The prefrontal cortex and working memory: physiology and brain imaging

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Sustained activity has been recorded in the prefrontal cortex during working memory tasks. First, we compare the anatomical distribution of this activity in humans and monkeys. Then, we show that it reflects many factors, maintenance of the items presented, preparation for the response, transformation of the items during the delay, task rules and task goals. Finally, we point out that sustained activity has also been recorded in other areas, such as the parietal cortex. We suggest that the key to prefrontal cortex lies not in the maintenance of sensory information but in the prospective use of that information for behaviour.

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Abbreviations
fMRI functional magnetic resonance imaging

Introduction

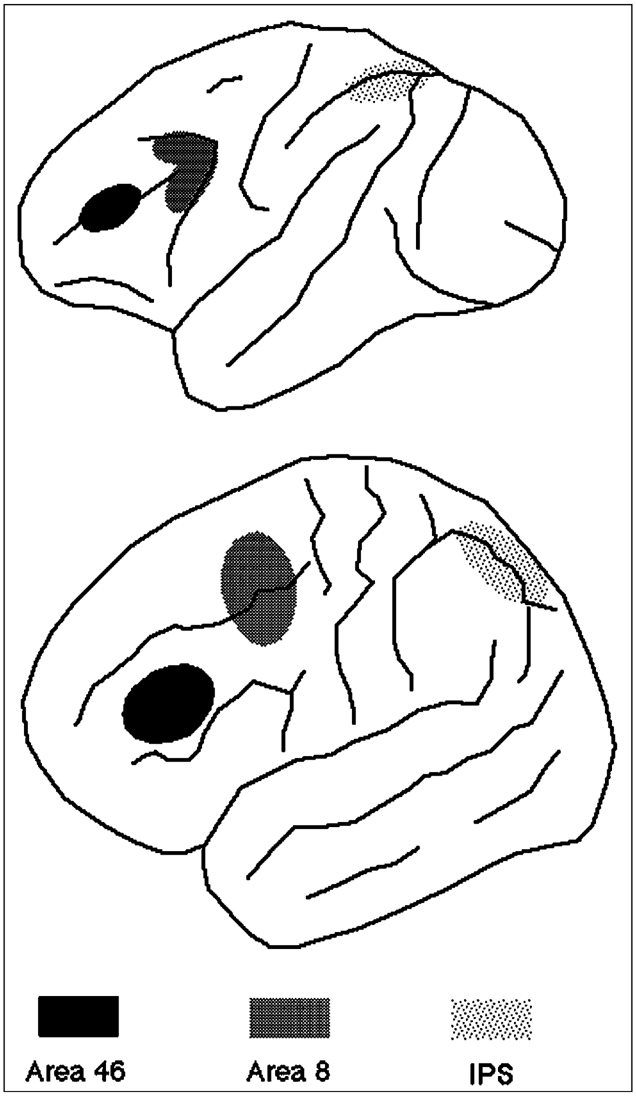
In a classic paper in 1987 Goldman-Rakic [1] proposed that the prefrontal cortex was essential for working memory. In using this term [2] she referred to the short-term maintenance in memory of information that is relevant to the task in hand. There were two main arguments. First, macaque monkeys with dorsal prefrontal lesions fail 'spatial delayed response' tasks in which they must maintain spatial information in memory for a delay of a few seconds. Second, many cells in this area show sustained firing during the delay, and different cells code for different spatial locations [3]. Since this paper was written it has become possible to measure delay-related activity in the human brain using functional magnetic resonance imaging (fMRI). The aim of the present review is therefore to combine the results from physiological and imaging experiments so as to answer three questions. The first of these is the nature of the relation between sustained activity in humans and monkeys as recorded during the delay on delayed response tasks; the second is the question of what such sustained activity reflects; the third is the difference in such activity between prefrontal cortex and other areas.

What is the relation between sustained activity in humans and sustained activity in monkeys?

