Processing of relevant information in the primate prefrontal cortex

by

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Abstract

Extracellular recordings of neural activity were made in areas around and ventral to the principal sulcus of the lateral prefrontal (PF) cortex in two monkeys (*macacca mulatta*). Activity was assessed during the performance of three visual memory tasks.

In the first task, the sensory and mnemonic receptive fields were studied, by requiring monkeys to simultaneously remember both the identity and the location of an object presented at different locations. We report that many conveyed both object and spatial information during the sensory and mnemonic period. Receptive field size was similar during the two periods (10.8 deg. during sensory, 9.3 deg. during mnemonic period). In addition, visual space contralateral to the recording site was preferentially represented.

In a second task, the effect of attention on the responses of PF neurons was studied. Visual scenes were presented which contained three objects, only one of which was relevant for behavior. We report that PF neural activity selectively represented information about this relevant object, and activity was often identical to when the relevant object was presented alone. In addition, we describe the time-course of this attentional effect, and show that the relevant object captures PF activity very early, as soon as 140msec after onset of the visual scene.

In a third task, the role of PF neurons in a visual-visual association task was assessed. Monkeys were presented with sample objects, and had to choose the test objects that had been associated with them during training after a short delay. The behavior of the monkeys suggested that they were using a prospective strategy to solve this task, i.e. they were recalling the associated visual information soon after sample presentation, and maintaining this in working memory. We report that many neurons showed activity consistent with prospective coding. Examination of the time course of this effect suggests that the recall took place several 100 msec after sample presentation, and that the strongest prospective effects appeared 300-500msec before test object presentation.

In conclusion, across these three tasks PF neural activity selectively represented information relevant to immediate behavioral demands.

Vita

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Contents

Note: In accordance with MIT departmental and Institute guidelines, this thesis is composed of three published papers in refereed journals, and this manuscript containing a general introduction and background literature survey.

Introduction

The prefrontal (PF) cortex is thought to play a major role in mediating between perception and action (Fuster, 1993). We do not always act immediately when confronted with new perceptions. It is often of advantage to wait, and act only when more information is available. However, waiting is advantageous only if current behavioral goals and information relevant to achieve these can be held in memory during this time. This kind of short-term memory, also known as working memory, has been the function most often associated with the PF cortex in the monkey electrophysiological literature (Goldman-Rakic, 1995). During working memory tasks, many PF neurons show elevated firing during the memory periods or delays. It is thought that this delay activity provides the neural basis of working memory.

Lesions to the PF cortex in humans produce a bewildering array of deficits including disturbances in attention, memory, response selection, planning and inhibitory control. In monkeys, PF lesions were initially correlated with a deficit in delayed alternation task (Jacobsen, C.F., 1936). More recently impairments on more complex behaviors such as sequence memory, stimulus selection and associative learning have

been described (Butters et al., 1971; Petrides, 1985; Petrides, 1991; Petrides, 1994; Rushworth et al., 1997). In general, it appears that PF lesions tend not to affect more simple functions such as visual discrimination or recognition, although one recent study has implicated the PF cortex in the processing of novel visual material (Parker et al., 1998).

While different tasks have been used to study delay activity, they all rely on a similar basic protocol: Monkeys are presented with a cue for a short period of time (usually under 1 sec.), and after a delay have to perform a certain action to obtain a juice reward. Neural activity during the delay can then be correlated with the characteristics of the cue, and/or the characteristics of the action to investigate how it covaries with each of these factors. For example, in the oculomotor-delayed-response (ODR) task, a particular direction is indicated to the monkey during the cue period, and after a delay the monkey executes a saccadic eye movement to the remembered location of this cue. Delay activity can then be correlated with the direction of the response to determine the spatial tuning characteristics of the neuron under study. Since the cue and the saccade are pointing in the same direction, ODR does not allow dissociation between these factors. A modified version of ODR known as anti-saccade task does however allow the independent assessment of the influence of the

sensory cue and the expected action on neural activity. In this task, monkeys need to choose the direction opposite to the one that was initially cued. Another widely used task is delayed-matching-to-sample (DMS), where a monkey is presented with a cue object, and after a brief delay, has to select this object from a number of test objects. DMS can be conducted either as Go-NoGo where the monkey has to indicate Yes or No depending on whether a single test object matches the sample or as forced-choice where it must select the correct object from a number of choices. In both cases, neural delay activity can be assessed only as a function of the cue, since the monkey cannot predict whether a particular trial is a match or non-match before test object presentation.

