Neural representation of visual objects: encoding and top-down activation
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Knowledge or experiences are voluntarily recalled from memory by reactivation of their neural representations in the association cortex. Mnemonic representations of visual objects, located in the ventral processing stream of visual perception, provide the best indication of how neuronal codes are created, organized and reactivated. Associative codes are created by neurons that have the ability to link the representations of temporally associated stimuli. Recent experiments suggest that not only bottom-up signals from the retina but also top-down signals from the prefrontal cortex can trigger the retrieval of associative codes, which may serve as a neural basis for conscious recall.

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Introduction
Neural representations of declarative knowledge or experiences are stored in the association cortex and reactivated on demand by the trigger of internal or external cues. Three routes of inquiry are central to understanding this process. First, finding where mnemonic representations are coded and how they are organized, second, discovering which neural processes create the representation. Third, identifying the mechanism that underlies reactivation of the representation voluntarily recalled. Early neuropsychological studies in humans suggested that long-term declarative memory is stored in the neocortical association area, which is also involved in sensory perception [1,2]. These studies showed that when the temporal lobes of epileptic patients are stimulated electrically via cortical surface electrodes, they sometimes recollect past perceptual experiences (‘experiential responses’) [3], but also see [2]. These observations suggested that the artificial electrical input to the putative memory storehouse reactivates the ‘brain’s record of auditory and visual experience’ [3].

Recent experimental studies in humans and non-human primates have moved beyond these classical clinical observations and have revealed clearer and more solid views on these issues, particularly regarding these memory system for visual objects.

The inferior temporal (IT) cortex — the final stage of the ventral processing stream devoted to object vision — has long been assumed to serve as the storehouse of visual long-term memory [2,4,5]. Using single-unit recordings in monkeys performing visual memory tasks, the neuronal correlates of long-term memory have been identified in the anterior ventral part of the IT cortex [5–7]. Specifically, a class of neurons (called pair-coding neurons) have been found to exhibit significantly correlated visual responses to arbitrarily assigned picture pairs in a visual stimulus–stimulus association task [8,9], demonstrating that IT neurons can establish new linkage between different stimuli that have meaningful connections.

This review describes recent studies aimed at furthering our understanding of roles of the neural representation of visual objects, which are making use of three complementary approaches. First, the analysis of single-unit responses will help to firmly establish the roles of higher-order visual representations (even beyond the IT cortex) as part of a dynamic network (Figure 1a). Characterization of bottom-up and top-down signals in such a network should provide information regarding the executive roles of the prefrontal cortex. Second, neural representations in the human cortex, which have recently been revealed by functional magnetic resonance imaging (fMRI) [10,11*], should be compared with the detailed knowledge of neuronal representations in the monkey cortex obtained by single-unit analysis. Third, monkey fMRI should facilitate these comparisons by bridging the gap between data from human fMRI studies and monkey single unit analysis. The functional magnetic resonance imaging (fMRI) advances should provide a powerful means of discovering how neural codes are linked to conscious experiences.

Active representation and subjective percepts
A striking feature of neural representation in the monkey IT cortex, compared to other early visual areas, is that the single-unit activities are more contingent upon the subjective perceptual experience under binocular rivalry conditions [12] (i.e. when different images are shown to the two eyes, the subject perceives only one of the two images and perception alternates spontaneously between each monocular view, known as one example of perceptual reversals). Cortical regions whose activity is related to rivalrous percepts have been systematically investigated in humans using functional brain imaging. The extrastriate areas in the fusiform gyrus, but not early visual areas, have been found to...
display significant enhancement of neural activity (i.e., increased magnetic resonance signal) during perceptual reversals [13,14**]. Tong et al. [15**] have demonstrated that when a house and a face are presented to different eyes during binocular rivalry, changes of stimulus-selective magnetic resonance signals in the fusiform ‘face’ area [16,17] and parahippocampal ‘place’ area [18,19] are differentially accompanied by changes of the subject’s percepts. Thus, activity in these object-representation areas seems to reflect the perceived stimulus rather than the actual retinal stimulus. In another study using superimposed visual stimuli, it was found that when the subject attended to one attribute of an object, such as the motion of a moving face, the magnetic resonance signal was enhanced not only in the area coding for the attended representation (i.e., motion area, middle temporal [MT]/medial superior temporal [MST]) but also in the area coding for the representation of the non-attended attribute of the same object (i.e., the face area) [20]. O’Craven et al. [20] interpreted this finding as evidence that the units of attention are not locations or individual features but whole objects, and that attention to the object binds the visual attributes of form and motion (for reviews on the binding problem, see [21**]).

