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[−] **Abstract and Keywords**

Damage to the human inferior parietal lobe produces an attentional disturbance known as contralateral neglect, and neurophysiological studies in monkeys have begun to unravel the cellular basis of this function. Converging evidence suggests that LIP encodes a sparse topographic map of the visual world that highlights attention-worthy objects or locations. LIP cells may facilitate sensory attentional modulations, and ultimately the transient improvement in perceptual thresholds that is the behavioural signature of visual attention. In addition, LIP projects to oculomotor centres where it can prime the production of a rapid eye movement (saccade). Importantly, LIP cells can select visual targets without triggering saccades, showing that they implement an internal (covert) form of selection that can be flexibly linked with action by virtue of additional, independent mechanisms. The target selection response in LIP is modulated by bottom-up factors and by multiple task-related factors. These modulations are likely to arise through learning and may reflect a multitude of computations through which the brain decides when and to what to attend.

Keywords: attention, parietal, saccade, learning

Introduction

SINCE the nineteenth century, neuropsychological evidence has suggested that the parietal cortex is important in spatial attention. Patients with damage to the parietal lobe can develop the syndrome of *neglect*, a specific inability to notice sensory stimuli in the contralateral space. A milder form of the disease is that of *extinction* or *perceptual rivalry*, where patients can perceive a contralateral object when it is presented alone but, if presented with two objects simultaneously tend to choose the ipsilateral one. Accompanying their attentional deficits, patients with parietal lesions can also have *optic ataxia*, difficulty looking at or reaching contralateral targets. These syndromes suggest that the parietal lobes are important for linking perception and action, and specifically in assigning importance (or 'interest') to the contralateral space (see also Vallar and Bolognini, chapter 33, this volume).

This view of the parietal lobe emerging from neurological studies is upheld in neurophysiological work in monkeys. Based on anatomical and physiological evidence, the monkey parietal lobe has been subdivided into two broad sectors that lie dorsal and ventral to the intraparietal sulcus (IPS) and are called the superior and inferior parietal lobes (SPL and IPL) (Fig. 1). Areas within the SPL are responsive primarily to touch (somatosensation) and skeletal (limb) movements and represent the near peripersonal space (Colby and Goldberg 1999), while areas in the IPL respond to visual inputs and movements of the eyes and head and represent the farther visual space (Colby and Goldberg 1999).
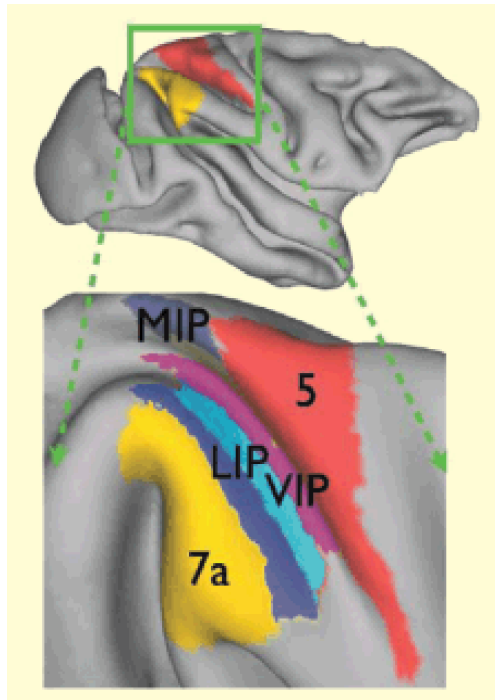
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Figure 12.1 The parietal lobe in the monkey. Lateral view of the rhesus monkey brain indicating the approximate location of individual parietal areas. The IPL is located ventral and posterior to the intraparietal sulcus and includes areas 7a, LIP (the lateral intraparietal area, ventral and dorsal divisions) and VIP (ventral intraparietal area). The SPL is located dorsal and medial to the sulcus and includes area 5 and the medial intraparietal area (MIP). Reprinted from *Current Opinion in Neurobiology*, 20 (6), Jacqueline Gottlieb and Lawrence H. Snyder, Spatial and non-spatial functions of the parietal cortex, pp. 731–40, Copyright (2010), with permission from Elsevier.

The IPL, which has been most intensively studied in relation to attention, is further subdivided into three areas. Area VIP (the ventral intraparietal area) lies in the fundus of the IPS and is a transitional area that responds to both visual and somatosensory stimulation. VIP neurons have bimodal receptive fields (RF) on the upper body and face (Colby et al. 1993). Area 7a is a visual area that covers the cortical convexity lateral to the IPL and conveys information about full-field visual motion, visual salience, and eye position (Constantinidis and Steinmetz 2005; Raffi and Siegel 2005). Finally the lateral intraparietal area (LIP) is a small area in the lateral bank of the intraparietal sulcus that has strong ties to the oculomotor system.

As will become clear in this chapter, area LIP has been intensively investigated and is believed to reflect internal processes related to attention, learning, and decision formation. LIP receives visual inputs from the lateral pulvinar thalamic nucleus and from cortical areas in the dorsal and ventral visual streams, and has strong anatomical connections to two oculomotor areas—the frontal eye fields (FEF) and the superior colliculus (SC) (Blatt et al. 1990; Lewis and Van Essen 2000). LIP neurons have visual RF located mostly in the contralateral hemifield and respond to small stimuli that drive attention and shifts of gaze (Blatt et al. 1990). This chapter will focus on physiological studies that explore the function of this area with respect to attention and eye movement control.

Adaptive Spatial Representation

Although LIP contains several types of cells, the vast majority of studies have focused on neurons that have visual receptive fields (RF)—i.e. respond to visual inputs in a limited range of retinal locations. In terms of its layout in the IPS the retinotopic map in LIP has only a coarse organization, and adjacent neurons can respond to disparate retinal locations (Ben Hamed and Duhamel 2002; Ben Hamed et al. 2002). Nevertheless, by virtue of their RF the neurons convey spatial information, encoding the location of objects in the external world.

The spatiotopic map in LIP is distinguished from maps in earlier visual areas by several characteristics. First, LIP

neurons encode not the mere presence of a visual input but are strongly modulated by the salience or behavioural significance of that input. Second, even though the RF of LIP neurons are retinotopic (meaning that they move relative to the external world each time the eye moves) neurons maintain an accurate memory of salient locations across shifts of gaze. And third, the visual responses that are encoded in LIP can be quite complex and are modulated by a variety of behavioural ('extraretinal') factors.

A good illustration of the sensitivity of LIP neurons to salience and behavioural significance comes from an experiment that trained monkeys to make eye movements across a stable visual scene (Gottlieb et al. 1998). A circular array containing several objects remained stable on the screen (Fig. 2, top cartoon). On each trial the monkey looked at (fixated) a peripheral location (FP1) where no array stimulus was in a neuron's RF (labelled RF1 in the cartoon) and then made a saccade to a central location (FP2) that brought the RF onto a portion of the stable array (RF2). This mode of presentation emulates natural viewing conditions, where stimuli are stable and inconspicuous in their environment but move on the retina by virtue of the observer's motion.

In one variant of this task, all eight stimuli remained stable and unchanging for a long block of trials, and one of these stimuli entered the RF by virtue of the monkeys' saccade. In a second variant, the visual stimulation to the neurons' RF was identical, except that the stimulus entering the RF was rendered salient by abruptly appearing and disappearing on each trial.

Even though the visual stimulation to their RF was identical in both cases LIP neurons distinguished between the stable and recent-onset contexts. Neurons had barely any response when a stable stimulus entered their RF (Fig. 2, left) but responded exuberantly if the same object had recently flashed on (Fig. 2, right). Note that this visual response arose even though the stimulus onset had occurred before the saccade and outside of the neuron's RF; thus, the neuron responded after the saccade as if it had 'remembered' the salient event that occurred before the saccade. Thus LIP neurons have a remarkable ability to filter out most objects in rich visual scenes and selectively respond to salient locations, and they track these locations across shifts of gaze.
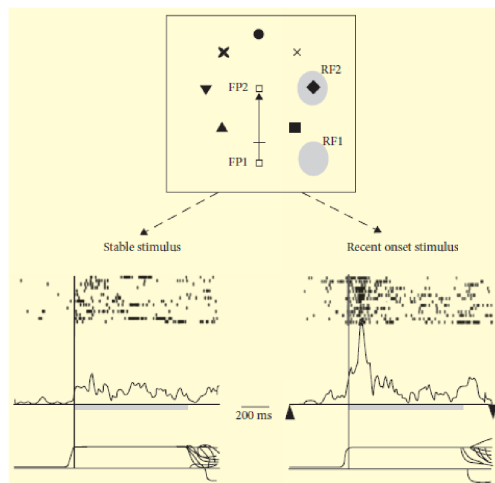
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Figure 12.2 LIP neurons respond selectively to salient events. The top cartoon shows the experiment design. A circular object array was continuously present on the screen. The monkey began each trial by looking at an initial fixation point (FP1), chosen so that the RF of the neuron under study was on a blank visual location (RF1). The fixation point then jumped to the centre of the array (FP2) and the monkey made a saccade to it (arrow). This saccade brought the neuron's RF onto one of the array objects (RF2). The bottom panels show the activity of one LIP neuron. Raster plots show the times of individual action potentials relative to the saccade that brings the stimulus in the RF (marked by the vertical bar). Traces underneath the rasters show average firing rate across trials. Bottom traces show the horizontal and vertical eye position, superimposed for multiple trials. The neuron had only weak activation if the stimulus entering its RF was stable for a long period of time (left). In contrast the neuron responded strongly if the same stimulus had been rendered salient by virtue of an abrupt onset (right). Adapted by permission from Macmillan Publishers Ltd: *Nature* 391 (6666) Gottlieb, J. P., Kusunoki, M., and Goldberg, M. E., The representation of visual salience in monkey parietal cortex, pp. 481–4 copyright, 1998, Nature Publishing Group.
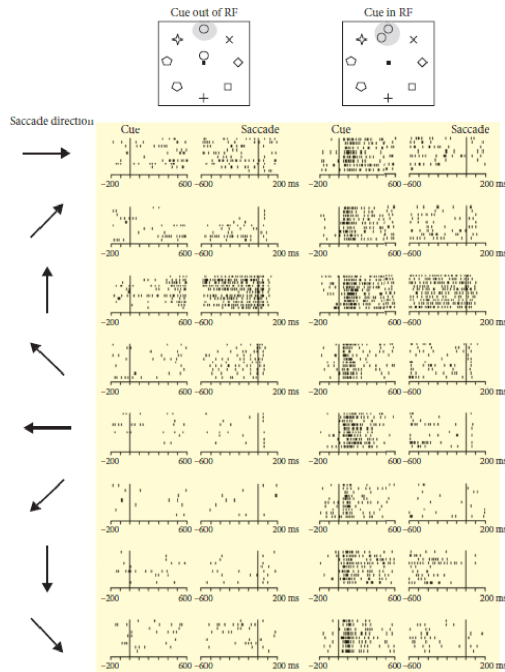
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Figure 12.3 LIP neurons respond selectively to relevant targets. The top panels show the task design. Monkeys viewed a circular array containing eight peripheral saccade targets, of which one was constantly in the neuron's RF (shaded oval). On each trial a cue was flashed for 200 ms and, after a 600–800 ms delay, monkeys were rewarded for making a saccade to the target matching the cue. The rasters show responses of a representative neuron sorted according to the direction of the saccade. If the cue was out of the RF (left column), the neuron had no response to the cue; however, gradually during the delay period it developed a response to target selection—e.g. became active only if the designated target was in its RF (upward saccades). If the cue was in the RF (right column) the neuron responded first to the cue and later encoded saccade direction. Reproduced from Gottlieb, J., Kusunoki, M., and Goldberg, M. E., Simultaneous representation of saccade targets and visual onsets in monkey lateral intraparietal area, *Cerebral* Cortex, 15 (8), pp. 1198–206 (c) 2005, Oxford University Press.

To see if neurons also encode top-down, deliberate selection, a modified version of the stable array task was used, in which the RF stimulus was inconspicuous and stable but on some trials, could become relevant for the task (Fig. 3). After achieving fixation on a given trial, monkeys saw a cue that matched one of the stable stimuli and instructed the monkey to make a saccade to it. The cue was flashed at the centre of gaze outside the neurons' RF, so that it did not activate the cell. However, LIP neurons responded selectively if the stable stimulus in their RF became the designated target. This is illustrated for the cell in Fig. 12.3, which responded if the designated target was in its RF (i.e. upward saccade in the left column) but remained quiescent if another stimulus was selected for the saccade (i.e. all other saccade directions). In a separate condition the cue itself appeared in the RF (Fig. 3, right column). In this condition neurons had two responses—the first to the flashed visual cue and the second to the selected target (which could be at any location in the array). While these responses occurred respectively, early and late during the delay, they overlapped in time in the neural population (Gottlieb et al. 1998, 2005). In other words, while some LIP cells were still responding to the cue location, others were beginning to select the target for the forthcoming saccade.

These findings show that LIP neurons encode a very selective visual representation that integrates information about visual conspicuity and task demands, and tracks salient locations across shifts of gaze. As mentioned above, the spatial accuracy of the LIP response can be best appreciated in Fig. 12.2, where neurons responded to a visual event (abrupt onset) whose location entered their RF, even though the event itself occurred at a separate retinal location (before the shift of gaze). This spatially accurate remapping is thought to reflect the integration of retinotopic visual information with extraretinal responses, about eye position and corollary discharge signals specifying the direction of the upcoming saccade (Bisley and Goldberg 2010). Such retinal–extraretinal integration may be the basis of spatial encoding in different reference frames (Pouget et al. 2002). It may also account for the fact that spatial deficits in neglect can occur in multiple reference frames, as patients ignore stimuli that are

contralateral with respect to the centre of gaze, with respect to their head or body or with respect to external landmarks (Behrmann and Geng 2002).