Both ODR and DMS tasks have provided important insights into PF function. An extensive body of work on ODR provided important details about PF spatial tuning characteristics: Many of these neurons are spatially tuned in that they are sensitive to only certain regions of visual space (Funahashi et al., 1989; Funahashi et al., 1990). An anti-saccade task revealed that although PF neurons represent both the cue direction and the saccade direction, the majority of neurons provided a mnemonic representation of the cue direction (Funahashi et al., 1993b). In addition, lesions to the PF cortex selectively impaired memory-guided but not visually guided saccades,

suggesting a close relationship between delay activity and working memory (Funahashi et al., 1993a).

While the ODR task focuses on the spatial tuning properties of PF neurons, the DMS task has been used to investigated how delay activity varies with the identity of a sample object presented as a cue. DMS is usually conducted at the center of gaze, and thus focuses on the foveal object tuning properties. Studies based on DMS or related paradigms have described object-selective responses in PF cortex (Miller et al., 1996; Rao et al., 1997; Scalaidhe et al., 1997; Wilson et al., 1993). There is currently some debate concerning the precise anatomical location of these neurons, which are object-selective and have receptive fields which include the fovea. However, it is undisputed that object identity is an important determinant of PF neural activity.

The fact that PF neural activity can be modulated by objects and locations has thus been well documented. It is difficult to compare these selectivities however given the previous published work: Object selectivity estimates are often based on data collected at the center of gaze only, or at a few extrafoveal locations. Spatial selectivity was typically characterized by assessing direction using a ring of locations equidistant from the fovea, rather than as a uniform sampling of visual space. The

first experiment in this thesis (Rainer et al., 1998a) will use a task that allows the simultaneous assessment of both object and spatial selectivity. By presenting several objects at many locations throughout the visual field, these selectivities can be directly compared and contrasted. In addition, it is unclear from previous work whether selectivity for objects and locations might be correlated, uncorrelated or maybe even anti-correlated. In other words, are the neurons most selective for spatial location also most selective for objects? The present experiment will allow a direct assessment of this correlation. The area of visual space where a cell shows spatial selectivity can be thought of as the receptive field of that cell, so this experiment will provide some quantitative receptive field data for the PF cortex. Such data is important, because it will allow the comparison of PF neurons with many areas of visual cortex, where receptive fields have been extensively studied.

When studying a visual or indeed any kind of receptive field, it is important to determine the reference frame to which the receptive field is aligned. Visual information is encoded in the retina in retinocentric coordinates. In order to direct action to objects however (e.g. reaching for something), the brain must ultimately have a representation of that object's location in world coordinates. This requires integration of retinal position signals with eye position (w.r.t. head), head position

(w.r.t. torso) as well as vestibular signals which provide information about absolute head position. There are accordingly at least three major types of reference frames: retinocentric, head-centered and body-centered. Retinocentric receptive fields are aligned to the retina, meaning that a neuron's firing pattern is exclusively determined by where on the retina a stimulus is presented. In a pure head-centered representation, receptive fields are aligned to the head and are independent of eye position. Spatial frames of reference have been most fully explored in the parietal cortex, including areas 7a, LIP and MIP(Andersen et al., 1997), which appear critical for coordinate transformations. For example, visual responses in area LIP are modulated by eye position in a monotonic fashion, which has been termed "gain field" because eye position appeared to modulate the gain of the visual response(Andersen et al., 1985). Thus, LIP neurons do not process visual information in pure head-centered coordinates. Instead, both eye and retinal position information are combined in a distributed "gain-field" representation. One advantage of this encoding scheme is that depending on connectivity, downstream areas can recover the original retinocentric map by averaging across neurons with the same retinal but different eye position signals. The same "gain-field" representation could be sampled in a different way to create a pure head-centered receptive field architecture. More recently, it has been shown that in addition to eye position, head position also modulates visual responses

in LIP and 7a, and that these cells accordingly have head gain-fields(Brotchie et al., 1995). The fact that proprioceptive information about eye and head position has a large influence on the representation of visual stimuli in parietal cortex implicates it in sensory-motor transformations and points to the importance of parietal areas for controlling limb movements.

