A neural basis for visual search in inferior temporal cortex

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WE often search for a face in a crowd or for a particular object in a cluttered environment. In this type of visual search, memory interacts with attention: the mediating neural mechanisms should include a stored representation of the object and a means for selecting that object from among others in the scene[1–4]. Here we test whether neurons in inferior temporal cortex, an area known to be important for high-level visual processing, might provide these components. Monkeys were presented with a complex picture (the cue) to hold in memory during a delay period. The cue initiated activity that persisted through the delay among the neurons that were tuned to its features. The monkeys were then given 2–5 choice pictures and were required to make an eye movement to the one (the target) that matched the cue. About 90–120 milliseconds before the onset of the eye movement to the target, responses to non-targets were suppressed and the neuronal response was dominated by the target. The results suggest that inferior temporal cortex is involved in selecting the objects to which we attend and foveate.

On each trial, the monkeys first fixated a dot on a computer display. One of two cues was then presented over the dot for 300 ms. The cues were carefully selected for each cell to include a 'good' stimulus that elicited a strong response from the cell and a 'poor' stimulus that elicited little or no response (Fig. 1). After a delay, the good and the poor stimulus were both presented extrafoveally as choice stimuli. The animal made a saccadic eye movement to the target stimulus that matched the cue, ignoring the non-matching stimulus (the distractor). The relative locations of target and distractor varied randomly across trials. All cells were tested in a blocked-trial design, in which one of the two cues was used for a block of 20–30 trials before switching to the other cue, and some were also tested in a more difficult unblocked design, in which the cue varied randomly from trial to trial.

The inferior temporal cells we recorded had activity related to the cue that was maintained throughout the delay, which is consistent with reports of 'delay activity' during delayed matching-to-sample tasks in this area[5–7]. For 52% of 83 cells recorded in the blocked design, the good cue evoked a significantly higher maintained discharge throughout the delay period than did the poor cue (t-test on the last 500 ms of the delay period, $P < 0.05$). The same was true for 38% of 29 cells recorded in the unblocked design, an example of which is shown in Fig. 2.

In addition to information about the cue, inferior temporal cells also communicated information about the target. Figures 2 (single cell) and 3 (population of cells) show the responses to choice arrays (in the contralateral hemifield) that were physically identical but in which either the good or poor stimulus

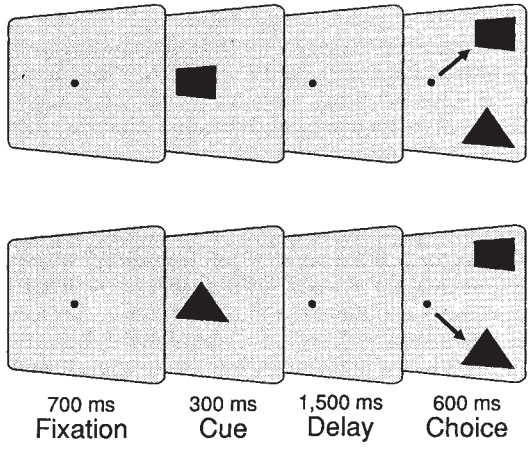

FIG. 1 Sequence of stimulus events. Before the experimental trials, we tested each cell with a variety of 1–1.5 deg^2 complex patterns (digitized magazine pictures) presented at the centre of gaze, and selected a 'good' stimulus and a 'poor' stimulus, represented here for simplicity by the square and triangle. Each trial began with a cue followed, after a 1,500–3,000-ms delay, by two choice stimuli presented peripherally. The animal made an eye movement (arrow) to the target that matched the cue in order to receive juice reward. Stimuli were extinguished 150 ms after the animal fixated the target. In other trials (data not shown), neither choice stimulus matched the cue and the animal was rewarded for maintaining initial fixation. The critical comparison was the neuronal response to choice arrays that contained the same stimuli (triangle and square, for example), but in which either the good or poor stimulus was the target. If, for example, a cell responded only to squares and not to triangles, we compared the response to the choice array preceded by the square (upper panel) to the response to the same array preceded by the triangle (lower panel). Target and distractor were typically located at an eccentricity of 4–5° and were separated by the vertical or horizontal meridian. In the former configuration, they were centred in the lower quadrants of each hemifield, and in the latter configuration one was centred in the upper field and one in the lower. Relative locations of target and distractor in each configuration were varied randomly. Cells generally responded best to stimuli presented at the centre of gaze, less well to stimuli in the contralateral field and weakly (in some cases not at all) to stimuli in the ipsilateral field.