Neurons Encode Visual Selection

As described above, LIP neurons respond selectively to salient or relevant information and can signal a vector, or pointer, from the centre of gaze to the selected location. Such a retinotopic vector is in principle suitable for both influencing visual processing and guiding shifts of gaze. For the visual system this vector could act as a top-down bias facilitating sensory processing at the selected locations. For the oculomotor system it could act as a motor command, specifying the direction and amplitude of a desired saccade. Indeed, if the same signal were broadcast simultaneously to the visual and oculomotor systems this could explain the close natural coordination between attention and gaze.

Psychophysical studies, however, show that despite their close relationship, eye movements and attention are not identical and show important dissociations. On one hand, when an overt saccade is made there does seem to be an obligatory link, since perceptual performance is by default improved at the saccade goal (Kowler et al. 1995). The converse association, however, is not absolute: attention (defined as an improvement in perceptual discrimination) can be allocated without shifts of gaze, as if by an internal—'covert'—movement of the mind's eye (Carrasco and Yeshurun 2009). Covert shifts of attention contribute to efficient visual analysis before a shift of gaze, and are also beneficial in social situations. For example, it is often desirable to attend to a dominant individual without shifting gaze, as direct eye contact can signify a threat. In more general terms, the capacity for covert attention points to the brain's capacity to generate mental processes and flexibly determine how (or even whether) to translate these processes into action.

From the point of view of neural processing this flexibility implies that the brain must have partially dissociable mechanisms of visual and oculomotor selection. Multiple studies have addressed the question of which process is more closely encoded in LIP, and the bulk of the evidence from these studies favours an interpretation in terms of visual selection.

Perhaps the simplest and strongest evidence in this direction is the fact that LIP neurons respond strongly to salient stimuli even when these do not evoke saccades. This can be appreciated in the experiment shown in Fig. 12.2, where monkeys were not rewarded for making saccades to the salient object or to the briefly flashed cue. And yet in this study (and many like it) LIP neurons emit some of their strongest responses to salient stimuli even as monkeys deliberately fix their gaze (Gottlieb et al. 2005; Powell and Goldberg 2000).

A follow-up experiment expanded on this observation by asking how neurons respond in a condition of visuomotor conflict—when monkeys make saccades *away* from a salient cue (Gottlieb and Goldberg 1999). On each trial in the task monkeys were first shown a cue that flashed briefly at one of two possible locations—either inside or opposite to the neurons' RF. Depending on the colour of the fixation point, monkeys had to make a saccade toward the cue (an easy or habitual 'pro-saccade') or a saccade to an unmarked location opposite the cue (a more difficult, controlled 'anti-saccade'). By randomly interleaving the two cue locations and two mapping rules, the task achieved a full dissociation, such that on any given trial the cue, the saccade goal, neither or both could be in the RF.
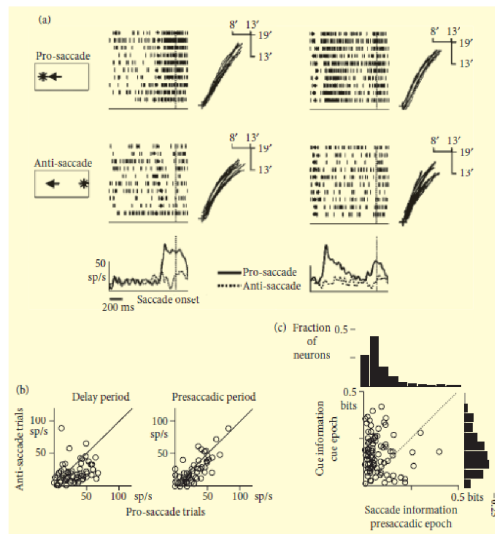
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Figure 12.4 LIP neurons convey more reliable visual than saccadic information. (a) The responses of a representative neuron on trials in which the monkey made a pro-saccade (top) or an anti-saccade (bottom) toward its RF. The raster plots show action potentials aligned on saccade onset, and the time of cue onset is indicated by a dot. The left column shows no-delay trials, in which the saccade was made immediately upon cue onset, and the right column shows delay trials in which a variable delay was imposed after cue presentation. The bottom panels show average firing rates for pro- and anti-saccades. The traces next to each raster show the two-dimensional trajectory (horizontal and vertical position) for the corresponding saccades, even though the eye movements were equivalent in both cases. (b) The vast majority of cells showed stronger responses on delayed pro-saccades relative to anti-saccade trials, both during the delay period and immediately before the saccade. (c) The vast majority of cells transmitted more information about the location of the cue in their visual response than about the location of the saccade goal in their pre-saccadic response. Each dot shows the information transmitted by one cell, and the histograms show the marginal distributions of cue and saccade direction information. Adapted by permission from Macmillan Publishers Ltd: *Nature Neuroscience* 2 (10) Gottlieb, J. and Goldberg, M. E., Activity of neurons in the lateral intraparietal area of the monkey during an antisaccade task, pp. 906–12, copyright, 1999, Nature Publishing Group.

As expected from the earlier results, LIP neurons had strong transient responses when the cue flashed in their RF, and these responses were highly consistent regardless of whether the cue instructed a pro- or an anti-saccade. Also consistent with prior studies, the neural responses continued until the saccade; however, this presaccadic response was inconsistent and dependent on visual stimulation. Fig. 12.4a shows the responses of a representative neuron while the monkey executed saccades toward its RF, sorted according to whether the saccade had been preceded by a flash at the same location (top row and solid traces, 'pro-saccades') or by a flash at the opposite location, outside the RF (bottom row and dotted traces, 'anti-saccades'). On pro-saccade trials the neuron had strong responses before the saccade (top row) and, if a delay was imposed between the cue and the saccade, it had an initial response to the cue followed by a dip in activity and a re-activation just before the movement itself (top right). However, *all* of the cell's responses (including the re-activation just before the saccade) vanished in the anti-saccade condition, when the saccades were identical but there had been no RF visual stimulation. Thus, the neuron's responses, even immediately before the saccade, were strongly dependent on visual stimulation. This visual dependence was the rule for most cells, with most neurons responding much more weakly before anti-saccades relative to pro-saccades (Fig. 4b), and limited the neurons' ability to encode the saccade goal. An information analysis that included all stimulus configurations showed that neurons conveyed reliable information about cue location (responding strongly if the cue appeared in their RF), but transmitted hardly any information about saccade direction even as monkeys were making that saccade (Fig. 4c). Thus, LIP neurons have robust responses to visual stimuli and visually guided saccades, but only weak responses for internally generated movements that are not congruent with a visual cue.

What do these findings imply about the relation between LIP activity and the oculomotor system? Converging evidence shows that saccade production depends on a gradual visuomotor transformation that is implemented in neural populations distributed throughout LIP, FEF, and the SC. Many neurons in the FEF and SC are similar to those

in LIP in that they have spatially tuned visual and pre-saccadic responses (Schall et al. 2011). However, in contrast with LIP, the FEF and SC also contain a distinct population of 'movement' neurons that are scarce or absent in LIP, and which very consistently encode an impending saccade. In contrast with the LIP neurons described so far, movement cells in the FEF and SC do not respond to visual stimulation but respond consistently before an actual saccade and, in FEF, these movement cells seem to reach a fixed threshold at the time of the eye movement onset (Hanes and Schall 1996). These cells therefore are reliable reporters of an actual saccade plan and of the integration of evidence toward such a plan (Schall et al. 2011; Stanford et al. 2010).

Given their anatomical connections, it is likely that LIP neurons influence, directly or indirectly, the movement mechanisms in the FEF and SC. Clearly, however. the integration of the LIP visual selection signal into a motor plan is not automatic but is gated in task-dependent fashion depending on what the subjects want to do about the visual cue. One gating mechanism is thought to involve inhibition of movement neurons by the substantia nigra and collicular 'fixation cells' (Lo and Wang 2006; Pouget et al. 2011), which are tonically active during sustained fixation and may prevent an automatic saccade if a movement has to be withheld (e.g. as in Fig. 2). To generate more complex behaviours such as an anti-saccade, the brain also requires additional mechanisms that generate an alternative action, and these mechanisms are not strongly encoded in LIP. Thus, LIP neurons can contribute to visual selection and suggest a possible saccade plan but, to reach a final action decision, their activity must be supplemented by additional mechanisms that proceed in parallel or in downstream structures.

A final noteworthy point is that rather than reflecting a feedforward motor effect, much of the saccade-related response in LIP may reflect *feedback* from downstream motor mechanisms. Information about saccade direction continues to accumulate in LIP after the saccade itself (Powell and Goldberg 2000) and for anti-saccades, seems to arise at delays longer than the natural latency of the saccade (Zhang and Barash 2004). It is therefore possible that the saccade response reflects, at least in part, corollary information about a saccade plan that is computed in downstream structures (for example, the FEF or the SC) and is fed back to LIP where it modulates a visual response (Sommer and Wurtz 2002). This hypothesis can explain both the presence of saccade activity in LIP and its dependence on visual stimulation.

**LIP Activity and Visual Attention**

As described above, the selective visual responses in LIP seem to have a direct correspondence with visual attention. Neurons respond selectively to salient or behaviourally relevant items, and emit these responses independently of a shift of gaze. Unlike neurons in earlier visual areas, LIP neurons are not feature-selective and do not describe the sensory world. Rather they convey a more abstract measure of 'target selection' that signals the attention-worthiness of an object or location.

According to an influential 'biased competition' hypothesis of attention, selective responses such as the one encoded in LIP can modulate perception through top-down feedback to earlier sensory representations (Desimone and Duncan 1995) that selectively increases the gain of neurons tuned to the selected features or locations (Reynolds et al. 2000; Reynolds and Chelazzi 2004; Reynolds and Heeger 2009). In addition, top-down signals can enhance competitive weight, allowing the selected item to suppress competition from irrelevant distractors (Reynolds et al. 1999; Reynolds and Heeger 2009). To see whether LIP neurons are indeed a possible source of attentional bias, several studies have tested the relation between LIP responses and perceptual selection as assessed by psychophysical measures of contrast sensitivity and visual search.

Bisley and Goldberg used a dual-task design that measured the monkeys' locus of attention based on contrast thresholds on a visual discrimination task (Bisley and Goldberg 2003). Monkeys were first shown a saccade target whose location they had to memorize throughout a memory (delay) period (Fig. 5a). On some trials a distractor was flashed during this period, which monkeys were instructed to ignore. While engaged in this task, monkeys received a secondary task designed to test covert attention. At some point after target presentation the monkeys were shown a visual cue—a C-like stimulus that could have two possible orientations. The cue's orientation instructed the monkey whether to proceed with the planned saccade or to cancel it and maintain fixation. By presenting this cue very briefly at several randomized locations and levels of contrast, experimenters could measure the monkeys' contrast sensitivity at these different locations. This in turn allowed the estimation of the monkey's attentional focus: the locus of attention was defined as the location that showed the lowest contrast threshold for

cue discrimination.

Using this approach, Bisley and Goldberg showed that while holding stable fixation, monkeys shifted their attention from the target to the distractor and back again, and these shifts correlated with the balance of LIP activity, between the target and distractor locations. As shown in Fig. 12.5b, LIP neurons responded to the target with a transient response followed by a lower-level sustained activation (blue trace), and also had a strong response to the distractor (red trace). This dual responsiveness confirms the earlier finding that, although selective, the population of LIP neurons can encode more than one stimulus at a time (Gottlieb et al. 2005). In contrast with this dual response, however, perceptual attention (the locus of lowered thresholds) was only found at a single location at a time—namely, the location that elicited the higher response in LIP. Attention was allocated to the distractor for as long as the distractor response exceeded that to the target, but shifted back to the target location when the balance of activity reversed in LIP.
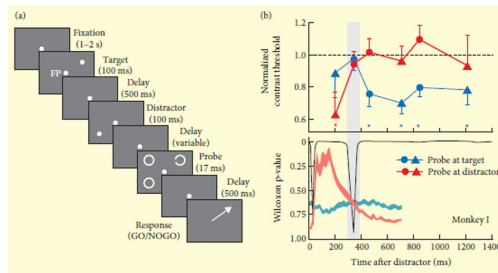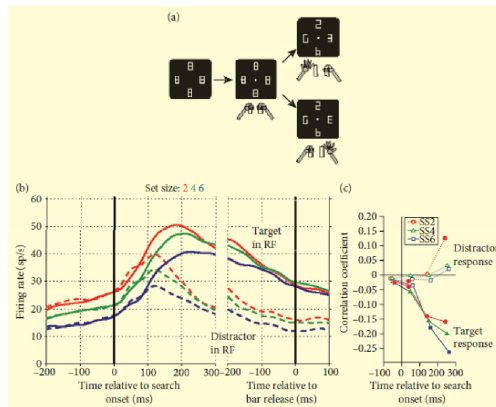

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Figure 12.5 LIP activity predicts the locus of attention. (a) The task design showing the parameters of target and distractor presentation, followed by the presentation of the no-go instruction (the Landoldt-C) that also served as an attentional probe. (b) Data from monkey I. The top panel shows normalized contrast thresholds for discriminating the probe when it appeared at the target versus distractor locations. Thresholds are normalized to a value of 1 that represents the threshold at the remaining two locations that contained neither the target nor the distractor. Stars indicate thresholds that are significantly lower than the reference value. The bottom panel shows the population response of LIP neurons to the target and distractor in their RF. The black trace shows the p-value from a moving window paired test, showing that these responses were reliably different for most of the delay period. The brief window of ambiguity when the two responses were equivalent (shaded window, downward deflection in the p-value trace) corresponds to times when attention shifted from the distractor to the target location. Adapted from Bisley, JW and Goldberg, ME, Attention, intention, and priority in the parietal lobe, *Annual Review of Neuroscience*, 33, pp. 1–21 © 2010, Annual Reviews.