Neurons in premotor cortex also appear to be crucial for guiding limb movements(Graziano, Gross, 1998). Many of these cells have visual receptive fields that are arm-centered, meaning that they are aligned to arm position and move when the arm moves. In addition, these neurons tend to be bimodal with joint visual and somatosensory sensitivity(Graziano et al., 1997). These neurons thus represent visual objects near parts of the body, and may be closely involved in guiding limbs towards or away from objects in the immediate vicinity. A recent finding(Olson, Gettner, 1996) has shown that reference frames can also be anchored to objects themselves. Monkeys were trained to make saccades to either the left or right side of a bar. Neurons in the supplementary eye field (SEF) – also known as medial eye field (MEF) – were tuned to the side of the bar that was the saccade target, rather than to the spatial position of the target. These findings are consistent with object-centered spatial neglect observed in human patients(Tipper, Behrmann, 1996) and show that

spatial reference frames for the control of movements are not exclusively egocentric as described above.

In addition to this electrophysiological literature, microstimulation and lesion work has provided important insight into the reference frames employed by cortical structures. For example, it is known that the MEF and the frontal eye field (FEF) use very different coding schemes in the control of eye movements(Schiller et al., 1979; Tehovnik et al., 1994; Tehovnik et al., 1998). The FEF employs a vector coding scheme; microstimulation results in the execution of a saccadic eye movement with a certain magnitude and direction. Prolonged stimulation results in "staircasing" of multiple such saccadic vectors. Microstimulation of the MEF results in a very different type of eyemovement: The eye moves to a certain position in its orbit, and remains there for the entire duration of the stimulation. These results suggest that different reference frames are used not only in the representation of sensory data for the control of movements, but also in the actual execution of these movements. Notably, no coordinate transformations are required to acquire peripheral targets for foveal viewing, because there is a linear relationship between the distance on the retina and the amplitude of the required saccade. As a consequence, establishing which spatial frame of reference is used in a given cortical area is important because

it allows investigators to draw inferences about the whether an area maintains a more

sensory- or motor-related representation. Presently, reference frames have been

studied in parietal and premotor areas, and these studies need to be extended to

prefrontal areas to characterize them in more detail.

It is become increasingly apparent in recent years, that the behavioral state of the

monkey can exert strong influences on neural responses. This was first demonstrated

extrastriate visual cortex (area V4) and inferior temporal cortex (Moran, Desimone,

1985). This study showed that the behaviorally relevant, attended stimulus primarily

determined the neural response. Attentional studies of this kind rely on the

comparison of neural responses to groups of identical sensory stimuli, as a function of

which stimulus is currently relevant. For example, when two dots are presented in the

receptive field of an MT neuron one of which is relevant for behavior, the neuron

tracks this attended dot (Treue, Maunsell, 1996). Attentional effects have now been

well characterized in many visual areas, including the parietal cortex and even in

primary visual cortex (Gottlieb et al., 1998; Luck et al., 1997a; Motter, 1993). Given

these results, one might hypothesize that attention should also have a significant

influence on neural responses in the PF cortex, because the PF cortex receives

projections from many of these areas. In addition, it is well known that working

memory is limited in capacity (Luck, Vogel, 1997b); (Baddeley, 1992; Baddeley, Della, 1996). Such capacity limitations necessitate mechanisms of attentional selection as a way of restricting access to working memory. The second experiment in this thesis (Rainer et al., 1998b) will describe the effect of spatial selective attention on PF neural responses. The behavioral task is a classic attentional paradigm, where identical arrays of three objects will be presented, while each of the objects will in turn be relevant for behavior. In addition, each of the objects will be presented alone while monkeys are performing the same task. This modification allows the direct comparison between the sensory effect (relevant object alone) to the attentional effect (relevant object embedded in array of distractors).