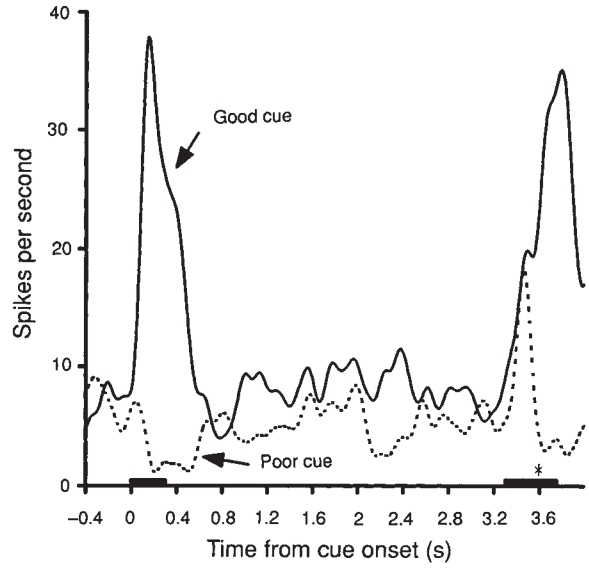

FIG. 2 Standard electrophysiological and eye monitoring techniques were used to record from cells in two monkeys (*Macaca mulatta*)[7,8]. Magnetic resonance imaging was used to place the recording electrodes into the anterior inferior temporal cortex, between the anterior middle temporal and the rhinal sulci. Graphs show average firing rates of one cell on trials with either good or poor stimulus presented as cue. The good stimulus elicited a strong excitatory response and the poor stimulus was slightly inhibitory. Firing rates in each 10-ms bin were convolved with a gaussian with a standard deviation of 40 ms[13]. Each frequency plot represents the average of 20 trials. Black horizontal bars indicate presentation of cue and choice stimuli. Average time of saccade onset to the target, 297 ms after array onset, is indicated by an asterisk. The average firing rates in the last 500 ms of the delay for all cells showing significantly different activity following the good versus poor cue, were 7.9 versus 5.6 spikes per second, respectively, in the blocked design, and 6.8 versus 4.0 spikes per second, respectively, in the unblocked.