These findings suggest that, just as LIP plays an indirect role in driving saccades, it may have an indirect role in controlling attention. Given a complex visual scene, the priority map in LIP may select several locations as candidates for enhanced discrimination; however, enhanced discrimination may only materialize at one of these locations, possibly due to a winner-take-all mechanism that operates downstream of LIP. This additional selection may be implemented in a discrete stage subsequent to LIP, or simply reflect the properties of sensory processing itself. It is important to note that the experiment of Bisley and Goldberg used very brief (16 ms) masked visual presentations and shows that attention has a unitary locus on these very brief time scales. It remains possible that attention rapidly shifts between locations, being effectively distributed across multiple locations on longer time scales.

While Bisley and Goldberg focused on saccade-related and bottom-up attention, a second set of studies focused on visual search tasks, where monkeys have to find targets that are embedded in distractor arrays. These studies capitalized on the classic observation that if the target is inconspicuous, the time required to find it increases as a function of the number of distractors, a set-size effect that is indicative of inefficient or attentionally demanding search (Haslam et al. 2001). An involvement of LIP in difficult search was suggested by two experiments using reversible inactivation with the GABA agonist muscimol. These studies showed that inactivation impairs visual selection during difficult search, whether the search occurs covertly or in conjunction with overt saccades (Wardak et al. 2002, 2004).

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Figure 12.6 LIP activity encodes covert top-down attention and the set-size effect. (a) The task design. An array of figure-8 placeholders remained stably on the screen. In interleaved blocks of trials the array contained two, four, or six placeholders. Each trial began when the monkey achieved fixation, bringing a placeholder into the RF. Two line segments were then removed from each placeholder, revealing a display with one target and several distractors. The target (a right or left facing letter 'E') appeared at a random location. Without shifting gaze, monkeys had to find the target and report its orientation by releasing a bar. (b) During the time between search onset (stimulus presentation) and the manual release LIP neurons encoded target location, responding more strongly when the 'E' relative to a distractor appeared in their RF. These responses declined as a function of set size. The set-size effect was evident even before search onset, when a different number of placeholders were present on the screen. (c) Correlation coefficients between neuronal firing rates and reaction times for trials in which the target (solid lines) or a distractor (dotted lines) were in the RF. Significant correlations (filled symbols) were found for the target response, showing that the larger this response the shorter the reaction time. In contrast, the distractor response was more weakly related to performance. Adapted from *PLoS Biol*, 6 (7), Balan, P. F., et al., Neuronal correlates of the set-size effect in monkey lateral intraparietal area, e158 © 2008, Creative Commons License.

To determine the neural responses underlying this function, Balan et al. (Balan et al. 2008) trained monkeys to discriminate a visual cue—an E-like shape—that appeared in the visual periphery in an array of distractors (Fig. 6a). Monkeys were required to maintain central fixation and suppress saccades to stimuli in the search array. They were rewarded for reporting the cue orientation by releasing a bar held in the right or the left paw. Performance showed a set-size effect in both reaction time and accuracy, indicating effortful, attentionally demanding search.

LIP neurons had robust responses encoding the cue location, responding more strongly if the cue rather than a distractor was in their RF (Fig. 6b). Consistent with the behavioural set-size effect, these responses diminished as a function of the number of distractors. The set-size related decline in activity was seen in the fixation period, when the monkeys viewed a variable number of placeholders but could not yet begin their search (Fig. 6b—200 to 0 ms). Behavioural testing showed that monkeys were insensitive to changes in location probability per se, suggesting that the set-size effect was not due to changes in the monkeys' estimate of the probability that a target will appear at a given location. A simple explanation is that this neural set-size effect reflected competitive visual interactions triggered by surrounding distractors (Falkner et al. 2006), suggesting that these interactions explain capacity limitations during visual search.

The robust responses that the cells had on this task underscore the fact that LIP encodes visual selection independently of a specific action, i.e. for guiding saccades or limb motor actions. Notably, however, while in saccade tasks neural responses typically increase up to the time of a saccade (e.g. Fig. 4a), in this task activity peaked in the middle of the reaction time and declined well before the motor response. This suggests that LIP accumulates visual information, and then passes control to skeletomotor mechanisms.

The results also provided data regarding the specific behavioural correlates of the response. If a distractor was in the RF, neurons showed an enduring set-size effect that persisted until the bar release (Fig. 6b, dashed traces). By contrast, if the target was in the RF, the set-size effect diminished gradually over time, so that the response reached a comparable *peak* level at all set-sizes (solid traces). These findings are consistent with a biased competition account whereby the influence of distractors is filtered through top-down control. In addition, the monkeys' reaction times were better correlated with the target than with the distractor response (Fig. 6c), suggesting that the top-down signal may primarily influence performance through its actions on target

representations.

In sum, the studies described in this section establish correlations between LIP activity and perceptually defined attention, whether attention is driven in bottom-up or top-down fashion, and whether it guides ocular or skeletal actions.

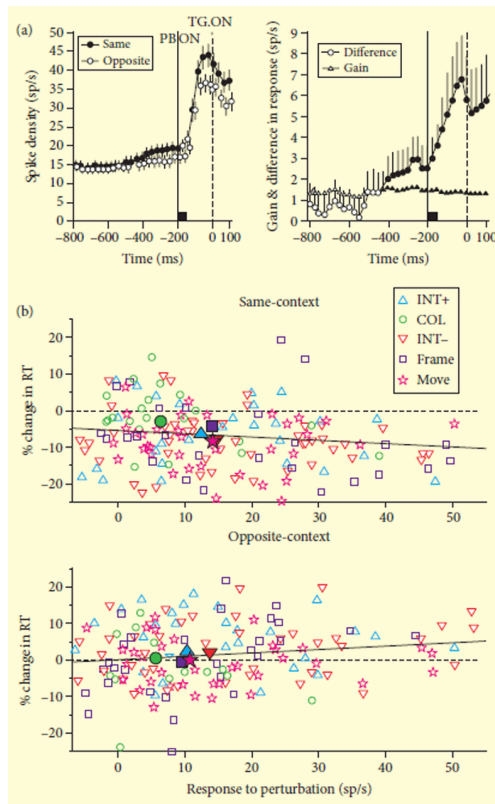**Combining Bottom-up and Top-Down Information**

Psychophysical studies show that the effects of salient distractors are not immutable but depend strongly on task context and the observers' search set (Burnham 2007). Given that LIP neurons integrate the influences of bottom-up and top-down factors, they are possible candidates for mediating interactions between these forms of control.

To address this question, Balan and Gottlieb (Balan and Gottlieb 2006) used the E-search task described in Fig. 12.6 but, in addition to the target, introduced a salient visual perturbation. On each trial the appearance of the search display containing a target and multiple distractors was preceded by a 50 ms visual perturbation—which could be a brief change in the position, luminance, or colour of a stable placeholder, or the brief appearance of a frame around a placeholder. The significance of the perturbation was varied in interleaved trial blocks. In some blocks the perturbation appeared at the same location as the search target—and was thus a valid cue to the target location. In other blocks the perturbation appeared at a different, unrelated location and was irrelevant to the search. These statistical associations remained constant during a block, and monkeys could exploit them to adjust their attentional strategy. Indeed, in SAME location blocks the monkey's reaction time was shorter than in OPPOSITE blocks, showing that the animals learned to use the perturbation as a valid cue or block its distracting effects, according to the context.

LIP neurons reflected these contextual adjustments, emitting enhanced responses to the perturbation in the relevant relative to the irrelevant context. Moreover, the relative size of their responses to the perturbation correlated with the behavioural effect. In the perturbation-relevant block, perturbation responses were higher overall (Fig. 7a), and an increase in the visual response correlated with a decrease in reaction time (Fig. 7b), consistent with the hypothesis that the perturbation facilitated target selection. In the perturbation-irrelevant block, by contrast, perturbation responses were lower (Fig. 7b) and a higher response was correlated with *longer* search reaction times, indicating that the perturbation had a distracting effect. Interestingly, the increment in the perturbation response in the relevant context was accompanied by an increase in the neurons' baseline activity even before the perturbation occurred, and the fractional increase in baseline activity was not different from the fractional increase in the visual response, suggesting a multiplicative gain (Fig. 7a). Multiplicative gain was shown previously to enhance responses to weak stimuli when these are the focus of attention (McAdams and Maunsell 1999; Williford and Maunsell 2006). In this task, however, response gain increased in a non-spatial fashion, before the animal could direct attention to a specific location. Thus, abstract knowledge of task context can produce multiplicative effects on baseline firing rates that influence sensitivity to subsequent sensory stimulation.

A task-dependent encoding of salient stimuli was also shown in a visual search task in which a pop-out (colour-contrasting) distractor was present along with an inconspicuous target (Ipata et al. 2006). Neurons showed variable responses to this distractor, which correlated with the monkeys' ability to suppress saccades to it, supporting the idea that LIP is a possible substrate for integrating top-down and bottom-up information.

Determinants of visual selection I: Semantic associations

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Figure 12.7 LIP neurons integrate bottom-up and top-down information. (a) Left panel shows the population responses on trials in which a salient perturbation was relevant ('Same') or irrelevant ('Opposite') for the location of the search target. Responses are aligned on the time of the perturbation (PB ON) and truncated after the appearance of the target (TG ON). An enhancement is seen in the relevant blocks starting 200–300 ms before onset of the perturbation. The right panel shows the difference and ratio (gain) between firing rates in the two conditions. While the difference increases sharply at the time of the visual response the gain remains constant throughout the trial. (b) The perturbation response in LIP correlates with the effect of the perturbation on search reaction times. In the Same context a larger perturbation response is associated with a large fractional decrease in reaction time, while in the Opposite context a larger response produces a larger increase in reaction time. Each point shows the data from one neuron and one perturbation type (increase or decrease in luminance, INT+ and INT–, isoluminant colour change (COL), appearance of a frame (FRAME) or movement of a placeholder (MOVE)). Adapted from Cohen, M. and Maunsell, J., Functional significance of nonspatial information in monkey lateral intraparietal area, *Journal of Neuroscience*, 29 (25), pp. 8166–76 © 2009, The Society for Neuroscience.

The studies described above show that the selective response in LIP can be a source of top-down bias that selectively guides visual processing. However, this raises an important question. How do LIP neurons know the 'relevance' of a visual cue and how do they know which target to select?

Psychophysical studies show that the significance of visual cues is established by multiple factors, which include the learned contextual and action associations of the cues, the usefulness of a cue in providing information, and the Pavlovian (reward) associations of the cues. The following sections discuss the role of these factors in modulating the LIP response and their possible contribution to a relevance computation.

A fundamental step in computing relevance is learning the associations between stimuli and the broader task, including the context, actions, or goals of that task. Imagine, for example, that you want to drive to a remote location. By virtue of information stored in long-term memory, you have learned to associate the task of driving with the category of a 'car'. This can in turn activate a visual template (of a 'big object with wheels') which can produce an attentional bias and ultimately allow you to focus on a car (Huang and Grossberg 2010; Navalpakkam and Itti 2005). The idea of associative top-down control is consistent with psychophysical evidence that attention can be guided by context or gist (Oppermann et al. 2012) or by the motor associations (affordances) of a visual cue (Roberts and Humphreys 2011a, 2011b).

Consistent with the importance of associative learning in behaviour, neurophysiological studies have shown that the target selection response in LIP is not stereotyped but is shaped by the motor, visual, and categorical associations of visual cues. Evidence regarding motor associations comes from the covert visual search task that was described in Fig. 12.6 (Oristaglio et al. 2006). As described above, in that task monkeys were required to find a visual cue while maintaining central fixation, and report its orientation with a manual release. Specifically, monkeys learned to release a bar held in the right paw if the cue was a right-facing 'E' but to release a bar held in the left paw if the cue was a left-facing 'E' (a '3'). This manual response occurred outside the monkeys' field of view and it was non-targeting—i.e. independent of the location of the cue. Nevertheless, each motor response had a non-spatial (semantic) association with a cue, and this association was encoded in LIP.

