Working memory: **Trouble in mind**

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Visual working memory has been found to depend on interactions between the prefrontal cortex and visual association areas; the neurons involved can be modulated by dopamine. These new findings have relevance for the treatment of Parkinson's disease and schizophrenia.

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Working memory is the temporary neural information store that provides continuity between our past experience and our present situation, and allows us to plan ahead for what we are likely to encounter in the immediate future [1]. Given the obvious need for such continuity, it is not surprising that deficits in working memory lead to a host of behavioural complications. These include problems with the organization of behaviour and with attention, as the importance of an object or action in the present is often dependent on its importance in the immediate past.

One area of the brain that appears to be particularly important in working memory is the prefrontal cortex — damage to this part of the brain causes severe working memory deficits. Recently, excitement has been generated by the discovery that there are interactions between the prefrontal cortex and the visual association areas that are involved in the maintenance of visual working memory. These interactions seem to be fine-tuned by modulatory inputs from several neurotransmitter systems, including the dopaminergic and cholinergic systems. Disruption of this fine-tuning process appears to impair the efficiency of the neural activity that underlies working memory, providing clues as to how working memory may be impaired in psychiatric disorders.

Vision and working memory

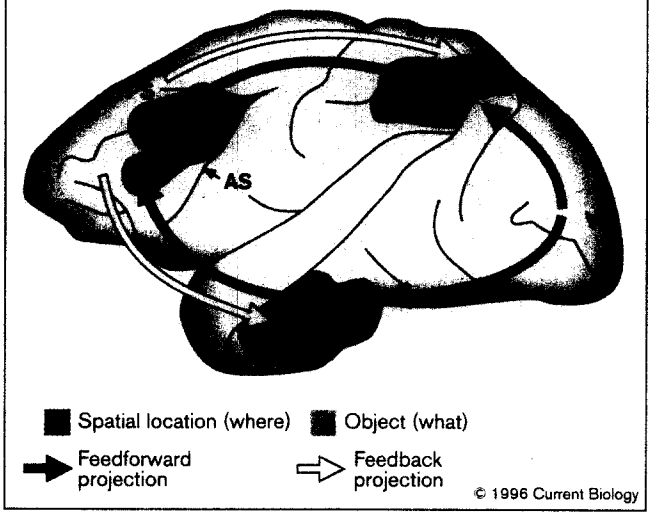
Visual processing in the primate cortex can be divided into two broad streams (Fig. 1): the ventral system (the 'what' stream), concerned with the identification of an object, and the dorsal system (the 'where' stream), concerned with the relative spatial position of an object [2,3]. The two streams ultimately project to different prefrontal cortical areas [4]. The ventral system projects to the cortex of the inferior convexity (IC), ventrolateral to the principal sulcus, and the dorsal system projects to the dorsolateral (DL) prefrontal region. As one moves along both of these visual streams from the retina, through the primary visual cortex to the visual association areas, the response characteristics of neurons change. Neurons higher up the pathways have larger receptive fields and respond to more complex stimuli. In the highest association areas, the activity of the neurons plays an important role in working memory. For example, in the primate inferior temporal (IT) cortex there are neurons responsive to complex biological stimuli such as faces.

A particular complex stimulus is encoded by the unique pattern of activity across a neural population in the higher association areas [5,6]. Such neurons are not only important for the recognition of a stimulus, but also seem to play a role in the maintenance of visual working memory. An effect of prior presentation of a visual stimulus on the responses of these neurons can be detected in either of two ways: by the suppression of a neural response, or by the enhancement of a neural response. Repeated presentation of a particular stimulus reduces the responses of IT neurons to it, but not to other stimuli. This selective suppression of neural responses to familiar stimuli may function as a way of making new or unexpected stimuli stand out [7]. This selective suppression can be found in the IT cortex of monkeys passively viewing stimuli, and even in anaesthetised animals, suggesting it is an automatic process which is independent of cognitive factors [7].

Enhancement of neural activity has been reported to occur when a monkey is actively carrying out a working memory task, such as delayed-matching-to-sample (DMS). In the basic form of this task, a sample stimulus is presented, followed, after a delay, by a test stimulus. The monkey has to indicate whether the test stimulus matches or differs from the sample stimulus. Some neurons in the monkey IT cortex maintain a high firing rate during the delay between stimuli (which can be as long as 10 to 15 seconds), as though they are actively maintaining a memory of the sample stimulus for comparison with the test stimulus [8]. However, if a new stimulus is presented during the delay between the sample and test, the maintained neural activity is abolished [9]. This neural activity seems to represent a form of visual rehearsal which can be easily disrupted, but which may still be an aid to short-term memory formation [7].