In all of these fMRI experiments, it has generally been assumed that the evoked neural activity bears a simple constant relationship to the stimulus or percept throughout the response period. This is usually the case, as confirmed by recent physiological studies that also revealed novel aspects of object representations in the monkey IT cortex, such as representation for disparity-defined three-dimensional shapes [22] and view-invariant representations of familiar objects [23]. However, it is not always the case, as Sugase et al. [24•] have demonstrated. They found that while the monkeys view pictures of faces and coloured shapes, the information carried by responses of IT neurons changes over time in a few tens of milliseconds, from a more global-level (face versus non-face, or human face versus monkey face) to a more specific-level (identity or facial expression) of stimulus discrimination. This finding suggests that individual neurons can use different coding strategies to carry information about multiple attributes of various stimuli [25], therefore, changes in the magnetic resonance signal need to be interpreted cautiously.

Creating the mnemonic representation

Lesion studies in primates have implicated the IT cortex in long-term memory storage of visual objects [2,4]. Neuronal correlates of associative long-term memory in the IT cortex were first reported by Miyashita [7] and by Sakai and Miyashita [8]. Their single-unit recording experiments identified two mnemonic properties of IT neurons. First, the stimulus selectivity of IT neurons can be acquired through learning in adulthood. Second, the activity of IT neurons can link the representations of temporally associated but geometrically unrelated stimuli.
This first property — the modifiability of the stimulus selectivity — was soon supported by Logothetis et al. [26] and recently by Kobatake, Wang and Tanaka [27]. They trained adult monkeys to discriminate complex shapes in awake conditions, and examined the stimulus-selectivity of cells in area TE of the IT cortex of these monkeys in anesthetized conditions. The proportion of TE cells maximally responsive to some member of the trained stimuli was significantly greater in the trained monkeys (25%) than that in the control untrained monkeys.

In contrast, the association effect upon IT neurons — the second part of the findings by Miyashita and colleagues — required more time to gain support. Guided by a theoretical conjecture that the modification of response properties for temporally associated stimuli might also be a mechanism for learning to associate different three-dimensional views of the same object [5,28], Logothetis et al. [26] found that TE neurons indeed respond more commonly to different three-dimensional views of the same object than would be expected by chance. However, two other groups [29,30], using two different association tasks, failed to find evidence of IT cell participation in association learning. Recently, Erickson and Desimone [31] have provided positive evidence for the association effects upon IT cells. They recorded neurons in the perirhinal area of the IT cortex from monkeys during performance of a visual cue-choice association task, and found the correlation between responses to a cue stimulus itself to be highly significant. They also reported that the learning effect was observed only for stimulus pairs that had been associated together for at least two days of training. Furthermore, Yakovlev et al. [32] reported that the stimulus-selective delay activity in IT neurons, originally reported by Miyashita and Chang [33], could work as a vehicle to generate long-term visual associations. Therefore, it has now been clarified that IT neurons have the ability to establish new linkages between different stimuli that have arbitrary but cognitively meaningful connections.

Consistent with these physiological observations, recent behavioral experiments have further characterized the roles of areas implicated in visual memory [34]. The perirhinal area of the IT cortex was initially assigned selective functions in visual stimulus recognition and stimulus–stimulus association [2,5,34,35]. Some views now emphasize a more general role in perceptual identification [36] or in visual learning procedures such as configural learning [37], whereas others point a role exclusively confined to declarative memory [38]. Novel aspects of the hippocampal functions have been also discussed [39,40]; see also the review by Sutherland and McNaughton in this issue, pp 180–186. On the other hand, although ablation studies [41,42] have revealed a functional double dissociation between two subareas in IT cortex (i.e. the perirhinal area and area TE), physiological studies have failed to identify functional differentiation among subdivisions of the IT cortex so far, except for two preliminary reports (Z Liu, B J Richmond, Soc Neurosci Abstr 1997, 23:1964; Y Nava, M Yoshida, T Ishii, Y Sakurai, Y Miyashita, Soc Neurosci Abstr 1999, 25:530). It is now vital to establish the functional differentiation at the single-unit level and to understand how these subareas interact with each other in storing information about visual objects.

**Activating the representation in the temporal cortex on demand**

In spite of the classical clinical observation that electric stimulation to the temporal lobe produced ‘experiential responses’ [3], there have been only a few lines of direct evidence supporting the notion of ‘reactivation of neural representations’ during memory retrieval. A neuronal correlate of the reactivation process was first reported as ‘pair-recall neurons’ by Sakai and Miyashita [8]. In a subsequent study, they [43] devised a new, modified pair association task. In this task, a colour switch, which is presented during a delay period between presentation of a cue object and the choice objects, indicates whether the correct choice should be the same as the cue (delayed-matching-to-sample), or should be the cue’s paired associate. Single-unit recordings in monkeys performing this task revealed that IT neurons selective to a memorized object are dynamically activated at the presentation of a colour switch, whereas neurons selective to irrelevant objects are suppressed. A similar prospective delay activity — an activity predicting the sought target rather than a cue stimulus itself — was also found in a Go/No-Go-type task for stimulus pairs that had been associated together for at least two days of training [31]. With these accumulating results, an outstanding question has been to discover the neural network that drives the memory-retrieval machinery in the IT cortex. A recent advancement is discussed in the next section.