In about half of the cells encoding target location, the cue-evoked response was not constant but depended on the manual release. Of these cells, some had stronger responses if the cue appeared in the RF and instructed a left bar release (Fig. 8a, left column, red vs. blue). Other cells had the complementary preference, responding best for the cue signalling right release. Control experiments showed that the effect was not linked to the cue's orientation or to the location of the limb. Thus, when monkeys were trained to indicate the orientation of a new set of cues (an upright or inverted U-like shape) a majority of neurons showed the same limb preference as they did for the E-like cues. Similarly, when monkeys were trained to perform the same task with their limbs crossed across the body midline, limb effects remained unchanged: neurons that preferred the right or left limb in the standard arm position continued to have the same preference in the crossed position (Fig. 8b), showing that the modulatory effects were linked to a specific limb regardless of its position in space.
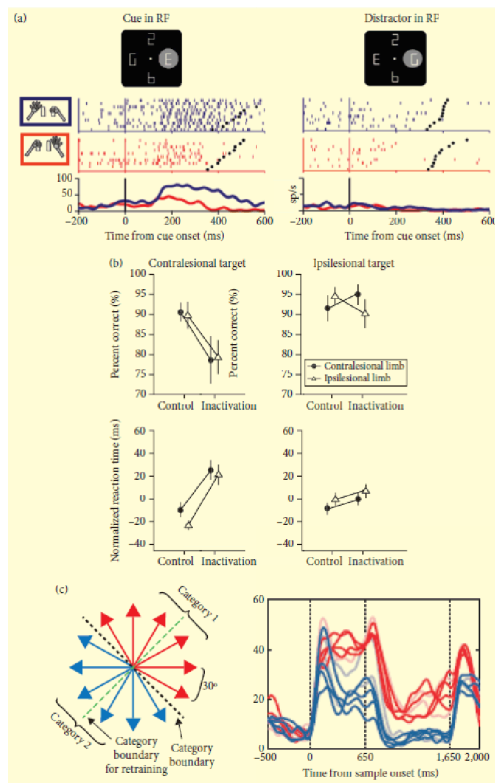
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Figure 12.8 LIP neurons encode motor and categorical associations. (a) Modulation by manual release. Responses of a representative neuron in the 'E' search task shown in Fig. 6. Monkeys were rewarded for maintaining fixation and reporting the orientation of the 'E'—right or left facing—by releasing a bar held, respectively, in the right or left paw. The bars themselves were outside of the field of view. Rightward-facing cues could appear on the left and vice versa, so the laterality of the motor response was independent of the laterality of the visual cue. The neuron responded only if the 'E' appeared in its RF but was silent if a distractor did (left vs. right column). In addition, when an 'E' appeared in its RF, the cell was more active if the monkey released the left bar than the right bar (blue vs. red traces). Raster plots in the top panels show individual trials. Each dot represents the time of an action potential aligned on cue onset, and the black dots show the time of manual release. Trials are sorted offline in order of manual reaction time. The bottom

panel shows the corresponding averaged spike density histograms (smoothed with a Gaussian kernel, sigma 10 ms). Adapted from Oristaglio, J., et al., Integration of visuospatial and effector information during symbolically cued limb movements in monkey lateral intraparietal area, *Journal of Neuroscience*, 26 (32), pp. 8310–9 © 2006, The Society for Neuroscience. (b) Muscimol inactivation impairs visual but not motor selection. Performance of the 'E' search task in control conditions and after muscimol inactivation of LIP in one hemisphere. The top row shows discrimination accuracy and the bottom row, reaction times. Symbols show average and standard errors. Data are segregated according to the hemifield of the target and the side of the active limb (contralateral or ipsilateral to the inactivation site). Adapted from Balan, P. F. and Gottlieb, J., Functional significance of nonspatial information in monkey lateral intraparietal area', *Journal of Neuroscience*, 29 (25), pp. 8166–76 © 2009, The Society for Neuroscience. (c) Modulation by stimulus category. The left panel illustrates the behavioural task. Monkeys viewed a sample stimulus containing random dot motion in one of eight possible directions. After a delay period (650 to 1650 ms) a test motion stimulus appeared and monkeys had to release a bar if the test stimulus matched the category of motion of the sample, but continue to hold the bar otherwise. Monkeys were initially trained to categorize directions according to one category boundary (black dotted line) and then retrained to use a different boundary (green dashed line). Top right panel shows a representative LIP neuron that had visual and delay period activity following presentation of a sample inside its RF as well as sensitivity to sample category. Firing rates were much more strongly modulated by changes in direction across, relative to within a category boundary, dissociating this modulation from simple selectivity for motion direction. Reprinted by permission from Macmillan Publishers Ltd: *Nature*, 443 (7107), David J. Freedman and John A. Assad, Experience-dependent representation of visual categories in parietal cortex, copyright (2006), Nature Publishing Group.

An important aspect of these limb effects is that, while they occurred reliably in over half the cells, they were not the neurons' primary response. Rather they *modulated* a primary response to visual selection. The cell in Fig. 12.8a, for example, had robust limb selectivity if the cue appeared in its RF. However, the neuron remained silent if a distractor was in the RF even though the monkeys performed the same manual action (right column). The primacy of the visual response was confirmed by a further experiment that used reversible inactivation, which showed that inactivation impaired only visual but not motor selection (Balan and Gottlieb 2009). Infusion of muscimol into LIP in one hemisphere impaired performance in spatially selective manner—i.e. if the cue was contralateral but not if it was ipsilateral to the inactivation site (Fig. 8b). However, inactivation caused no deficits in the manual release—neither a global impairment in the manual action nor a limb-specific deficit. These findings suggest that the limb responses in LIP do not indicate a primary involvement of this area in the execution or release of a grasp. Rather they are effects of a visuo-manual association on the target selection response.

Other experiments have shown that LIP neurons can also reflect more abstract properties such as the categorical membership or visuo-visual associations of an instructive cue (Freedman and Assad 2011). In a task where monkeys were trained to report the category of a motion stimulus using a delayed match to sample task, neural responses to the stimulus were category selective, with different neurons responding more for one or the other category (Freedman and Assad 2006). Similar differentiation was found in different tasks testing visuo-visual associations (Fitzgerald et al. 2011) or visual search based on feature conjunctions. Although using very different tasks, these studies converge on a similar conclusion—that LIP neurons reflect not only the location but the learned visual, action, and semantic associations of task-relevant cues.

These findings were proposed to contribute to abstract decisions based on the semantic associations of visual cues (Freedman and Assad 2011) and, given the role of LIP in visual selection they may also contribute to the learning of relevance and top-down control. This hypothesis raises new questions about this control. In the traditional view of attention, top-down signals for features or locations are thought to arise from different neurons and recruit different attentional mechanisms (Desimone and Duncan 1995; Maunsell and Treue 2006). The multifaceted nature of the LIP response, however, suggests that top-down signals may be selective for both space and high-level features (Gottlieb and Snyder 2010). For example, if neurons such as the limb-selective cells in Fig. 7a provide the top-down bias, this implies that a different populations of neurons provide the bias for cues signalling right—or left—release. In other words, directing attention to a given location may be accomplished by different neuronal populations depending on the significance of the attended object. While counterintuitive at first glance, such a differentiated (combinatorial) signal may provide an efficient interface with visual and motor mechanisms, which are themselves selective for feature and/or categories. An alternative possibility is that neurons with dual spatial/non-spatial selectivity represent only the hidden layer in a network computing relevance, and the output of the network (the attentional bias itself) may be conveyed by the neurons that lack associative effects. Future experiments are needed to clarify this question.

A second set of questions concerns the mechanism generating associative effects. One possibility is that the

effects reflect online feedback from structures that accumulate evidence regarding categories or actions. Alternatively, however, it is possible that through prolonged training, visual associations produce plasticity in visual areas themselves or in the connections between these areas and LIP. Such plasticity can be produced in simple reinforcement models (Ferrera and Grinband 2006) and is consistent with the presence of semantic/categorical effects in earlier visual areas such as V4 (Mirabella et al. 2007).

Determinants of visual selection II: Utility and information

While semantic associations are necessary for determining relevance, to efficiently guide attention the brain must also estimate the *usefulness* of a visual cue. To appreciate this distinction, consider the pattern of eye movements made by a subject during natural behaviour—a simple task such as filling a kettle for making tea (Fig. 9a). Consistent with the seminal work of Yarbus in the early twentieth century, the vast majority of eye movements made in such conditions are directed to task-relevant cues. However, these movements do not target *all* the stimuli that have task associations, which in the tea-making example would include the kitchen walls, cabinets, and floor. Instead, they are highly selective for stimuli that bring new information for the subject's immediate actions. This suggests that additional mechanisms must operate within the set of task-associated cues, to further select those stimuli that inform—and thus increase the likelihood of success of—a future action.

Consistent with this idea, multiple studies have shown that oculomotor decisions are sensitive to expected reward and have proposed that the target selection response in LIP (and possibly other areas) encodes the value of alternative options (Kable and Glimcher 2009; Sugrue et al. 2004, 2005). Monkeys are easily trained to direct gaze for liquid rewards, and human subjects make optimal tradeoffs between expected gain and salience during visual search (Navalpakkam et al. 2010). Reward effects have been described in multiple structures including the FEF (Ding and Hikosaka 2006), and SC (Ikeda and Hikosaka 2003). Multiple studies have shown that in LIP the target selection response increases monotonically with the desirability of a specific reward, whether desirability is manipulated through the magnitude, probability or timing of the eventual reward, and whether animals perform instructed or free-choice tasks (Dorris and Glimcher 2004; Louie and Glimcher 2010; Louie et al. 2011; Platt and Glimcher 1999; Sugrue et al. 2004). These findings suggest the powerful hypothesis that the target selection response in LIP encodes a common currency of visual utility, with utility being computed based on a variety of factors (Kable and Glimcher 2009; Sugrue et al. 2005).

An important question, however, is if neurons encode expected reward per se or the specific form of utility that is important for attention—the utility of information, which depends on the observer's uncertainty at a point in time (Sprague and Ballard 2005; Tatler et al. 2011). Consider again the eye movements of the subject in Fig. 12.9a. To complete her task the subject is simultaneously manipulating the kettle and walking from the stove to the sink. Both her hand and leg actions have high *value* and are necessary for the task. However, our subject guides her eye movements exclusively to the targets of the hand actions, since these have higher uncertainty and have more to gain from new information.

While the specific utility of information has not been examined in the oculomotor domain, insights into this question come from reinforcement learning studies of attention in humans and rats (Pearce and Mackintosh 2010). A central idea in these studies is that attentional weight is assigned not based on expected reward but based on the *prediction errors* associated with a cue. A prediction error is a measure of the difference between the agent's expectations and the actual experienced outcome. Outcomes that are better or worse than expected generate respectively, positive and negative errors, and these errors drive learning in iterative algorithms. Reinforcement learning theories of attention postulate that the 'informativeness' of a sensory signal can be estimated through the absolute value of the prediction errors associated with that signal. Cues that are reliable predictors will reduce uncertainty and have low associated errors, while cues that make uncertain predictions will have higher prediction errors.
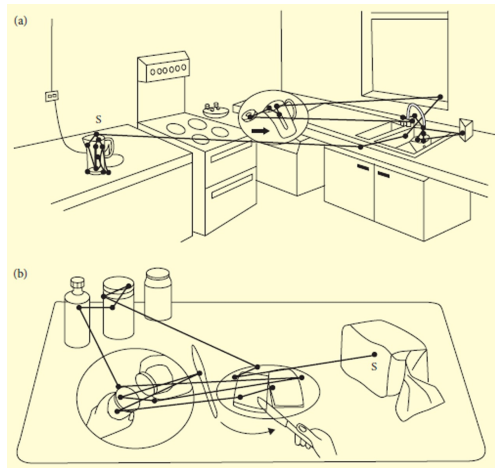
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Figure 12.9 Eye movements during active tasks. (a) Eye movements of a subject filling water in a tea-kettle. (b) Eye movements of a subject preparing a sandwich. Reproduced from *Visual Neuroscience*, 26 (1), Land, M. F. Vision, eye movements, and natural behavior, pp. 51–62 © 2009, Cambridge University Press.

Consistent with this framework, psychophysical studies show that human attention is guided by the predictive qualities of visual cues (Hogarth et al. 2010). Furthermore, studies in rats suggest that this guidance may involve two distinct mechanisms (Pearce and Mackintosh 2010). One mechanism, dubbed 'attention for action', is thought to depend on the frontal lobe and assigns priority to stimuli that have low prediction errors—i.e. reliable predictors that can guide future actions (e.g. the tap or sink in Fig. 9a). A second mechanism, dubbed 'attention for learning', involves the amygdala and parietal lobe and assigns value to novel or uncertain cues in order to learn *about* such cues.

So far little is known about the importance of prediction errors in the visual and oculomotor system, as most studies have focused on the role of expected reward. A key question for future work therefore is to integrate this work with a reinforcement learning framework and understand how parietal and frontal neurons assign priority based on predictive or informational properties of visual cues.

## Determinants of attention III: Pavlovian (emotional) associations

A central assumption of reinforcement theories of attention is that attention is guided by the *absolute* magnitude of prediction errors regardless of their sign. In this way attention is guided by the information value of a stimulus independent of whether the stimulus brings 'good' or 'bad' news. This seems to correspond to our intuition that attention should proceed in a 'rational', 'value neutral' fashion: while seeing a tiger on your hiking trail is an unpleasant prospect, there should not be a problem in attending to confirm that there is, in fact, a tiger in the bush. Put differently, reliable information is valuable whether it brings good or bad news.

In contrast with this purely informational view, however, converging psychophysical evidence shows that attention does have strong emotional components and is sensitive to the social or affective valence of external cues (Vuilleumier 2005). Stimuli that are initially neutral but gain positive reward associations can automatically attract attention even when they are irrelevant to a task (Anderson et al. 2011; Libera and Chelazzi 2009) while stimuli with negative associations can repel gaze and reduce fixation time at their locations (Hogarth et al. 2010). Unlike the goal-directed attention discussed above, these effects produce task-independent attentional biases. Affective biases in attention are strong in psychiatric disease (Williams et al. 1996). For example, patients with drug addiction have automatic biases toward drug-related cues that may reinstate drug craving and cause relapse even after periods of abstinence (Flagel et al. 2009).

Despite the possible importance of emotional attention, little is known about its neural mechanisms. However, a recent experiment shows that conditioned cues produce valence-specific biases in spatial attention and in the neural responses in LIP (Peck et al. 2009).