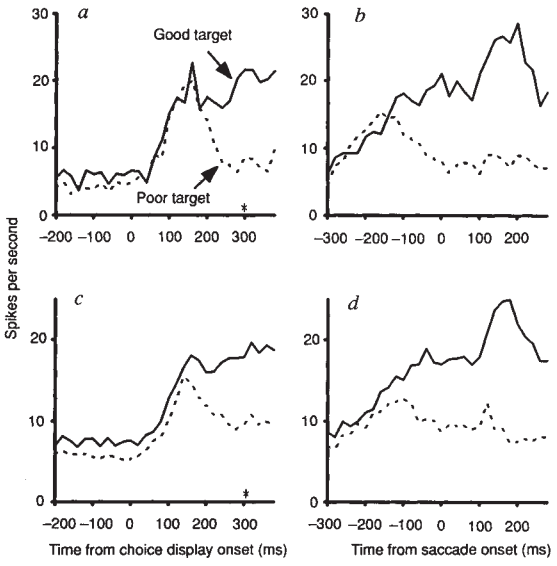

FIG. 3 Average firing rates to identical choice arrays, in which either the good (solid lines) or poor (dashed lines) stimulus was the target (that is, preceded by good or poor stimulus as cue). Graphs show the average response of all cells that responded to choice arrays (58 in the blocked design and 22 in the unblocked). The bin width is 20 ms. *a*, Responses of cells in the unblocked design, time-locked to array onset. Average time of saccade onset, 300 ms after array onset, is indicated by an asterisk. *b*, Same data as in *a*, but responses are time-locked to saccade onset. *c*, Responses of cells in the blocked design, time-locked to array onset. The average saccade latency in this design was 306 ms. *d*, The same data as in *c*, but time-locked to saccade onset. Data in all graphs are from trials in which the target and distractor appeared in the hemifield contralateral to the recorded cell. Data are averaged from trials in which the target was in the upper quadrant and the distractor in the lower, and vice versa. The target effect was much smaller when target and distractor were located in opposite hemifields, a finding which is consistent with those of Sato[9] and of J. Moran and R.D. (unpublished data), who found reduced spatial attentional effects in inferior temporal cortex when attended and ignored stimuli were in opposite hemifields. With the choice array confined to the contralateral field, 33% (blocked) and 50% (unblocked) of the cells gave significantly different responses to the array, depending on the relative locations of the good and poor stimuli. Thus some spatial (retinotopic) information is retained in inferior temporal cortex in spite of the large receptive fields.

was the target. Especially in the blocked design, the elevated activity in the delay following the good cue persisted into the initial neuronal response to the choice array. Relative to the preceding delay activity, however, this initial response to the array was about the same regardless of which choice stimulus was the target. By contrast, the late phase of the response changed dramatically, depending on whether the animal was about to make a saccade to the good or poor stimulus. If the target was the good stimulus, the response remained high, but if the target was the poor stimulus, the response to the good distractor stimulus was suppressed even though it was still within the receptive field. It is as though 90–120 ms before the start of the saccade (~200 ms after choice array onset), the target stimulus 'captured' the response of the cell, so that neuronal activity would reflect only the target's properties.

In the 90-ms period before saccade onset, 78% (blocked) and 91% (unblocked) of the cells gave a larger response when the good stimulus was the target, out of the 58 and 22 cells, respectively, that responded to the extrafoveal choice array. The larger response when the good stimulus was the target was significant for 48% (blocked) and 45% (unblocked) of all cells according to a *t*-test ($P < 0.05$) performed separately on each cell. Only one cell showed a significant effect in the opposite direction. Previous studies have shown that when animals are cued to attend to stimuli at one location and ignore stimuli at another, inferior temporal responses to the ignored stimuli are suppressed[8,9]; however, this is the first evidence for such suppression when the location of the attended stimulus is not known in advance and object features themselves guide selection.

To test whether the target-selection results would generalize to larger search displays, ten additional cells were studied in one monkey in the same task, but with extrafoveal choice arrays consisting of five stimuli arranged in a hemicircle within the contralateral field. All ten showed the same pattern of results as the cells tested with two-stimulus arrays: if the target on a given trial was a good stimulus for the cell, the response remained high, but if the target was a poor stimulus, the response was suppressed beginning 90–120 ms before the saccade, even though the good stimulus was still within the receptive field. Saccadic latencies increased by 26 ms per stimulus, with choice arrays of 1, 2, 3 and 5 stimuli.

Figure 4 illustrates that both of the components necessary for this type of visual search—internal representation of cue and selection of target—are reflected in the responses of inferior temporal neurons. It remains to be determined whether these two components are causally linked, that is, whether it is the maintained activity initiated by the cue or some other mechanism (such as interaction with separate attentional systems) that ultimately results in suppression of inferior temporal responses to non-targets. The possibility of a link is supported by the fact that more than three-quarters of the cells with significant target effects in the 90 ms preceding a saccade also showed significant cue-initiated delay effects. In either case, target information in inferior temporal cortex is available to drive oculomotor systems, resulting in eye movements to the chosen object[10–12]. More generally, networks in inferior temporal cortex may select the