In a variant of the DMS task, a sample stimulus was presented, followed by a sequence of test stimuli, and the monkey had to indicate which of the test stimuli matched the sample [10]. Under these conditions, a proportion of

Figure 1



The location of the 'what' and 'where' pathways in the primate brain, and the proposed feedback projections from prefrontal cortex during working memory tasks (see text for details). PS, principal sulcus; AS, arcuate sulcus; PP, posterior parietal cortex; IT, inferior temporal cortex; DL, dorsolateral frontal cortex; IC, inferior convexity of the frontal cortex; V1, primary visual cortex.

IT neurons gave an enhanced response to the test stimulus that matched the sample stimulus. Robert Desimone [7,11] has suggested that the basis of this enhanced response lies in signals coming in a top–down direction from the ventral prefrontal cortex, an area which has been implicated in short-term visual memory [4]. Like IT neurons, some neurons in the IC show a maintained firing rate during the delay interval [7,11]. This maintained firing is temporarily interrupted by additional stimuli shown during the delay interval, but the activity rapidly recovers. Desimone speculates [7,11] that this maintained information about the sample stimulus may be fed back from the prefrontal cortex to the IT neurons, so that they give an enhanced response to the correct test stimulus.

A similar feedback system seems to function in the dorsal stream. Neurons in the posterior parietal (PP) cortex and the DL region are sensitive to the spatial relationships in the environment. A recent study has shown that there is co-activation of these areas during spatial memory tasks [12], and the reversible inactivation of either area through cooling leads to deficits in such tasks [13]. Neurons in both areas show a maintained response during the delay interval, like those in the IT and IC regions, and the maintained activity in the PP cortex can be disrupted by cooling of the DL region [14]. This suggests that feedback from prefrontal areas is important for the maintenance of the neural activity in the higher visual association areas that is associated with visual working memory (Fig. 1).

Fine-tuning memory

It is well known that there is extrathalamic modulation of the cortical visual system at all levels, and that this includes the prefrontal cortex and the higher association areas [15]. Recent studies have concentrated on the dopaminergic innervation of the prefrontal cortex, and it has been shown that changes in dopamine levels are associated with working memory deficits in monkeys [16]. These studies have an immediate clinical relevance, as changes in the dopamine innervation of the prefrontal cortex have been implicated in working memory deficits in both Parkinson's disease and schizophrenia. Williams and Goldman-Rakic [17] have established that the prefrontal cortex is a major target of the brain stem dopamine afferents that synapse onto the spines of pyramidal neurons. The same spines often also have excitatory synapses from the sensory inputs arriving at the prefrontal cortex, and this arrangement has the potential to allow direct dopamine modulation of local spinal responses to excitatory input [18].

Dopamine receptors of a particular sub-type (D1) are concentrated in the prefrontal cortex, primarily on the spines of pyramidal cells [19], and iontophoresis of a D1 antagonist enhances the activity of neurons in the DL region during the inter-trial periods of a spatial memory task. These DL neurons seem to display spatially tuned 'memory fields' [20]. The neurons respond maximally during the delay period to targets which had appeared in one or a few adjacent locations (the memory field), but do not respond to targets in any other location. Different neurons seem to encode different spatial locations, so it is possible that a precise spatial location could be encoded by a population of neurons.

The D1 antagonist causes an enhancement of the delay activity for stimuli in a cell's memory field, but not for any target locations outside this memory field. This effect is dose-dependent: higher levels of D1 antagonists inhibited cell firing at all stages of the spatial memory task, it did not matter whether the target stimulus was shown in the memory field or outside it [20]. These results suggest that intensive D1 receptor blockade may render prefrontal cells unresponsive to their normal functional inputs, and Williams and Goldman-Rakic [20] suggest that this may be through indirect mechanisms involving inhibitory local circuits. This possibly explains the reports that deficits in working memory are produced by injection of D1 antagonists [21], and delay period activity is inhibited by non-selective dopamine antagonists [22].

A clinical application?

Visual working memory thus seems to be dependent on interactions between the prefrontal cortex and the higher association areas. This activity is modulated by dopamine through the D1 receptors. D1 is merely one of a number

of dopamine receptor subtypes found within the prefrontal cortex; these have different distributions and seem to have different functions. Moreover, it seems that other neurotransmitter systems, such as the cholinergic system, may also play a modulatory role in prefrontal memory function [23]. This is underlined by the facts that most drugs that have been used to alleviate the symptoms of schizophrenia act through D2 dopamine receptors, and that the new wave of neuroleptic drugs used in psychiatric treatment act through serotonin (5-HT) receptor. Nevertheless, Williams and Goldman-Rakic' results [20] show that specific doses of selective D1 antagonists can alter the ability of primates to carry out a memory task, and suggest that the use of antagonists or agonists selective for specific receptor subtypes, combined with electrophysiology in awake, behaving monkeys, may be the way to cut through the Gordian knot of neurotransmitter interactions in prefrontal cortex.

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