In the experiment, the monkeys performed a probabilistic reward task where each trial had a 50% prior probability

of ending in a reward or no-reward. At the outset of a trial monkeys viewed a peripheral conditioned stimulus (CS) that provided full information about the trial's reward. Some cues brought 'good news', signalling that the trial will end in a reward (CS+); others brought 'bad news', signalling that, even if correctly completed, the trial will end in no reward (CS–). If attention depends solely on predictive validity it should be directed in a similar fashion to the positive and negative cues, as both conveyed reliable information. By contrast, if attention depends on reward associations, it may be differently allocated to the positive and negative cues.
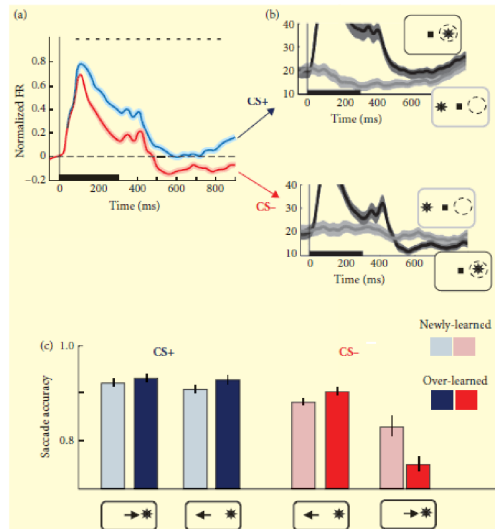
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Figure 12.10 Pavlovian cues bias attention and LIP activity. (a) Population responses to Pavlovian cues. A cue flashes in the RF for 300 ms (dark bar) and is followed by a delay period during which monkeys maintain fixation. LIP neurons have transient and sustained responses that are selective for cue value, being stronger for a positive cue predicting a reward (CS+, blue) relative to a negative cue predicting no reward (CS–, red). The stars show time bins with a significant difference between the two conditions. The bottom dashed line shows the pre-cue level of activity. Shading shows the standard error of the mean. (b) Cue-evoked biases are spatially specific. The dark traces in each panel are the same as, respectively, the blue and red traces in panel **A**, but shown on an expanded vertical axis. The grey traces show responses when the cues appeared opposite the RF. Responses evoked by an RF cue are higher than (CS+) or lower than (CS–) those evoked by a cue at the opposite location. (c) Attentional biases are spatially specific. Panels show mean and SEM for saccade accuracy across all sessions. Opaque colours show trials with over-learned CS, which had consistent reward associations for tens of thousands of trials. Pale colours show trials with novel CS, which were introduced and trained within a single session. Measurement of anticipatory licking showed that monkeys learned the value of the novel CS within the first 5–10 trials. Data collection began after this learning was complete. On CS– trials (red) accuracy is somewhat lower than on CS+ trials, indicating a modest effect of motivation. The strongest effect, however, is on CS– congruent trials, when the saccade is directed toward the CS– location (rightmost bars). Moreover, the accuracy on these trials decreases further with training, being lower after over-learned relative to newly learned cues. Adapted from Peck, C. J., Jangraw, D. C., et al., Reward modulates attention independently of action value in posterior parietal cortex, *Journal of Neuroscience*, 29 (36), pp. 11182–91 © 2009, The Society for Neuroscience.

Consistent with the latter possibility, attentional biases differed according to affective value—such that 'good news' cues (CS+) attracted attention, while 'bad news' (CS–) cues repelled attention from their location. As shown in Fig. 12.10a, upon presentation of a CS, LIP neurons had a fast transient visual response followed by sustained activity that lasted after disappearance of the cue. The sustained response that followed a CS+ was excitatory, resulting in a higher response when the cue appeared in the RF relative to when it appeared at the opposite location (Fig. 10b, top, black vs. grey traces). By contrast, the response evoked by a CS– was suppressive, producing lower activity at the cue location relative to the opposite location (Fig. 10b, bottom).

To see whether these neural biases had behavioural correlates, monkeys were trained to maintain fixation for a brief delay period then make a saccade to a second target that appeared unpredictably either at the opposite or same location as the cue. By comparing saccades that were directed toward versus opposite the CS location, investigators could detect whether the CS had attractive or repulsive effects.

Consistent with the neural biases in LIP, saccades were slightly facilitated if they were directed toward a CS+ location but strongly impaired if directed toward a CS– location (Fig. 10c). Performance on a CS– trial was much better if the saccade was directed away from the CS–, showing that the impairment was spatially specific and distinct from a global decrease in motivation on unrewarded trials (Fig. 10c, rightmost two bars). Moreover, the impairment on CS– congruent trials affected both reaction times and accuracy. The dysmetria (inaccuracy) produced by a CS– is particularly important because it distinguishes this repulsion from inhibition of return, which has only been reported to prolong latency (Fecteau and Munoz 2006). In addition, by reducing accuracy, the CS– produced many targeting errors and lowered the monkeys' rate of reward, showing that the CS– repulsion interfered with the monkeys' task. Nevertheless, despite its detrimental consequences, this repulsion *increased* rather than decreasing with training, becoming stronger for over-learned relative to newly learned cues (Fig. 10c, solid vs. pale colours).

These effects therefore seem to be neuronal correlates of the emotional biases documented in human subjects. Like these biases, the effects produced by the CS depended on the valence of the cue, arose automatically, and persisted despite their maladaptive effects.

Taken together with the previous discussion, these findings indicate the need to distinguish between two classes of reward-based attention mechanisms. One is a goal-directed mechanism that estimates the operant value of a cue in informing future actions. This mechanism requires knowledge of the task demands and may involve cortical areas that can plan a series of actions (Gershman and Niv 2010). A second mechanism, however, seems independent of action relevance and may be guided solely by conditioned Pavlovian associations, such as those encoded, for example, by dopamine (DA) neurons of the midbrain (Flagel et al. 2011). As described above, affective biases operate automatically and can produce maladaptive effects. However, because they are computationally simpler and quickly learnt, they may be useful in detecting biologically relevant information.

Conclusions

Converging evidence from anatomical, single-neuron recordings and inactivation studies implicates area LIP in the allocation of visual attention. Neurons in this area encode a sparse visual representation that selects candidate stimuli for shifts of attention and gaze, and integrates sensory and behavioural information.

The complex behavioural influences in LIP raise important questions about the nature of top-down control. Understanding these influences requires that we consider the multiple mechanisms by which the brain assigns relevance, including the task associations, information content, and emotional value of cues. Thus a critical goal for future research will be to integrate evidence from behavioural and computational research toward a better understanding of the neurophysiological mechanisms.

Disclosure Statement

The authors declare that they have no conflict of interest.

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Neuronal Mechanisms of Attentional Control: Frontal Cortex

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The Oxford Handbook of Attention

Edited by Sabine Kastner

[−] **Abstract and Keywords**

Covert spatial attention prioritizes the processing of stimuli at a given peripheral location, away from the direction of gaze, and selectively enhances visual discrimination, speed of processing, contrast sensitivity, and spatial resolution at the attended location. While correlates of this type of attention, which are believed to underlie perceptual benefits, have been found in a variety of visual cortical areas, more recent observations suggest that these effects may originate from frontal and parietal areas. Evidence for a causal role in attention is especially robust for the Frontal Eye Field, an oculomotor area within the prefrontal cortex. FEF firing rates have been shown to reflect the location of voluntarily deployed covert attention in a variety of tasks, and these changes in firing rate precede those observed in extrastriate cortex. In addition, manipulation of FEF activity—whether via electrical microstimulation, pharmacologically, or operant conditioning—can produce attention-like effects on behaviour and can modulate neural signals within posterior visual areas. We review this evidence and discuss the role of the FEF in visual spatial attention.

Keywords: prefrontal cortex, frontal eye field, saccadic eye movements, visual cortex, spatial attention, selective attention

The Activity of Frontal Eye Field (FEF) Neurons during Endogenous Spatial Attention

IT is now well established that the responses of neurons within visual cortex to a stimulus are enhanced when a subject pays attention to that stimulus, compared to when the stimulus is ignored. In a typical neurophysiological experiment, the subject (e.g. a monkey) is trained to pay attention to different stimuli appearing at peripheral locations while maintaining central fixation. In other words, the subject *covertly* attends to the different peripheral stimuli. The responses of visual cortical neurons to physically identical stimuli presented to their receptive fields (RFs) are then compared between the different conditions. During covert attention, the visual response of neurons to the RF stimulus is enhanced when the animal pays attention to that stimulus, compared to when the animal attends elsewhere (e.g. Motter 1993). Moreover, this enhancement leads to changes in orientation tuning, direction of motion tuning, contrast sensitivity, colour tuning, and the representations of multiple, competing RF stimuli (Reynolds and Chelazzi 2004). It is assumed that the perceptual benefits of covert attention are supported by these correlative changes in neuronal sensitivity within visual cortex. If this assumption is correct, then the crucial question to be addressed is: what mechanisms give rise to these correlates of attention? What neural circuits modulate the 'gain' of visual signals when particular stimuli are selected by covert attention? In this chapter, we discuss evidence that implicates the FEF as one of the structures causally involved in that control.

The FEF is an area of prefrontal cortex (PFC) with a well-known role in the control of saccadic eye movements (Schall 1995). That is, this area is involved in the *overt* shifting of attention, via shifts of gaze, from one stimulus to another. In recent years, however, single-neuron recordings in behaving monkeys have yielded much data supporting a role of the FEF in the control of *covert* attention as well. Firing rates of FEF neurons are enhanced when the animal pays attention to a stimulus within an FEF neuron's receptive field (RF), similar to what is observed

in posterior visual areas. The firing rates of FEF neurons thus signal the location of spatial attention, even in the absence of eye movements, and they've been shown to do so in a variety of covert attention tasks. For example, such modulation occurs during change blindness tasks (Armstrong et al. 2009), change detection tasks (Gregoriou et al. 2009; Kodaka et al. 1997), and during covert visual search (Monosov and Thompson 2009; Thompson et al. 2005a, 2005b; Buschman and Miller 2009). Simultaneous recordings from visual area V4 and the FEF during the deployment of covert attention have revealed that modulation of neuronal firing rates arises earlier in the FEF (Gregoriou et al. 2009). Critically, in this task the target stimuli appeared well before the cue directing attention to a particular location, allowing the onset of attentional modulation to be measured independently of the visual latency of the neurons and without being obscured by visual onset transients. Within the FEF itself, spiking activity reflects target selection earlier than the local field potential (LFP), which suggests that the attentional signal may emerge from within the circuitry of the FEF (Monosov et al. 2008).

In addition to facilitating comparisons of the latency of attentional signals between areas, simultaneous recordings from frontal and extrastriate regions also provide insight into the interaction of these reciprocally connected areas during the deployment of spatial attention. Onset of a spatial cue toward the RF is followed by a rise in firing rates in both FEF and V4, and an increase in gamma-band LFP power in both areas (Gregoriou et al. 2009). Changes in FEF firing rate precede the increase in gamma power in both areas, which in turn precede significant increases in V4 firing rates. Synchrony between the spike times and LFP phases, as measured by the spike-field coherence, also increases in the gamma band, both within and between areas. If this synchrony were the product of a common driving input to the two areas, then the difference in phase between the activity across areas would be expected to be zero; instead, both spike-field and field-field coherence showed that V4 activity lagged FEF activity by approximately half a gamma cycle (8–13 ms). Granger causality analysis of the gamma power in LFPs of the two areas suggests that this synchrony is initiated by the FEF: although within 200 ms of the spatial cue there is significant Granger causality both from FEF to V4 and from V4 to FEF (as might be expected given that each receives projections from the other), the cue-evoked rise in Granger values occurs significantly sooner in the FEF to V4 direction than the reverse (100 ms vs 160 ms after cue onset, respectively). This work begins to bridge the gap between the bodies of research previously focused on characterizing the effects of attention in each area independently. Neurophysiological studies of this type seem to complement a variety of observations in the human literature. For example, attentional state has been found to modify propagation of TMS-induced activity from frontal to posterior visual areas (Morishima et al. 2009). In fMRI studies, measures of frontal activity and frontal-extrastriate connectivity have proven effective predictors of both attentional modulation of visual cortical responses and task performance (Bressler et al. 2008; Gazzaley et al. 2007; Zanto et al. 2010).

Exogenous Attention

The above-mentioned evidence primarily addresses the involvement of the FEF in *endogenous* spatial attention, that is, attention that is directed to a location by virtue of internal goals. This type of attention is also referred to as *top-down*, *voluntary*, or *goal-directed* attention. Less clear is the role of the FEF in *exogenous* attention. Unlike endogenous attention, which is deployed according to the goal or task relevance of particular stimuli, *exogenous* attention is governed primarily by the physical salience of sensory stimuli. This type of attention is also referred to as *bottom-up*, *involuntary*, or *stimulus-driven* attention. One major question of recent interest is the relative contribution of frontal and parietal regions to exogenous attention, particularly the FEF and the lateral intraparietal area (LIP), respectively. Both the FEF and the LIP have been proposed to contain 'salience maps', combining task goals and stimulus salience into a priority map of space for directing gaze and attention (Bisley and Goldberg 2010; Thompson and Bichot 2005; Moore and Fallah 2001). One such exogenous form of attention is 'pop-out', in which a stimulus with unique features is easily distinguished from among any number of dissimilar distractors (Treisman and Gelade 1980). Neurons in both LIP (Ipata et al. 2006) and FEF (Bichot et al. 2001) have been found to respond more strongly to pop-out stimuli than to stimuli that share features with the distractors. Buschman and Miller sought to clarify the contributions of parietal and frontal regions to exogenous and endogenous attention by simultaneously recording from areas LIP, FEF, and lateral prefrontal cortex (LPFC) during both pop-out search and an attentionally demanding covert visual search (Buschman and Miller 2007). All three areas showed target selectivity under both pop-out and covert search conditions, but the relative timing of the emergence of these effects in the different areas was markedly different in the two tasks. In pop-out, target selectivity appeared first in the responses of LIP neurons, followed by LPFC and finally FEF neurons. In all three areas a significant

subpopulation of neurons showed target selectivity before the animal's behavioural response. In the search task, selectivity arose in the FEF and LPFC significantly earlier than in LIP, which didn't select target location until after the monkey's saccade. These results suggest that while the FEF and LPFC may exert control over target selection in top-down, covert search, this function might be performed first in LIP during stimulus-driven, pop-out search.