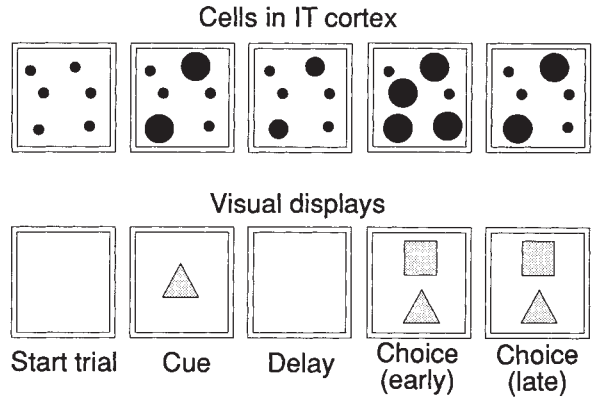

FIG. 4 Upper diagrams are schematic representations of activity in a population of inferior temporal (IT) neurons during performance of the task. Each dot represents an individual cell, and the size of the dot indicates relative firing rate. Lower diagrams illustrate the visual displays during the relevant portions of the task. A specific cue activates the subpopulation of IT cells tuned to any of the various features of the cue. During the delay period, this subpopulation remains more active than other cells. When the choice array first appears, cells are initially activated by whichever stimulus they prefer in the array, regardless of which is the target. In some cases the initial responses are identical, but in others the response to the array with the good target starts off at a higher rate becuase of persisting activity from the delay. Later, within 90–120 ms of saccade onset, the cells tuned to the properties of the target stimulus remain active, whereas cells tuned to the properties of the distractor are suppressed. Whether this final divergence in activation results from competitive interactions within IT cortex (for example, through mutual inhibition between cells selective for target and distractor), or from interactions between IT cortex and an attentional control system, is not yet known.

visual objects that are acted upon by motor systems when selection is guided by object features. □

Received 19 February; accepted 11 March 1993.

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ACKNOWLEDGMENTS. We thank M. Mishkin for advice and support, T. White for computer programs, and J. Hart and R. Hoag for help with the monkeys. This work was supported in part by the Human Frontier Science Program Organization, the Office of Naval Research, the Air Force Office of Scientific Research, and the North Atlantic Treaty Organization.

Induction of LTP in the hippocampus needs synaptic activation of glutamate metabotropic receptors

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UNDERSTANDING the mechanisms of long-term potentiation (LTP) should provide insights into the molecular basis of learning and memory in vertebrates. Ionotropic glutamate receptors play a central role in LTP; AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) receptors and NMDA (*N*-methyl-D-aspartate) receptors mediate synaptic responses that are enhanced in LTP and, in addition, NMDA receptors are necessary for the induction of LTP in most pathways[1]. There is also circumstantial evidence that metabotropic glutamate receptors (mGluRs) may be involved in LTP because the specific mGluR agonist aminocyclopentane dicarboxylate can augment tetanus-induced LTP[2] and, under certain circumstances, can itself induce a slow-onset potentiation[3,4]. But the absence of any effective mGluR antagonist has prevented the determination of whether mGluRs are involved in the induction of tetanus-induced LTP. We report here that (*RS*)-α-methyl-4-carboxyphenylglycine is a specific mGluR antagonist in the hippocampus and have used this compound to examine the nature of the involvement of mGluRs in LTP. We show that synaptic activation of mGluRs is necessary for the induction of both NMDA receptor-dependent and NMDA receptor-independent forms of LTP in the hippocampus.