To answer this question we will concentrate on studies of spatial memory, so as to ensure comparability of data on humans and monkeys. Several imaging experiments have used fMRI to measure sustained activity while human subjects remember spatial locations. The locations are presented, followed by a delay, and then recall is tested. Such activity has been recorded in posterior prefrontal cortex during the delay in the task [4–8]. It tends to lie within the area identified anatomically as area 8 [9], and delay-related activity has also been reported in this area in monkeys (Figure 1; [10,11]).

In these imaging studies of spatial memory no significant activity was reported in the more anterior prefrontal area 46 (Figure 1). In monkeys, area 46 lies in the anterior two-thirds of the principal sulcus (Figure 1; [9]), but most physiological studies have recorded delay activity related to spatial targets in the posterior third of this sulcus [3,12,13••]. Several studies have explored the cortex more anteriorly, however, and have found some cells showing sustained activity on spatial memory tasks [3,13••,14]. It could, therefore, be argued that the failure to find significant activity in area 46 in the human brain reflects the relatively poor sensitivity of fMRI [15]. This argument is stronger given the observation that only 18% of the task related cells in area 46 show greater delay-related activity when the monkey has to remember a spatial cue compared with control conditions in which they do not because a cue is provided throughout the delay [14]. Three recent imaging studies have reported sustained activity in area 46 when subjects remember spatial items. In one, single spatial locations were used, but sustained activity in area 46 was only found in some subjects (Curtis C, pers comm; [16,17••]). In another, delay-related activity was only found if lists of five rather than three spatial items were used and the delay was long (18 or 24 s) [18•]. The final study required subjects to remember the detail of complex spatial patterns [19••]. Comparing the data on humans and the data on macaques, it appears that it is more difficult to find sustained activity related simply to maintenance in area 46 in fMRI studies of humans.

Figure 1



Drawing of macaque brain and human brain (left hemisphere) with the approximate location of prefrontal areas 46 and 8 and the cortex of the intra-parietal sulcus (IPS) highlighted. Area 46 lies in the anterior two-thirds of the principal sulcus in the macaque brain and anteriorly in the middle frontal gyrus in the human brain.

What does sustained activity reflect?

Goldman-Rakic [1] interpreted sustained activity as reflecting primarily the maintenance of sensory items in memory. She assumed that monkeys with prefrontal lesions failed delayed response tasks because in the absence of this activity they did not represent the spatial locations in memory. Since then, however, further studies have indicated that sustained activity can reflect many factors [17••,20].

Maintenance of sensory information

On an oculomotor spatial delayed response task, the monkey makes a saccade at the end of the delay to the location at which the target was presented. Delay-related activity could therefore reflect either maintenance of the spatial location or preparation to make the saccade. It is possible to isolate activity related to maintenance by varying the response [13••,20], and on this task the majority of cells in the posterior third of the principal sulcus (Figure 1) code for the retained location [13••,20].

In imaging studies one can also arrange that during the delay the subjects can only maintain the spatial location of the cues because they do not yet know what sort of response will be required. Under these conditions there is sustained activity in area 8 [7,8], and this probably corresponds to the activity recorded in this area under similar conditions in monkeys [11]. If the load of the items to be remembered is small, there is little delay activity in area 46 when human subjects can only maintain spatial information about the cues and not prepare their response [7,18•]. However, delay-related activity has been reported in area 46 when subjects remember houses [21], faces [22,23] or complex spatial patterns [19••], even though at that stage the subjects do not know what response to make. It could be that memorising such stimuli requires active rehearsal or recoding of the items [17••].

Response preparation

On an oculomotor delayed response task, a minority of cells in the principal sulcus code for the upcoming response [13••,20]. Pochon *et al.* [24] used spatial working memory tasks, and compared a condition in which subjects could prepare their response with another in which they could not. There was significant sustained activity in area 46 only when the subjects could prepare their response. Curtis and D'Esposito [16] directly compared trials in which preparation was or was not possible on an oculomotor delayed response task, and again there was significantly more activity in area 46 when the subjects could prepare their response.