Given the apparent overlap in the set of areas representing exogenous and endogenous attentional signals, a natural question to ask is how the two types of attentional modulation interact. Burrows and Moore recently examined the effect of saccade planning, and the accompanying attentional deployment toward the saccade target, on the representation of bottom-up, pop-out salience in area V4 responses (Burrows and Moore 2009). Monkeys passively viewed pop-out arrays either while fixating or just prior to directing a saccade to a target located away from the array. During fixation the V4 neurons showed an enhanced response to pop-out stimuli. The same neurons that exhibited this pop-out selectivity during fixation showed no selectivity just prior to a saccade away from the pop-out array, suggesting that this exogenous attentional signal is limited by the availability of endogenous resources. A model of exogenous salience by Soltani and Koch suggests that although feedforward and lateral connectivity within extrastriate cortex are sufficient to generate pop-out selectivity, such signals can be either disrupted or enhanced by incorporating top-down feedback with or without a saccade preparation signal, respectively (Soltani and Koch 2010). These results suggest a role for oculomotor or attentional feedback signals, perhaps from LIP or FEF, in maintaining pop-out selectivity in extrastriate cortex, in addition to mediating the behavioural consequences of such salient stimulus properties.
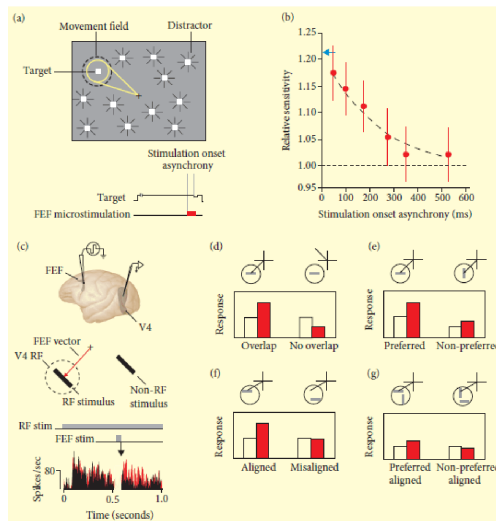
FEF Microstimulation

Although a relationship between attention and gaze control has been noted for some time (e.g. Ferrier 1890; Ribot 1890), only in the last twenty years or so has this relationship been thoroughly examined psychophysically and neurophysiologically. Gaze shifts, which are most often achieved by saccadic eye movements (saccades) seem to occur in conjunction with shifts in attention, as shown by the decrement in target detection thresholds observed near the endpoints of upcoming saccades (Hoffman and Subramaniam 1995; Peterson et al. 2004). Conversely, covert attention has been shown to alter the metrics of saccades, impacting latencies (Rizzolatti et al. 1987) and trajectories of both cue-driven and electrically evoked saccades, with the magnitude of the deviation increasing with difficulty of the attention task (Sheliga et al. 1995; Kustov and Robinson 1996). Additionally, if the eyes are maximally rotated in their orbits, spatial cues in the visual hemifield toward which no further movement is possible no longer produce their typical reaction time benefits, suggesting a functional coupling between eye movements and attention (Craighero et al. 2004).

Prompted by the psychophysical evidence of a link between saccades and attention, Moore and Fallah (2001, 2004) examined whether manipulating neural activity within the FEF could affect the deployment of spatial attention. Neurons in the FEF exhibit both visual and motor properties, responding to stimuli positioned at particular locations and/or prior to saccades toward those locations; in other words, FEF neurons can have receptive fields (RFs) or movement fields (MFs) or both (Bruce and Goldberg 1985). Microstimulation of the FEF at sufficiently high currents evokes saccades of an amplitude and direction such that gaze shifts to the location of the RFs/MFs of neurons near the electrode tip (Bruce et al. 1985; Robinson and Fuchs 1969). Moore and Fallah stimulated FEF sites using currents too low to evoke eye movements (subthreshold currents) while monkeys monitored a target stimulus among distractors for a small change in luminance (Fig. 13.1a). On trials in which microstimulation occurred, monkeys were able to detect smaller luminance changes than on control trials. This effect was spatially and temporally specific—an increase in sensitivity was observed only if the target location matched the endpoint of saccades evoked from the microstimulation site, and was strongest when onset of microstimulation immediately preceded and temporally overlapped the luminance change (Fig. 13.1b). The magnitude of the change in sensitivity produced by microstimulation was comparable to removing the distractors altogether.

In addition to producing perceptual benefits, voluntary deployment of covert attention is known to modulate visual responses of neurons in visual cortex (Treue and Maunsell 1999; Desimone and Duncan 1995). Armstrong and colleagues investigated whether subthreshold microstimulation of the FEF could alter responses in area V4 of visual cortex in a manner similar to that observed during spatial attention. Microstimulation of the FEF enhanced responses of V4 neurons to visual stimuli (Fig. 13.1c). This modulation was stronger in the presence of distractors (Moore and Armstrong 2003), and was critically dependent upon an overlap in the RF of the V4 neuron and the

endpoint of saccades evoked from the microstimulation site (Fig. 13.1d). The enhancement also depended upon the placement of the visual stimulus precisely at the endpoint of evoked saccades and not merely anywhere within the larger V4 receptive field (Fig. 13.1f; Armstrong et al. 2006). This enhancement was larger for the V4 neuron's preferred stimulus than a non-preferred stimulus, resulting in an increase in the ability of a V4 cell to discriminate between a preferred and non-preferred orientation (Fig. 13.1e; Armstrong and Moore 2007). Placing both a preferred and non-preferred stimulus within a V4 neuron's RF produces a response that is intermediate in magnitude between its response to either stimulus alone (Reynolds et al. 1999). The responses of V4 neurons to such competing RF stimuli could be biased toward one stimuli or the other with FEF microstimulation, depending on which stimulus was aligned with the stimulated FEF vector (Fig. 13.1g). These effects of FEF microstimulation mirror those of voluntary covert spatial attention on V4 responses (Reynolds et al. 1999; Reynolds and Chelazzi 2004).

Ekstrom and colleagues also examined the influence of FEF microstimulation on visual cortical activity, but did so using functional magnetic resonance imaging (fMRI), thus allowing them to see effects in all visual areas. They evaluated blood-oxygen-level-dependent (BOLD) responses throughout the visual cortical hierarchy following visual stimulation alone, subthreshold FEF microstimulation, or microstimulation combined with visual stimuli of varying contrast (Ekstrom et al. 2009). The impact of microstimulation depended upon the presence of distractors, and was more effective for low-contrast stimuli, consistent with electrophysiological studies of attentional modulation of visual cortical responses (Reynolds et al. 2000). Analogous effects have also been observed in humans, where TMS of the FEF increases extrastriate cortical sensitivity, as assessed by the ability of TMS to evoke visual percepts (Silvanto et al.
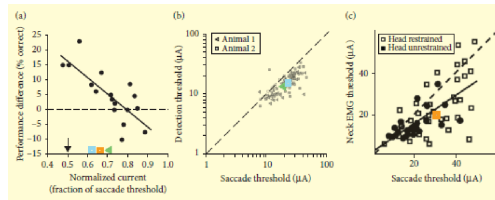

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Figure 13.1 Effects of subthreshold FEF microstimulation on covert spatial attention and on the responses of neurons within posterior visual cortex. (a) Change detection task used to test the effect of FEF microstimulation on attention. Monkeys were trained to maintain central fixation and to pay attention (spotlight icon) to a peripheral target while ignoring flashing distractors. The target was transiently dimmed at random times and the monkey had to indicate it with a manual response. The event plot at the bottom shows the temporal relationship between the timing of the target dimming and the train of FEF microstimulation, the *stimulation onset asynchrony*, which was varied across experiments. (b) FEF microstimulation increased the monkeys' sensitivity to the target dimming depending on the stimulation onset asynchrony. Relative sensitivity values denote performance relative to control trials and are given as ratios, unity being equal performance and greater values indicating improvement. The black arrow shows the improvement that results from removing the distractors in control trials. (c) Modulation of visually driven responses of area V4 neurons with microstimulation of the FEF. Sites within the FEF were electrically stimulated while recording from neurons in area V4. Cartoon shows a side view of the macaque brain. Top: the locations of the FEF in the anterior bank of the arcuate sulcus and of area V4 in the prelunate gyrus and below the inferior occipital sulcus are shown (both shaded). Monkeys performed a fixation task while oriented bar stimuli were presented inside the recorded V4 neuron's RF (dotted circle) and at another location outside the RF. The stimulation and recording sites in the FEF and area V4, respectively, could be chosen such that the FEF saccade vector (arrow) and the area V4 neuron's RF overlapped spatially. Bottom: mean response of a V4 neuron during control trials (black) and on trials in which a 50 ms microstimulation train (FEF stim) was applied to the FEF site (red). (d) Dependence of V4 modulation on the spatial overlap of stimulated FEF representation (black arrow) and the V4 RF (black circle). 'Response'

schematically depicts the V4 activity during control (open) and stimulation (red) trials. (e) Dependence of V4 modulation on the efficacy of the RF stimulus. (f) Dependence of the V4 modulation on the alignment of the RF stimulus with the stimulated FEF vector *within* the V4 RF. (g) Effect of FEF microstimulation on the responses of V4 neurons to competing (preferred and non-preferred) RF stimuli. Effects depicted in (d–g) mirror the modulations observed during covert spatial attention. Data from *Journal of Neurophysics* 91, Moore T and Fallah M. Microstimulation of the frontal eye field and its effects on covert spatial attention, pp. 152–62 © 2004, American Physiological Society and Nature 421, Moore T, Armstrong KM., Selective gating of visual signals by microstimulation of frontal cortex, pp. 370–373 © 2003, Nature Publishing Group.

2006) or by the size of event-related potentials (Taylor et al. 2007) or BOLD signals (Ruff et al. 2006) evoked by visual stimuli. Lastly, similar results have even been obtained in the owl brain, where microstimulation of a forebrain gaze control area homologous with the primate FEF, the archopallial gaze field (AGF), modulates the gain of tectal visual and auditory responses (Winkowski and Knudsen 2008).

One early concern with the experiments linking microstimulation of the FEF to attention was the possibility that microstimulation did not directly manipulate the brain's attentional circuitry, but simply produced a localized visual percept (a 'phosphene') that in turn drew the animal's attention. Humans report perceiving brief flashes of light during microstimulation of V1 and a variety of other cortical and subcortical areas (Brindley and Lewin 1968; Nashold 1970), and behavioural studies in monkeys are consistent with the animal experiencing a similar phenomenon (Bartlett and Doty 1980). However, humans do not report visual percepts during microstimulation of the FEF, despite experiencing involuntary eye movements (Blanke et al. 2000; Penfield and Rasmussen 1950). Attempts to introduce an 'artificial phosphene' in the form of a veridical visual cue have had either no or negative effects on an animal's attentional performance and neural discriminability in visual cortex (Armstrong and Moore 2007; Cavanaugh et al. 2006; Müller et al. 2005), suggesting that the attention-like effects of FEF microstimulation are not simply due to a visual percept. A more recent study provides further support that FEF microstimulation directly drives attentional deployment and does so in conjunction with the preparation of saccades (Schafer and Moore 2007). In this study, the authors exploited the fact that visual motion can distort the position of objects (Devalois and Devalois 1991) such that the endpoints of saccades to a drifting grating tend to be biased in the direction of motion (Schafer and Moore 2007). Subthreshold microstimulation of the FEF not only increased the tendency of monkeys to choose targets aligned with the stimulated representation, but it also enhanced the motion-induced bias (MIB) of saccadic endpoints made to the targets. The latter stimulation effect was unambiguously perceptual rather than motor, since introduction of a fixed saccadic vector would have reduced, not enhanced, the MIB. This effect is also inconsistent with a microstimulation-induced visual percept, as such a percept should also be expected to reduce, not enhance, the MIB.