The anti-saccade task described above actually represents a special case of a more general kind of task, known as paired associate task. In this task, a cue stimulus (some kind of sensory stimulus, usually visual) is arbitrarily paired with either another stimulus or an action. This pairing needs to be learned through training, and this training phase usually precedes electrophysiological recording, although some studies have recorded activity during training (Asaad et al., 1998; Chen, Wise, 1996; Mitz et al., 1991; Watanabe, 1990). The main advantage of paired associate tasks is that they circumvent a major limitation of simpler tasks like ODR or DMS. Paired associate

tasks allow us to assess whether neural activity is related to the (sensory) cue, or to the anticipated test object (or action) at the end of the delay. For example, it has been shown that V4 neurons, which do not normally respond to somatosensory stimulation, show directional tuning following haptic cues in the context of a haptic-visual paired associate task ((Haenny et al., 1988a; Haenny, Schiller, 1988b; Maunsell et al., 1991b))(Haenny et al., 1988a; Maunsell et al., 1991a). Paired associate tasks have also been used previously in the prefrontal (PF) cortex. For example, reward expectancy has been demonstrated by comparing activity to different food items (e.g. potato, raisin) to activity when a stimulus was presented that had been associated with that food item during training (Watanabe, 1992; Watanabe, 1996). Many neurons showed prospective coding for the rewards in this visual-reward paired associate task. These PF signals were presumably coding some attribute of the reward, and could thus have been gustatory, olfactory or visual in nature. Given that PF cortex is adjacent to and interconnected with orbitofrontal cortex which processes information related to taste (Critchley, Rolls, 1996), it is unclear what modality this prospective activity is coding. While visual-visual paired associate tasks have not been used to characterize PF neural activity, they have previously been used to study response properties of inferior temporal (IT) neurons (Miyashita, 1988; Naya et al., 1996; Sakai, Miyashita, 1991). It was found that certain IT neurons ("pair-coding neurons")

had a tendency to show similar activity to associated objects, suggesting a role for IT

cortex in the storage of long-term associations. There is behavioral evidence

suggesting that monkeys use a prospective strategy to solve paired associate tasks.

For example, during a auditory-visual paired associate task, visual but not auditory

interference during the delay disrupted monkeys' performance suggesting a reliance

on a prospective code (Colombo, Graziano, 1994). In addition, several lesion studies

suggest an involvement of the PF cortex in visual-visual associative tasks. For

example, it was found that disconnection of the PF cortex from IT cortex selectively

disrupted visual-visual associative task (Gutnikov et al., 1997). Another recent study

used a similar task, and found that when sample and target objects were presented in

the same visual hemifield, monkeys' performance was unaffected by section of both

the posterior and anterior corpus callosum. However, when sample and target were

presented in opposite hemifields, performance was intact for the posterior section, but

devastated after section of the anterior corpus callosum. The authors argue that this

implies a role for the PF cortex in recalling the target from storage (Hasegawa et al.,

1998). These experiments suggest a role for the PF cortex in visual-visual

associations. The third experiment in this thesis (G. Rainer et. al., 1999) will address

this issue by using a visual-visual paired associate task to study PF neural activity. It

will investigate whether signals coding the anticipated visual object are present in PF cortex, and the time-course of such signals.

All three experiments presented here are designed to further characterize the delay activity observed in PF cortex, and investigate how it relates to the psychological concept of working memory.

Conclusions

The first experiment described in this thesis shows that the object and spatial selectivity observed in the PF cortex can be well described by the receptive field model that has been extensively used to characterize visually responsive neurons in many cortical areas. PF neurons thus had receptive fields that consisted of a particular contiguous region of space. Visual stimuli presented in this region of space elicited different responses, with some object eliciting high, robust responses while others elicited little or no response from the neurons. The amount of object selectivity varied from neuron to neuron, but was generally lower than the spatial selectivity. This may reflect a difference in sampling: Spatial selectivity within the region of interest can be sampled exhaustively (given a predetermined sampling rate), whereas this is not possible for object selectivity. To date, it is an open question how object-selectivity arises and is organized in cortical neurons, with the exception of primary visual cortex (V1). Thus, object selectivity was assessed in the present task by presenting a number of objects (two to five) that appeared qualitatively different from each other, and that allowed monkeys to perform the task at a high rate. This represents a very sparse sampling of object-tuning space, certainly more sparse than the sampling of

actual retinotopic space. The reported object selectivity thus actually represents a lower bound on the actual object selectivity of PF neurons. One would predict, for example, that more neurons would be revealed as object-selective if more objects could be used to assess this selectivity. Another interesting possibility would be to compare the object and spatial selectivity across different cortical areas. Using the same task in different areas is important because tasks used in different areas tend to reflect hypotheses of investigators about these areas functions, and this sometimes makes objective assessment of an area's function more difficult. Another finding we report is that sensory receptive fields and mnemonic receptive fields (MFs) were in general in the same spatial location, and that PF neurons had a tendency to preferentially process visual information from contralateral, but not foveal, visual space. Visual space ipsilateral to the recording site was also represented, but fewer neurons were processing ipsilateral information and the latencies of these visual responses were longer. Both PF cortices thus process visual information in an area around the point of current fixation. This suggests that the PF cortex may be closely involved in the maintenance of a representation of the current visual environment and in the selection of targets for subsequent foveal viewing.