Transformation

On an oculomotor delayed response task, the target location is the same as the location of the cue. However, Funahashi and Takeda [13••,20] included a condition in which the monkey had to respond to the location at 90° to the cue location; in this way they were able to show that during the delay period there was a conversion of activity in the principal sulcus from a subpopulation of cells representing the cue location to a subpopulation of cells representing the response location. In other words, the sustained activity also reflects the transformation from the sensory input to the response. There was a more rapid increase in the population activity coding for the response in the rotation condition, and this could reflect the greater demands for transformation in this condition. Similarly, changes have been noted in an experiment in which monkeys had to choose object X if they had seen object

A before the delay; the activity early in the delay reflected memory of A, but late in the delay the impending choice of object X [25].

Human subjects can also be required to transform the material during the delay. Several experiments have instructed subjects to re-order either spatial [6] or verbal items [26–28] during the delay. These experiments have reported either activity in area 46 only when such manipulation is required [6,27] or greater activity for manipulation than for simple maintenance of the items in the order presented [26,28].

Task rules

These transformations are specified by the task rules. Miller and co-workers [29,30•] have trained monkeys on different task rules, for example matching or non-matching, and have reported that many cells in the lateral prefrontal cortex fire differentially during the delay according to the specific rule in operation. In these experiments, the instruction concerning the rule was given at the beginning of each trial. The justification for using the word 'rule' is that this differential activity occurs even when new stimulus sets are used; thus, the rule is abstract.

In human studies, the rules are given by the instructions. Bunge *et al.* [31•] have reported delay-related activity in the ventral prefrontal and polar cortex that was sensitive to task rules, and this probably corresponds to the activity reported in monkeys [29,30•]. Sakai and Passingham [32••] presented both spatial and verbal items in a memory task, and compared four rules, to remember the spatial items in a forwards or backwards order, and to remember the letters in a forwards or backwards order. There was sustained activity in frontal polar cortex after the instructions were given but before the memory items were presented. Furthermore, there was a stronger correlation of activity between frontal polar cortex and area 8 (spatial) when the instruction was to reverse the order of the spatial items, and in activity between frontal polar cortex and Broca's area 44 (verbal) when the instruction was to reverse the order of the letters. On the basis of these results, the authors argued that the activity reflects the specific task operation to be performed ('task set').

Goals/rewards

Monkeys are taught the rules of a task by the presentation of rewards. Sustained activity during the delay also reflects their expectation of rewards. Some cells show activity when the monkey is expecting a reward and others when it is not expecting to receive a reward [33]. There are also cells that show differential activity depending on the type of reward the animal is expecting, for example raisin, potato or cabbage [33]. In this study, cells coding for reward were most common in the ventral prefrontal cortex, but in other studies cells coding for expected reward have been recorded in the orbito-frontal cortex [34]. However, when monkeys are tested on an oculomotor delayed response task, cells can be found in lateral prefrontal cortex that either code for both spatial location and reward [35•] or show differential activity during the delay depending on the size of the reward that the animals are expecting [36]. This suggests integration in this area of information about the current sensory stimuli and expected outcomes.

As is the situation in monkeys [34], activity in the human orbito-frontal cortex can reflect such expectancy [37,38]. However, there is also greater activation in the frontal polar cortex when subjects expect high reward, and there was activation in the same area when subjects performed a difficult working memory task [39]. The crucial observation is that in this area there is an interaction between the delay-related activity and the size of the expected reward [40•]. As is the situation in the monkey brain [35•,36], there is integration on the lateral surface between memory-related activity and reward expectancy.

What is special about sustained activity in prefrontal cortex?

The evidence that there is sustained activity in the prefrontal cortex is not sufficient on its own to justify the claim that the key to this area is working memory. As already mentioned, on spatial working memory tasks there is similar activity in other areas, such as the parietal cortex in both monkeys [10] and humans [5,7,8,19••,41••]. However, there must be differences in the activity of prefrontal cortex and parietal cortex because inactivation of prefrontal but not parietal cortex interferes with delayed response performance [42].