Even in the absence of an evoked visual percept, any localized perception of the microstimulation itself could serve as a cue which the animal uses to guide attention, rather than directly driving attentional deployment. To address this potential confound, in the form of either a phosphene or more abstract sensation, a recent study directly probed the ability of animals to detect microstimulation of the FEF (Murphey and Maunsell 2008). It was found that monkeys could indeed detect when stimulation occurred, and could do so at currents below the threshold for producing eye movements. The mean value for detecting microstimulation was approximately 66% of the threshold for evoking saccades (Fig. 13.2b). Interestingly, the previously reported attentional benefits of FEF microstimulation were found to decrease as the current approached the saccade threshold, disappearing when the current reached ~75% of the saccade threshold (Moore and Fallah 2004, Fig. 13.2a). This observation served as the basis for subsequently fixing all 'subthreshold' currents to 50% of the saccadic threshold in this and further studies (e.g. Moore and Armstrong 2003). Thus, the results by Murphey and Maunsell (2008) suggest that the currents at which microstimulation can be detected (relative to saccadic threshold) do not appear to overlap with the currents at which microstimulation produces attentional benefits. More recent work by Corneil and colleagues suggests a possible mechanism for both the detection of microstimulation and the negative effects of increasing microstimulation current on behavioural performance. In natural vision, saccades are often accompanied by head movements. Recording muscle activity from head-restrained and head-unrestrained monkeys, they found that FEF microstimulation evoked neck muscle contraction, even for small saccades in head-restrained monkeys (Corneil et al. 2010; Elsley et al. 2007). Furthermore, the current required to evoke muscle activity was found to be lower than that required to evoke saccades, averaging ~70% of the saccade threshold (Fig. 13.2c). These results suggest that the basis of monkeys' ability to detect FEF microstimulation might be neck muscle proprioception, rather than visual phosphenes. Moreover, these results suggest that the attention-related enhancement observed with lower currents (relative to saccadic threshold) were not accompanied by such effects.
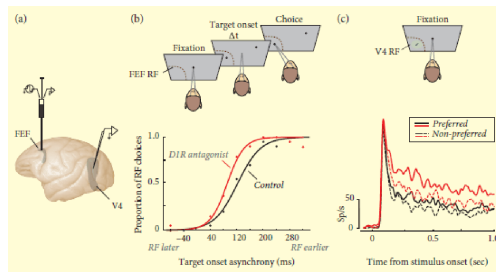
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Figure 13.2 Relationship of attention effects of FEF microstimulation and the detection of microstimulation itself to the current threshold to evoke a saccade. (a) Performance improvement with microstimulation (positive values) as a function of current magnitude, expressed as a fraction of threshold current for evoking saccades (normalized current). Arrow denotes the normalized current value (50%) used in studies of the effects of FEF microstimulation on attention and visual cortex (e.g. Moore and Armstrong 2003) (adapted from Moore and Fallah 2004). Green triangle and blue square show the mean normalized current at which two monkeys detected FEF microstimulation (Murphey and Maunsell 2008). Orange square shows mean normalized current at which stimulation-evoked neck EMG becomes measurable. Adapted from *Journal of Neurophysiology*, 91 (1), Tirin Moore and Mazyar Fallah, Microstimulation of the Frontal Eye Field and Its Effects on Covert Spatial Attention, pp. 152–62 © 2004, The American Physiological Society. (b) Current detection threshold across FEF sites as a function of threshold for evoking saccades. Detection thresholds are consistently lower than saccade thresholds. Green triangle and blue square show the means for two monkeys. Adapted from Murphey D. K., Maunsell J. H. R., Electrical microstimulation thresholds for behavioral detection and saccades in monkey frontal eye fields, *Proceedings of the National Academy of Sciences of the United States of America*, 105, pp. 7315–20 © 2008, The National Academy of Sciences. C. Threshold for neck muscle EMG across FEF sites as a function of saccadic threshold, for head-restrained (open squares) and head-unrestrained (filled circles) monkeys. Orange square shows mean head-restrained value. Adapted from Corneil B. D., Elsley J. K., Nagy B., Cushing S. L., Motor output evoked by subsaccadic stimulation of primate frontal eye fields, *Proceedings of the National Academy of Sciences of the United States of America*, 107, pp. 6070–5 © 2010, The National Academy of Sciences. Dotted diagonal lines in b and c denote the line of unity.

In spite of the above, a remaining limitation with any microstimulation result is that effects cannot be definitively attributed to the neurons near the electrode tip, as microstimulation is known to activate areas projecting to or receiving input from the stimulated site (via orthodromic or antidromic potentials), and could even activate cells in remote regions whose axons pass in proximity to the electrode tip (see Clark et al. 2011 for review). Indeed, it is known that microstimulation of the SC, to which the FEF projects, produces attention-like behavioural benefits similar to those seen with FEF microstimulation (Cavanaugh and Wurtz 2004; Müller et al. 2005). With only these experiments to go by, either set of results could in fact be entirely dependent on activation of neurons in the other brain area. Different methods of manipulating neural activity are therefore desirable in the search for causal attribution of attentional deployment to a specific brain area.

Dopamine-Mediated FEF Control of Visual Cortical Signals

In spite of a wealth of evidence for a role of PFC dopamine in attention (Robbins and Arnsten 2009) and good evidence that attentional control is achieved in part by the PFC's modulation of signals within sensory cortices (Barcelo et al. 2000; Moore 2006), these two lines of evidence have remained largely separate. However, recent neurophysiological work suggests that the PFC's control of signals within visual cortex may rely on PFC dopamine receptors (Noudoost and Moore 2011a). Dopaminergic innervation of the PFC originates from neurons within the ventral tegmental area making up the mesocortical pathway. As elsewhere in the brain, within the PFC dopamine receptors are classified into two classes, D1 and D2 (Missale et al. 1998). Compared to other subtypes, D1 receptors (D1Rs) are more abundant in PFC, suggesting a more prominent role in regulating cognitive functions (Lidow et al. 1991; Lidow et al. 1998; Goldman-Rakic et al. 1992). Within the PFC, D1Rs exhibit a bilaminar pattern of expression, while D2 receptors (D2Rs) are less abundant and appear to be expressed primarily within infragranular layers (Farde et al. 1987; Gaspar et al. 1995; Santana et al. 2009). As dopamine is a neuromodulator, evidence from a variety of experimental approaches suggests that when acting via D1Rs, dopamine's effects on PFC neurons are complex. However, these effects appear to have two general properties. First, dopamine can alter the strength and reliability of converging excitatory (glutamatergic) synapses (Seamans and Yang 2004). Second, dopamine's modulatory influence can exhibit an inverted-U-shaped property wherein a positive effect on PFC activity is observed at 'low' dopamine levels, but a negative effect is observed at 'high' levels (Vijayraghavan et al. 2007).
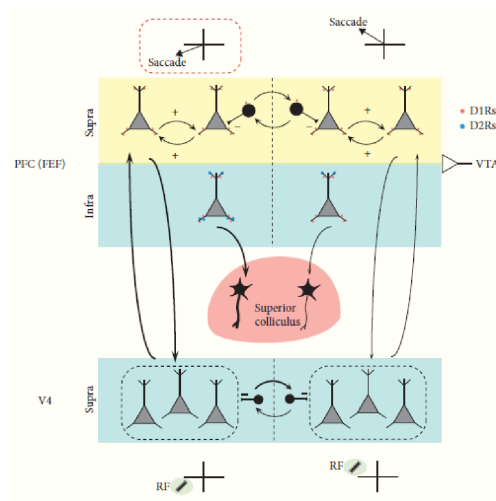
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Figure 13.3 Dopamine-mediated FEF control of saccadic target selection and visual cortical processing. (a) Local manipulation of dopamine D1 receptor (D1R)-mediated activity within the FEF during single-neuron electrophysiology in area V4. Lateral view of the macaque brain depicts the location of a recording microinjectrode within the FEF and of recording sites within area V4. (b) Free-choice saccade task used to measure the monkey's tendency to make saccades to a target within the FEF RF vs one at an opposite location. In the task, two targets appear at varying temporal onset asynchronies. The RF target can appear earlier or later than a target outside of the RF. The monkey's bias toward either target is measured as the asynchrony at which the monkey chooses the target with equal probability. The bottom plot shows the leftward shift in the asynchrony curve, indicating more RF choices, following manipulation of D1R-mediated FEF activity. (c) Visual responses of a V4 neuron with an RF that overlapped the FEF RF measured during passive fixation. The plot shows mean visual responses over time to bar stimuli presented at the preferred (solid) or non-preferred (dotted) orientation both before (black) and after (red) the FEF D1R manipulation. Reprinted by permission from Macmillan Publishers Ltd: *Nature*, 474, Noudoost, B. and Moore T. Assad, Control of visual cortical signals by prefrontal dopamine, copyright (2011), Nature Publishing Group.

Noudoost and Moore (2011a) studied the impact of manipulating D1R-mediated activity within the FEF on saccadic target selection and on visual responses of extrastriate area V4 neurons (Fig. 13.3). With respect to the latter, since the FEF appears to be the part of the PFC from which modulation of visual cortical signals originates during spatially directed attention, we might expect that if dopamine plays a role in visuospatial attention, then changes in dopaminergic activity within the FEF should alter signals within visual cortex. Manipulation of D1R-mediated FEF activity was achieved via volume injections of a D1 antagonist (SCH23390) into sites within the FEF where neurons represented the same part of visual space as simultaneously recorded area V4 neurons. As mentioned above, modulation of PFC activity via D1Rs is complex and thus infusing a D1 antagonist can be expected to increase (at relatively low concentrations) or decrease (at relatively high concentrations) local FEF activity (Williams and Goldman-Rakic 1995; Vijayraghavan et al. 2007). Thus, the manipulation of D1R-mediated FEF activity might be expected to either increase or decrease target selection and visual cortical responses. In this particular case, it was the former. Following the D1R manipulation, visual targets presented within the affected part of space were more likely to be chosen by monkeys as targets for saccades than during control trials. Thus, the D1R manipulation increased saccadic target selection (Fig. 13.3b). In addition, the responses of area V4 neurons with RFs within the part of space affected by the D1R manipulation were measured. It was found that during passive fixation those responses were altered in three ways (Fig. 13.3c). First, there was an enhancement in the magnitude of responses to visual stimulation. Second, the visual responses became more selective to stimulus orientation. And third, the visual responses became less variable across trials. Importantly, all three changes in V4 visual activity have also been observed in monkeys trained to covertly attend to RF stimuli (Motter 1993; McAdams and Maunsell 1999; Mitchell et al. 2007). Thus, manipulation of D1R-mediated FEF activity not only increased saccadic target selection but it also increased the magnitude, selectivity, and reliability of V4 visual responses within the corresponding part of space. The manipulation effectively elicited correlates of covert attention within extrastriate cortex in the absence of a behavioural task. Interestingly, infusion of a D2 agonist into FEF sites resulted in equivalent target selection increases as the D1 antagonist. However, only the D1 antagonist produced attention-like effects within area V4. Thus, in addition to being dissociable at the level of functional subclasses of FEF neurons (Thompson et al. 2005b), the control of attention and target selection appear to be dissociable at the level of dopamine receptors as well.

The effect of manipulating D1R-mediated FEF activity on V4 neurons shows that changes in FEF neuronal activity are sufficient to exert a long-range influence on representations within visual cortex, an influence suggested, but not demonstrated, by previous studies (Moore and Armstrong 2003; Gregoriou et al. 2009). In addition, these studies demonstrate that dopamine, acting via D1Rs, is involved in the FEF's influence on visual cortical signals as well as on saccadic preparation. As there is a wealth of evidence implicating D1Rs in the neural mechanisms of

spatial working memory, specifically in regulating the persistent activity of neurons within dorsolateral prefrontal cortex (dlPFC) (Williams and Goldman-Rakic 1995; Vijayraghavan et al. 2007), the above results suggest that D1Rs may be a part of a common mechanism underlying spatial attention and spatial working memory (Noudoost and Moore 2011a, b). Like dlPFC neurons, FEF neurons also exhibit persistent, delay-period activity, even in tasks not involving saccades (Armstrong et al. 2009). Persistent activity within the PFC is thought to be generated by recurrent glutamatergic connections between prefrontal pyramidal neurons (Goldman-Rakic 1995). Dopaminergic modulation of persistent activity within the PFC appears to be achieved by the influence of D1Rs on these recurrent connections (Gao et al. 2001). The above results suggest a model in which D1Rs contribute to signatures of attention within visual cortex by a mechanism similar to their influence on persistent activity, namely by modulating long-range, recurrent connections between the FEF and visual cortex (Fig. 13.4). Consistent with this idea is the finding that FEF neurons exhibiting persistent activity tend to exhibit greater attentional modulation than those without (Armstrong et al. 2009). In the model, attention (and/or saccadic preparation) is directed toward particular locations according to the pattern of activity across the map of visual space within the FEF, similar to what has been proposed for parietal area LIP (Bisley et al. 2011). Cortical columns with greater activity would correspond to locations of greater attentional deployment (and/or saccadic preparation) and consequently higher 'gain' of spatially overlapping visual cortical signals, compared to non-overlapping signals. A possible role of dopamine would be to control the extent of the FEF gain modulation, effectively setting its dynamic range. Thus, optimum dopamine levels would translate into larger differences between attended and unattended stimuli while suboptimal dopamine would result in small differences and perhaps a less stable attentional focus. At least superficially, such a role of dopamine in attentional deployment would be consistent with the perceptual deficits characteristic of ADHD patients, patients who generally exhibit prefrontal dopaminergic abnormality (Ernst et al. 1998).