To directly test this hypothesis, an attentional task was used to study the involvement of PF neurons in selection and maintenance of relevant information. Two effects related to attentional selection were described. First, a particular object was relevant for an extended period of time (~20 minutes). This was reflected in PF activity as elevated baseline activity of neurons selective for this relevant object throughout this entire period. Because neurons signaled which object was relevant even before the onset of the array from which the relevant object had to be selected, it is possible that this elevated activity was actually involved in the process of selection. It might, for example, provide an attentional template for the relevant object and bias the competition among the presented objects in favor of the one that is currently relevant. While the identity of the relevant object was constant for a longer period, the location of this object varied randomly from trial to trial. Monkeys thus could not predict where the relevant object would be on any given trial. Consistent with this constraint, neural signals reflecting the location of the relevant objects were not reflected in the baseline of neural activity. They appeared about 140msec after the onset of the array of objects from which the relevant object needed to be selected. The relevant location was thus reflected in PF activity very early, and one may thus speculate that PF cortex might provide a top-down attentional signal to areas of visual cortex. In additional to the selectional mechanisms, we report that attention has an important influence on PF

delay activity. This effect manifested itself in different neural responses to identical sensory configurations, depending on which object was relevant. We report that a large majority of neurons selectively represented only the relevant object. In fact, activity was often indistinguishable from conditions when the relevant object was presented alone. This finding has implications for working memory, because it suggests that PF cortex does not simply buffer sensory visual inputs. Instead, it employs mechanisms of attentional selection restricting access to working memory to only those stimuli that are behaviorally relevant.

To test whether this representation of relevant information is restricted to spatially selected information or is a more general feature of PF neurons, we tested whether relevant information was represented when it needed to be retrieved from long-term memory. This is in some ways a stronger test than spatial selection, because the actual stimulus was not physically present during the cue period, and needs to gain access to working memory in competition against a recently seen stimulus. Training monkeys to associate two arbitrary visual objects takes many weeks, and one might have expected a result similar to the one observed in IT cortex where some neurons ("pair-coding neurons") tended to show similar activity to associated objects. This kind of training usually starts out with presenting the to-be associated objects side-by-side,

and moving them apart in time, turning a discrimination task into a memory task. It is easy to envisage how this kind of training might lead to "pair-coding" responses, because in the initial phases of training these objects are presented side-by-side. IT receptive fields being generally bilateral and relatively large, this would lead to two populations representing the two objects being simultaneously active. Known principles of synaptic modification such as LTP might lead to a strengthening of connections between these populations, ultimately leading to similarity in response. The situation in PF cortex is different however. Receptive fields tend to be confined to one visual hemifield and tend to be relatively small compared to IT (little quantitative receptive field data is actually available for IT). One might thus hypothesize that "pair-coding" responses might be less common in PF cortex. This is exactly what we report. During the cue period, neural response was determined by the physical characteristics of the objects, not their associative significance. Somewhat curiously, the strongest signal related to the cue objects actually occurred just after these objects were extinguished. In the delay period, we observed the appearance of a signal consistent with the expected targets that we called a prospective signal. This is consistent with a recall of the associated object from long-term memory, and its' maintenance in working memory. It is clear why such a recall would be advantageous. It allows monkeys to optimize their behavior because they can

compare the contents of working memory to the test object presented at the end of the

delay, rather than having to recall information from long-term memory during this

presentation. These findings suggest that PF cortex does not play a major role in the

long-term storage of associations, but plays an important role in the short-term

storage of information relevant to behavioral demands.

Across the studies reported here, PF cortex has been characterized as an area where

many neurons show visual responses in both sensory and memory periods. The

memory-related delay activity appears as an active, dynamic representation of

currently relevant information, and does not simply provide a short-term buffer for

incoming visual information.

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