There are two clues. First, Pochon *et al.* [24] used fMRI to measure delay-related activity on two spatial tasks. In one task the subjects could prepare their response and in the other they could not. Though there was activity in parietal cortex when subjects could prepare, there was no significant difference in activity between the tasks; however, activity in area 46 was confined to the task in which the subjects could prepare. The second clue comes from a study by Sakai *et al.* [41••], in which the subjects had to remember spatial sequences, but before recall of these items a spatial distractor task was presented. The degree of sustained activity in area 46 closely predicted the accuracy of recall after distraction, but the delayed-related activity in parietal cortex was as great on trials in which the subjects later made errors as on those trials in which they were correct. The authors suggest that during the delay the subjects actively rehearsed and re-organized or transformed the items so as to make them resistant to distraction, and that the delay-related activity that occurs in the dorsal prefrontal cortex on trials that will be performed correctly reflects this operation. There is more activity in this area when subjects use such strategies to aid memory [43,44•].

These results suggest that what is special about sustained activity in prefrontal area 46 might not be simply the maintenance of sensory information. This conclusion is supported by a positron emission tomography (PET) study by Owen *et al.* [45] in which they scanned subjects during an 'n-back' spatial working memory task that involved responding to the location two back in the remembered sequence of the trial. When subjects performed this task there was more activity in prefrontal area 46 than during a task in which they had just to maintain the items in memory. However, this was not true for parietal cortex, although it could be that the methods used were not sensitive enough to detect a difference in this area.

Conclusions

Anatomically, prefrontal cortex lies at the top of the sensory and motor hierarchy [46]. It receives information from all sensory modalities and sends outputs to the motor system [47]. As it is the unique pattern of connections that determine the operations that an area performs [48••], it is not surprising that sustained activity in this area can be shown to reflect information about sensory cues, responses, task rules and task goals [49,50]. We suggest that prefrontal cortex could be unique in being able to integrate this information so as to select the appropriate behaviour. This could involve the transformation of sensory input into a response code. Activity that reflects such a transformation might be found more anteriorly within the prefrontal cortex, for example in area 46. We suggest, therefore, that the key to this area lies not so much in the maintenance of sensory information as in the prospective use of that information.

Given our stress on the transformation from a sensory to a response code, one area for future research lies in the study of interactions between activity in the prefrontal cortex and activity in areas involved in specific response modalities. The feasibility of doing this using imaging has been shown by Rowe *et al.* [51] and Sakai *et al.* [32••,41••]. The ultimate aim of systems neuroscience, including imaging neuroscience, is to understand how the brain works as a whole. In this enterprise Goldman-Rakic was a pioneer [1,10,42,52].

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This single unit recording study tested an oculomotor delayed response task with manipulation of the maintained spatial information. Monkeys were required to make a saccade 90 degrees clockwise from the cue location after the delay. During the delay in the prefrontal cortex there was a transformation from a population of neurons that code stimulus information to neurons that code response information. This is further illustrated by Funahashi and Takeda [20] when they analyse the same data in terms of population vectors.

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The authors gave difficult spatial patterns to remember, and showed that the sustained activity in prefrontal area 46 as well as parietal areas predicted performance at the response phase. Using a sophisticated analysis of logistic regression, they showed that differential delay activity occurred even for those trials in which the activity during encoding was strong, demonstrating that it was not a simple consequence of effective versus ineffective encoding.

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The authors compared the activity of task rule neurons in the prefrontal and premotor cortex using a match or non-matching task with abstract patterns. They found more such cells in the premotor cortex but the authors suggest that this could be because the tasks were overtrained. Interestingly, the task rule activity appeared earlier in the premotor cortex, which is thought to be downstream of the prefrontal cortex.

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This fMRI study used a multi-task paradigm with four types of working memory tasks. There was sustained activity in the frontal polar cortex during the period between the task instruction and the actual performance of the task. This area interacted differently with posterior regions depending on both the domain of the material (spatial or verbal) and the task operation to be performed on that material (remembering the items in a forwards or backwards order). This suggests the role of the frontal polar cortex in establishing task sets.

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