Operant Conditioning of FEF Activity

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Figure 13.4 Possible influence of dopamine receptors on recurrent networks within the PFC (specifically FEF) and between the PFC and V4. The diagram depicts two adjacent FEF or V4 columns representing different but adjacent locations in saccadic or visual space, respectively. The columns are assumed to interact competitively (black inhibitory neurons). Positive arrows between FEF neurons within the same column depict the recurrent excitatory connections thought to underlie the persistence of spatial signals while remembering saccades or locations. Recurrence between the FEF and V4 is proposed to underlie the influence of the FEF on the gain of visual inputs within V4. Dopaminergic input from the ventral tegmental area (VTA, input at right) to the PFC may modulate recurrence both within the FEF and between FEF and V4 through D1Rs and to influence competition between spatial representations. For example, increases in recurrence in a particular column while remembering or attending to a corresponding location (thicker arrows at left) can be modulated by the level of dopamine. Biases in competitive interactions between columns within visual cortex can also be achieved by experimental manipulation of D1R-mediated FEF activity. Also shown are the projections from infragranular FEF neurons to the superior colliculus (SC). Other anatomical details are omitted for simplicity. Red circles represent D1Rs and blue circles D2Rs. Note the localization of D2Rs primarily in infragranular, SC-projecting layers which is consistent with the observation that changes in D2R-mediated FEF activity only affect target selection, and not visual cortical activity. Adapted from *Trends in Cognitive Sciences*, 15 (12), Behrad Noudoost and Tirin Moore, The role of

Previous studies have demonstrated the ability of humans and monkeys to voluntarily manipulate activity within motor cortical areas via operant conditioning, even when actual movements are withheld (Fetz and Finocchio 1975; Fetz 1969). Recently Schafer and Moore employed a similar operant training paradigm to examine the extent to which FEF neurons could be controlled voluntarily (Schafer and Moore 2011). Monkeys were provided with real-time auditory feedback based on the firing rate of FEF neurons, and rewarded for either increasing or decreasing that activity to some threshold (in alternating Up and Down blocks of trials) while remaining fixated (Fig. 13.5a). Overall, monkeys were able to alter the average firing rate of FEF neurons in Up vs Down operant control trials and maintained that firing rate for several seconds. Interestingly, the magnitude of voluntary modulation was uncorrelated with the visual or oculomotor properties of the recorded neurons; neurons exhibiting little or no saccade-related activity were equally likely to be controlled as those solely modulated by saccades, but not visual stimuli. Thus, the degree of voluntary control appeared to be equal across functionally defined classes of FEF neurons. Furthermore, voluntary control of FEF firing rates was associated with a frequency-specific modulation of power in the local field potentials (LFPs) at the recording site. Despite the fact that the neurofeedback and rewards were not contingent upon the LFPs, power in the beta (13–30 Hz) and gamma (30–70 Hz) frequency bands were increased during Up trials, compared to Down. LFP and EEG power in both of these frequency bands is believed to be a signature of visual attention (Benchenane et al. 2011; Womelsdorf and Fries 2007; Wróbel 2000).
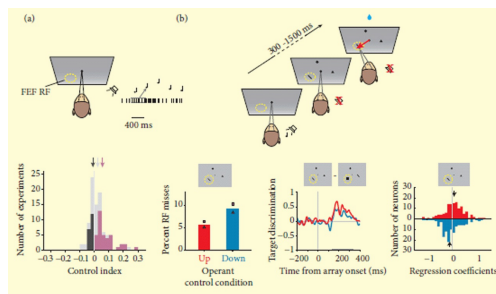
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Figure 13.5 Operant control of FEF neurons and its effects on selective attention measured behaviourally and neurophysiologically. (a) Operant control task in which the monkey fixated a central spot on an otherwise blank video display and was rewarded for increasing or decreasing the firing rate of FEF neurons. Dotted circle shows the FEF RF; speaker icon and musical notes depict auditory feedback of FEF neuronal activity (spike train) during a sliding 500 ms window (open rectangle). Bottom: population histogram of control indices across a population of FEF neurons. The control index measures the change in FEF firing rate in the rewarded direction (Up or Down); positive values denote correct control. Light grey histogram shows all experiments, purple histogram shows experiments with individually significant positive control, and dark grey histogram shows experiments with significant negative control. (b) Behavioural and neurophysiological consequences of operant FEF control. Top: visual-search probe trials, in which a search array appeared, the auditory feedback ceased ('x' on speaker icon), and the monkey was rewarded (blue droplet) for directing a saccade toward an oriented bar target. Bottom left: mean proportion of target misses opposite the RF was increased during downward operant control of FEF activity in both monkeys (square and triangle symbols). Bottom middle: target discrimination by FEF neurons, defined as the difference in FEF responses between 'Target in RF' and 'Target opposite' trials, was increased during upward operant control relative to downward. Bottom right: correlation of spontaneous activity with FEF responses to the target array. Population histogram shows the regression coefficients describing the relationship between spontaneous activity and responses to targets during upward (red) and downward (blue) operant control. The direction of operant control determined the sign of the relationship between pre-target (baseline) and target-driven FEF activity.

In addition to demonstrating that FEF neuronal activity could be modulated via endogenous means, Schafer and Moore also probed the consequences of that control on behaviour. The particular behavioural (or cognitive) strategy employed by the monkeys to achieve control of FEF activity could be unrelated to the saccadic or attentional functions attributed to this area, and instead simply be an effective strategy for modulating neuronal activity across any number of brain areas. For example, neuronal control might be achieved merely by non-specific changes in arousal or vigilance. Thus, it is important to probe for specific effects of the neuronal control strategy on the monkeys' behaviour or neurophysiology, and determine the degree to which the monkeys converged upon the same strategy. Schafer and Moore therefore introduced probe trials during the voluntary control paradigm to assess the consequences of voluntary control. In these probe trials, which occurred randomly on 29% of trials, the auditory feedback ceased abruptly and a visual search task was suddenly initiated. In this

task, an array of visual shapes appeared on the screen and the monkey was rewarded for making a saccade to an oriented bar target if it was present in the array, or for withholding the saccade if the target was absent (Fig. 13.5b). If the monkey's strategy for altering FEF firing rates was one of general vigilance or arousal, any effects of neuronal control on visual search performance should be independent of task conditions, and in particular, independent of target location. Instead, the behavioural effects of neuronal control were limited to trials in which the target appeared within the RF of the controlled FEF neurons. When the target appeared within the RF, failures to detect the target ('misses') were more frequent on the Down trials than the Up trials, while the frequency of such errors for targets appearing outside the RF was unaffected by voluntary control. In contrast to the effects of voluntary control on visual search performance, Schafer and Moore failed to find any clear effects of control on the metrics of saccades. The probability of a saccade being directed toward stimuli within the FEF RF, across all visual search conditions, was equal for Up and Down conditions, as was the reaction time for saccades to RF targets. In addition, the saccadic main sequence, the trade-off between saccadic amplitude and saccadic velocity (Bahill 1975; Boghen et al. 1974), also appeared to be identical between movements made during Up and Down trials.

Previous work by Schall and colleagues has established that neurons in the FEF signal the identification of target stimuli during visual search tasks (e.g. Thompson et al. 1996). Schafer and Moore took advantage of this property of FEF neurons and measured the neurons' ability to identify targets in the probe search trials during Up vs Down neuronal control. They found that target discrimination was greater during Up trials than Down trials, reflecting both a larger response to the target during Up trials and smaller response to the distractor in Down trials. Importantly, the change in target discrimination by FEF neurons was dependent on the direction of neuronal control, rather than simply their spontaneous firing rate just prior to the visual search probe trial. Pooling across Up and Down conditions, there was no correlation between spontaneous firing rate and subsequent target-driven responses. However, dividing Up and Down trials revealed a positive correlation between spontaneous firing rate and target-driven responses during Up trials, but a negative correlation during Down trials. Distractor responses were not correlated with spontaneous activity for Up or Down trials. These results therefore show that the strategy employed by monkeys to exert voluntary control on FEF neuronal activity qualitatively altered how exogenous visual signals interacted with endogenous neural activity.

Spatial Attention and Working Memory

Long before their role in attention was made apparent, FEF neurons were known to display spatially selective persistent activity during the delay period of a memory-guided saccade task (Bruce and Goldberg 1985), as do neurons in nearby dlPFC (Goldman-Rakic 1995). Evidence suggests that maintaining a location in working memory may automatically direct attention to that location: when subjects remember a location, visual processing at that location is enhanced compared to elsewhere in space, as measured by visual discrimination (Awh et al. 1998), visually evoked ERPs in visual cortex (Awh et al. 2000; Jha 2002), or visually evoked BOLD responses in visual cortex (Postle et al. 2004). Performing an attentionally demanding task removed from a memorized location impairs memory performance (Awh et al. 1998; Smyth 1996). The known role of the FEF in both working memory and attention, in combination with demonstrated links between these two processes on a behavioural level, naturally raises the question of whether signals representing attention vs memory are distinguishable within the FEF on the cellular level.
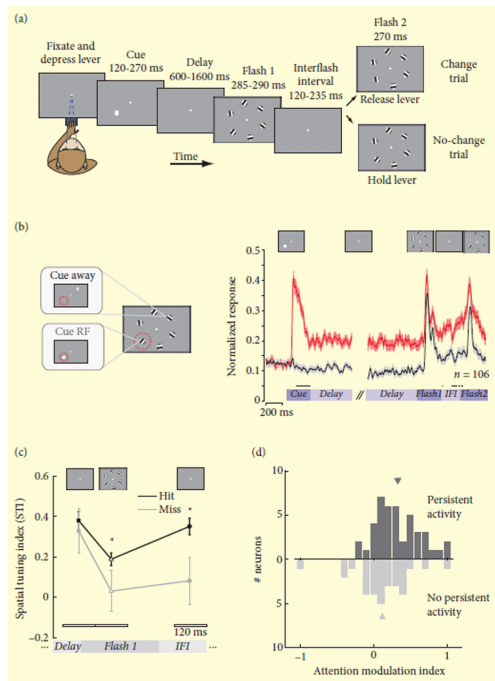
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Figure 13.6 (a) Change detection task used to measure the selection and maintenance of spatial information by FEF neurons. In the task, the monkey maintained fixation throughout the duration of the trial. To initiate a trial, the monkey manually depressed a lever, and after a few hundred milliseconds, a peripheral cue was presented briefly, indicating the target location. Following a fixed delay period, an array of six oriented gratings was flashed twice. On trials in which the target stimulus changed orientation across flashes (change trial), the monkey was rewarded for releasing the lever. On trials where the target stimulus did not change (no-change trial), the monkey was rewarded for continuing to hold the lever. (b) Trials in which the monkey was cued to attend to the opposite array location are labelled '*Cue away*', while trials in which the monkey was cued to attend to the FEF RF are labelled '*Cue RF*'. Histograms show the average response of the population of FEF neurons (n = 106) on correct trials in which the monkey was cued to attend to the RF location (red) and cued to attend away (grey). Panels along the top show a schematic diagram of the display seen by the monkey during the task and the trial epochs are also indicated at the bottom. (c) FEF neuronal responses distinguished between Cue RF and Cue away trials (spatial tuning index) across the flash1 and inter-flash-interval (IFI) epochs more effectively on correct (hit) trials than on incorrect (miss) trials. (d) Dark and light histograms show the distribution of attention modulation indices for neurons that had persistent delay period activity and for neurons that lacked persistent activity, respectively. Adapted from Armstrong K. M, Chang M. H., Moore T., Selection and maintenance of spatial information by frontal eye field neurons, *Journal of Neuroscience*, 29 (50), pp. 15621–9 © 2009, The Society for Neuroscience.

To investigate the relationship between attentional modulation and sustained memory activity within the FEF, Armstrong and colleagues recorded FEF activity during a change blindness task. In change blindness tasks, observers have difficulty detecting localized changes between two visual scenes when they are flashed in quick succession (Cavanaugh and Wurtz 2004; Rensink 2002). Directing spatial attention to a particular location can greatly increase the ability of observers to correctly detect changes (Rensink 2002). Monkeys were cued to one of six possible locations; after a variable delay, oriented grating stimuli appeared at all six locations, followed by a brief blank interval, after which the oriented grating stimuli reappeared, with or without a change in the orientation of the grating at the cued location (Fig. 13.6a). Animals indicated a change in grating orientation by releasing a bar to receive juice. The activity of FEF neurons with RFs at the cued location was enhanced during the delay immediately following the cue, during the presentation of the visual stimuli themselves, and in the interval between the two flashed grating stimulus arrays (Fig. 13.6b). FEF thus showed persistent activity maintaining memory of the cue location, and enhanced activity during visual stimulation which could direct attention to the target grating. FEF neurons with RFs at the cued location had greater activity during the interval between the two visual stimuli on correct detection trials (hits) than on incorrect non-responses (misses), such that FEF activity during this period could reliably predict the monkey's subsequent detection performance (Fig. 13.6c). Most interestingly, those neurons which showed persistent activity during the delay period were also those with the greatest enhancement

of activity during the presentation of the visual stimuli (Fig. 13.6d), suggesting mechanistic overlap between the maintenance of location information and the deployment of visual attention.

To uncover any potential difference between the representation of location memory vs the locus of attention, one might wish to dissociate the remembered location from that of targets requiring attentional deployment. To date no FEF recordings have been made during a task requiring both spatial memory and attention to a separate location, but this type of experiment has recently been conducted in dlPFC. The dlPFC is reciprocally connected with the FEF (Stanton et al. 1993), and while most of the dlPFC electrophysiology has focused on working memory rather than spatial attention tasks (Funahashi et al. 1989; Rainer et al. 1998), it also exhibits an enhanced target response during covert visual search (Buschman and Miller 2007). Lebedev and colleagues trained monkeys to remember one location while attending to a second, visually cued location, which was monitored for a change in target luminance (Lebedev et al. 2004). The remembered and attended locations could be varied independently from trial to trial, allowing construction of tuning curves for each. A majority of neurons in the dlPFC showed spatially selective activity reflecting the remembered location, the attended location, or both. Significantly more neurons represented the attended location than the remembered location, but nearly a third of those showing any selectivity were modulated by both the remembered and the attended location, referred to as multitasking neurons. Interestingly, it was found that within cells signalling both location memory and locus of attention, spatial tuning curves usually differed for the remembered vs attended location, often even favouring diametrically opposite positions (Messinger et al. 2009). This dissociation in mnemonic vs attentional tuning, as well as generally stronger tuning, makes multitasking neurons more informative than specialized neurons in extracting the remembered or attended location from neural activity. To what extent this differential tuning in PFC arises through the training of an explicit and perhaps unnatural dissociation of the locus of attention from working memory, and whether a similar dissociation in mnemonic and attentional tuning could arise in the more topographically organized FEF under similar behavioural conditions, is not yet known.

Future Directions

Thus far there has been only limited success in correlating the functional properties of FEF neurons between saccadic and cognitive tasks. For example, delay activity in memory-guided saccade tasks appears to be equally frequent across neurons with varying visual and motor properties (Sommer and Wurtz 2000). In addition, neurons that exhibit covert attentional modulation are likewise distributed among neurons with or without motor properties (Zhou and Thompson 2009), and only purely motor neurons appear to be exempt from that modulation (Thompson et al. 2005b). An important goal of future research will be to determine which types of neurons send feedback to visual cortical areas and influence visual representations during the selection or maintenance of relevant information.

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