**Top-down activation through the fronto-temporal feedback pathway**

A candidate for a component of the neural circuit for top-down activation is the prefrontal cortex. Although prefrontal lesions do not usually result in severe amnesia [44], some neuropsychological observations indicated that the prefrontal cortex may play a role in the strategic control of memory retrieval [45,46]. In addition, the capacity for interhemispheric transfer through the anterior corpus callosum — a key structure interconnecting the prefrontal cortices — suggested executive processes undertaken by the human prefrontal cortex [47]. Inspired by these clinical observations, we introduced the posterior-splinterminal paradigm into the associative memory task in monkeys [48••]. In the posterior-split-brain monkeys, whose posterior corpus callosum and anterior commissure are sectioned, the cortex receives bottom-up visual information only from the contralateral visual field. We found that long-term memory acquired through stimulus–stimulus association does not transfer interhemispherically via the anterior corpus callosum. Nonetheless, when a visual cue was presented to one hemisphere, the anterior callosum could instruct the
other hemisphere to retrieve the correct stimulus specified by the cue. Therefore, although visual long-term memory is stored in the temporal cortex, memory retrieval is under the executive control of the prefrontal cortex.

In spite of predictions from these behavioural experiments, no neuronal correlate of top-down signalling from the prefrontal cortex to IT cortex was detected in long-term memory retrieval (see also Fuster et al. [49] for modulatory influences upon IT cortex). The first direct evidence has been demonstrated by Tomita et al. [50••], who conducted single-unit recording in posterior-split-brain monkeys. In the absence of bottom-up visual inputs, single IT neurons were robustly activated by the top-down signal (Figure 1b), which conveyed information on semantic categorization imposed by visual stimulus–stimulus association (Figure 2). Behavioural performance was severely impaired, consonantly with a loss of the top-down signal. Control experiments confirmed that the signal was transmitted not through a subcortical but through a fronto-temporal cortical pathway.

Tomita et al. [50••] also demonstrated that the top-down signal had longer latency by around 100 ms than the bottom-up signal (Figure 1b). The longer latency is most likely ascribed to multi-synaptic conduction delay reflecting the signal transformation within the prefrontal cortex. During this delay, the prefrontal cortex might prompt IT neurons to maintain cue-related information, seek out and retrieve the relevant target in the IT cortex, and also verify whether the retrieved object is relevant one. In support of this, prefrontal neurons have been reported to share cellular specificities for object and face stimuli with IT neurons and to show sustained responses to object stimuli in a working memory task [51,52,53•]. A recent report [54•] on prospective coding of prefrontal neurons similar to that found in IT neurons [8,43] also supports this view. Human PET and fMRI studies in memory retrieval tasks have shown that the prefrontal cortex is engaged in retrieval attempts, and in contextual monitoring or memory judgement (for example, see [55–60]). A deeper understanding of the signal transformation within the prefrontal cortex would help to elucidate the mechanism of top-down control in memory retrieval.

Prefrontal cortex: executive control based on relevant information

Representations of current perceived stimuli and volitionally retrieved information related to the stimuli are maintained as working memory for a brief period of time...
for further use [61,62]. To make appropriate decisions for action, relevant information needs to be selected from among the information in working memory and, using retrieved knowledge or experiences as a guide, needs to be integrated further into a behavioral plan and decision. Recent physiological studies in macaque monkeys have provided further evidence at single-unit level that the prefrontal cortex plays a major role in these executive processes (for example, see [63•,64,65,66•]). Bichot and Schall, using a conjunction visual search task, have shown that responses of frontal eye field neurons during target selection depend on the visual similarity of distractors and a target specified at the beginning of daily session, and also on prior experiences [64•]. This suggests that the frontal eye field represents locations of relevant objects based on visual salience and knowledge. Other studies (for example, see [65]) using the delayed matching to sample task showed that neurons in the prefrontal cortex are involved in representations of behaviourally relevant information. In these studies, the process of the decision-making itself, however, might be difficult to be observed, because the monkeys made prompt decisions based on one obvious cue or matching target. Kim and Shadlen [66•] trained monkeys to discriminate the direction of motion of random dots and to judge direction by making appropriate eye movements after a delay. They were able to demonstrate that neurons in the prefrontal cortex represent not simply the final outcome of sensory processing but also the conversion of visual motion information into a categorical decision about direction.

