at least as much of a role in general visuospatial cognition as it does in the generation and control of eye movements. By dissociating object-centered location from saccade direction as we have done in the bar task, we show that neuronal activity in SEF neurons is related less to the programming of saccades and more to the representing of spatial locations that can be used by to guide of behavior. In addition, the facts that 1) object-centered selectivity is induced or enhanced with learning in the absence of any major changes in eye movement control and 2) object-centered selectivity is present even when it is not required to direct accurate saccadic behavior, suggest that object-centered neuronal

responses are less like motor-control signals and more like signals related to general spatial awareness. Obviously these claims can and should be tested using paradigms other than the delayed saccades, such as arm reaches or lever releases. Whether the results point to a dependence on oculomotor behavior or not, however, our results allow us to state with certainty that one of the major roles of neurons in the SEF is to flexibly encode locations using multiple spatial reference frames.

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