Establishing a physiological role for mGluRs in LTP requires the use of specific mGluR antagonists. The involvement of mGluRs in LTP has been suggested on the basis of the actions of the drugs aminophosphonobutanoate (AP4)[5] and aminophosphonopropionate (AP3)[6–8]. But these compounds do not affect mGluR-mediated responses in the hippocampus, as determined electrophysiologically[9–12]. Moreover, the uncompetitive nature of the actions of AP3 and AP4 on metabolic manifestations of mGluR activity makes it difficult to interpret their effects on LTP. Recently, however, it has been reported that (*RS*)-α-methyl-4-carboxyphenylglycine (MCPG) is a selective and competitive mGluR antagonist with respect to aminocyclopentane dicarboxylate (ACPD)-stimulated phosphoinositide hydrolysis and ACPD-induced electrophysiological responses in rat brain and spinal cord[13]. To confirm the effectiveness of MCPG as an mGluR antagonist, we first tested it on a system devoid of ionotropic glutamate receptors. MCPG (500 μM) reversibly abolished Ca^{2+}-mobilizing responses induced by the stimulation of mGluR1α-transfected cells[14] by 1*S*,3*R*-ACPD, an active enantiomer of ACPD[15] (Fig. 1*a*). We next determined its effectiveness as an mGluR antagonist in the hippocampus. In CA1 neurons, MCPG (500 μM) reversed the inhibition by 1*S*,3*R*-ACPD[16] of both action potential accommodation and the ensuing after-hyperpolarization (AHP) (Fig. 1*b*). In contrast, MCPG (tested at 1,000 μM) had no effect on the inhibition by carbachol of action potential accommodation and the AHP (Fig. 1*c*). We also tested the effects of MCPG on the four components of the synaptic response that can be elicited by low-frequency stimulation of the Schaffer collateral-commissural pathway. MCPG (500 μM) had no effect on either of the γ-aminobutyric acid ($GABA_A$ or $GABA_B$) receptor-mediated components of inhibitory postsynaptic potentials (i.p.s.ps) (Fig. 2*a*), NMDA receptor-mediated excitatory postsynaptic currents (e.p.s.cs) (Fig. 2*b*) or AMPA receptor-mediated excitatory postsynaptic potentials (e.p.s.ps) (Fig. 2*c*). MCPG did, however, block reversibly the generation of slow-onset synaptic potentiation[4] induced by 1*S*,3*R*-ACPD (Fig. 2*c*). These data show that MCPG is sufficiently potent and selective to be used as an mGluR antagonist to study the physiological roles of mGluRs in the hippocampus.

AP3 has been reported to have variable effects on the induction of LTP in the CA1 region, ranging from no effect[17] to complete block[6] with D,L-AP3 and blockade of a later component of LTP with L-AP3[7]. We did similar experiments using L-AP3 (1,000 μM) but have been unable to block LTP in area CA1 (followed for up to 3 h after the tetanus) (Fig. 3*a*). In contrast, MCPG (500 μM) reversibly blocked the induction of LTP without affecting basal synaptic transmission or established LTP (Fig. 3*b*, *c*). In each of the 5 slices tested, there was short-term potentiation (STP) lasting about 30 min, but never LTP. These data show, therefore, that the synaptic activation of mGluRs is necessary for the induction of LTP in the CA1 region of the hippocampus. Because NMDA receptors are also necessary for the induction of LTP in this region of the hippocampus[18], ionotropic and metabotropic glutamate receptors serve as complementary but essential triggers for LTP induction.

In the CA3 region of the hippocampus, LTP in the mossy fibre pathway does not involve NMDA receptors[19] and no trigger for induction has been positively identified. We therefore tested MCPG on mossy fibre LTP. MCPG (500 μM) had no effect on basal synaptic transmission but reversibly blocked the induction of NMDA-receptor-independent LTP (Fig. 4). In contrast to area CA1, there was no STP in the presence of MCPG; tetanic stimulation resulted only in post-tetanic potentiation (PTP) which lasted for less than 5 min.

These data provide compelling evidence that the synaptic activation of mGluRs is necessary for the induction of LTP. The failure, in the present study, of L-AP3 to block LTP in area CA1 is not inconsistent with this finding because L-AP3 is, at best, a very weak mGluR antagonist of physiological responses in this region[9–12]. In an earlier report[7], L-AP3 reduced the duration of LTP to between 2 and 3 h. It is possible that this difference reflects an effect of L-AP3 on processes involved in