**Macaque fMRI as an approach to the causal role of brain activation**

Because most neuroimaging studies in humans depend upon correlations between cognitive processes and brain activations, the causal relationship between them requires the implementation of other methods. To verify the behavioral significance of brain activations, neuropsychological studies on memory retrieval were performed on patients with focal brain lesions (for examples, see [67–69]). By combining PET and a repetitive transcranial magnetic stimulation (rTMS), Kosslyn et al. [70•] examined the contribution of area 17 in visual imagery (see also the review by Pascual-Leone, Walsh and Rothwell in this issue, pp 232–257). Area 17 was activated during the imagery task and, moreover, performance of the task was impaired after rTMS to the activated area. The convergence of these complementary methodologies should, therefore, provide a promising direction in which to take future research. To identify the neural bases of cognitive functions in depth, however, would require studies using monkeys as an experimental model, because most of the detailed anatomical knowledge of the cortex and its functional properties derives from studies in monkeys. The origin and nature of fMRI blood oxygen level-dependent (BOLD) signals in primates should also be clarified by combining fMRI with electrophysiology.

Recently, fMRI studies in macaque monkeys have been emerging [71•–73•,74–76]. Stefanacci et al. [71•] and Dubowitz et al. [72•], using fMRI, obtained the first BOLD images of the monkey visual cortex activated by non-retinotopic stimuli (passive viewing of animated movies without eye-fixation). By mapping topographical organization of the primary and secondary somatosensory cortices, we showed the feasibility of monkey fMRI for distinguishing between adjacent functionally distinct regions [73•]. Dishbrow et al. [74] also showed topographical activation of the primary somatosensory cortex. Logothetis et al. [75•], who designed a customised magnetic resonance machine with a vertical magnet, make further progress in improving both imaging technique and spatial resolution (now at the level of the submillimeter). By using these techniques, they demonstrated distinct retinotopic activation patterns in the primary visual area. They also showed activation of the superior temporal sulcus, frontal cortex, and amygdala in response to images of monkey faces. Further studies will improve our understanding of the causal relation of activation and behaviour by use of combined fMRI and electrophysiology or lesion studies [76]. Moreover, iso-orientation columns in the visual cortex of cats have recently been visualized using fMRI at 4.7 and 9.4 Tesla [77•]. Achievement of spatial resolution about 100–300 µm in this study is a potentially substantial advance, which would enable us to noninvasively investigate the neural bases of cognitive functions at the level of individual columns.

**Conclusions**

The role of IT cortex in higher-order visual representation of objects has been established by recent studies in monkeys. Associative long-term memory is stored in the IT cortex, neurons of which can acquire stimulus-selectivity through learning, and can link representations of temporally associated stimuli. Recently, the mnemonic representation was found to be activated on demand of combined fMRI and electrophysiology or lesion studies. The executive control, as a function of the prefrontal cortex, has been decomposed to subprocesses such as selection and decision making, and the identification of their individual neural bases is proceeding. Further research into the signal transformation within the prefrontal cortex will elucidate the machinery of top-down control in memory retrieval.

Numerous neuroimaging studies are carried out in order to clarify the cognitive functions of the human brain. Because most neuroimaging studies rely upon correlations between cognitive processes and brain activations, their conjuncture with other complementary methods such as neuropsychological studies and transcranial magnetic stimulation should be promoted in order to clarify the behavioral significance of observed brain activities. The recently emerging fMRI studies of the monkey brain, we hope, will direct us toward an understanding of the causal relation of activated brain areas and cognitive functions, in cooperation...
with electrophysiology or lesion studies. Monkey fMRI studies will also allow us to directly compare the brain activity of humans and monkeys within the same methodology. As most of the detailed knowledge of the anatomy and function of the cortex has come from studies in monkeys, sharing the same methods with studies in humans and monkeys will, in turn, advance our understanding of the neural organization of human cognitive functions.

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frontal cortex to IT cortex [48,50].
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This suggests that frontal eye field represents locations of behaviorally relevant objects based on visual saliency and experience.


The authors trained monkeys to perform a visual conjunction search task; the target was specified as a combination of color and shape at the beginning of each session. Neurons in the frontal eye field during target selection responded more frequently to the target. In addition, neurons responded greater to distractors sharing a feature in common with the target, and to a distractor sharing no feature with the target. This suggests that frontal eye field represents locations of behaviorally relevant objects based on visual saliency and experience.


By training monkeys to discriminate the direction of motion of dynamic random dots and to judge direction by making appropriate eye movements after a delay, the authors demonstrated that some neurons in the prefrontal cortex represented the final outcomes of sensory processing but that conversion of an analog motion representation to a binary decision variable. This observation may reflect the processes by which primate neurons extract relevant visual information and make decisions.


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