

Single Neuron Activity in Human Hippocampus and Amygdala during Recognition of Faces and Objects

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Summary

The hippocampus and its associated structures play a key role in human memory, yet the underlying neuronal mechanisms remain unknown. Here, we report that during encoding and recognition, single neurons in the medial temporal lobe discriminated faces from inanimate objects. Some units responded selectively to specific emotional expressions or to conjunctions of facial expression and gender. Such units were especially prevalent during recognition, and the responses depended on stimulus novelty or familiarity. Traces of exposure to faces or objects were found a few seconds after stimulus removal as well as 10 hr later. Some neurons maintained a record of previous stimulus presentation that was more accurate than the person's conscious recollection. We propose that the human medial temporal lobe constructs a "cognitive map" of stimulus attributes comparable to the map of the spatial environment described in the rodent hippocampus.

Introduction

Patients with bilateral insult to the medial temporal lobe cannot transform present experience into future conscious recollection (Scoville and Milner, 1957; Penfield and Milner, 1958; Zola-Morgan and Squire, 1993), and various combinations of experimental lesions of the amygdala, hippocampus, entorhinal cortex, parahippocampal gyrus, and perirhinal cortex in animals result in impaired performance on delayed match- or nonmatch-to-sample tasks (Zola-Morgan and Squire, 1993; Mishkin and Murray, 1994). These and other observations suggest a fundamental dichotomy that critically depends on the hippocampus and related limbic structures. The distinction is made between memory processes that involve conscious or intentional recollection of previous experience (explicit or declarative) and those that do not (implicit or nondeclarative). Explicit memory has been shown to depend on medial temporal lobe integrity (Squire, 1992; Schacter and Tulving, 1994).

Despite these striking observations, the neuronal processes underlying the unique role of the hippocampus in human memory remain unknown. Several theories have emphasized the critical anatomic position of the hippocampus, which receives converging uni- and multimodal input from neocortical regions and projects

back to these regions. This convergent input may: promote consolidation of conjunctions of stimuli or stimulus features represented in separate neocortical regions, increase synaptic efficacy in the hippocampus, and contribute to the stabilization of memory traces (Marr, 1972; Wickelgren, 1979; McNaughton and Nadel, 1990; Cohen and Eichenbaum, 1993; Jung and McNaughton, 1993; Alvarez and Squire, 1994; O'Reilly and McClelland, 1994; Treves and Rolls, 1994).

Several recent studies have examined changes in blood flow in the human hippocampus and adjacent structures during encoding and retrieval of information (Grasby et al., 1993; Buckner et al., 1995; Schacter et al., 1995, 1996a, 1996b; Haxby et al., 1996; Nyberg et al., 1996; Stern et al., 1996). Yet, few studies have examined neural activity in these regions by direct recording of neuronal discharge during mnemonic processes. Animal studies have concentrated on two observations: the persistence of neuronal activity over a delay period following presentation of a stimulus to be remembered (Fuster and Alexander, 1971; Kubota and Niki, 1971; Fuster and Jervey, 1981; Miyashita and Chang, 1988; Funahashi et al., 1989; Wilson et al., 1993; Miller et al., 1996), and differential neuronal responses to familiar versus novel stimuli (Baylis and Rolls, 1987; Brown et al., 1987; Miller et al., 1991; Fahy et al., 1993). The evidence for these phenomena in the hippocampus is limited in primates and lacking in humans (Watanabe and Niki, 1985; Brown et al., 1987; Heit et al., 1988; Cahusac et al., 1989; Riches et al., 1991; Otto and Eichenbaum, 1992; Saltzman et al., 1993; Colombo and Gross, 1994). Furthermore, the relation of neuronal responses to conscious recollection can only be studied in humans.

In this study, we examined the activity of single neurons in the human medial temporal lobe during a recognition memory task. Recordings were carried out in nine patients with intractable epilepsy who underwent implantation of intracranial electrodes in order to identify the seizure focus for potential surgical resection. Based on clinical criteria, electrodes containing microwires were stereotactically implanted, using magnetic resonance imaging (MRI) and angiographic guidance, in bilateral medial temporal lobe targets (Figure 1A).

Stimuli for the memory task were faces and inanimate objects. The perception and memory of faces are of critical importance in social behavior in humans as well as in nonhuman primates. Electrophysiological studies in primates and data based on lesions and functional neuroimaging studies in humans suggest that certain brain regions are specialized for the processing of faces (Bruce et al., 1981; Rolls, 1984, 1992; Damasio et al., 1990; Desimone, 1991; Perret et al., 1992; Sergent et al., 1992; Allison et al., 1994a; Puce et al., 1995). In particular, faces can be readily characterized by independent attributes, such as identity, expression, and gender, which have segregated cortical representation (Fried et al., 1982; Rolls, 1984; Perrett et al., 1984; Baylis et al., 1985; Hasselmo et al., 1989; Young and Bruce, 1991).

To investigate medial temporal neuronal activity related to encoding and retrieval of faces, we recorded

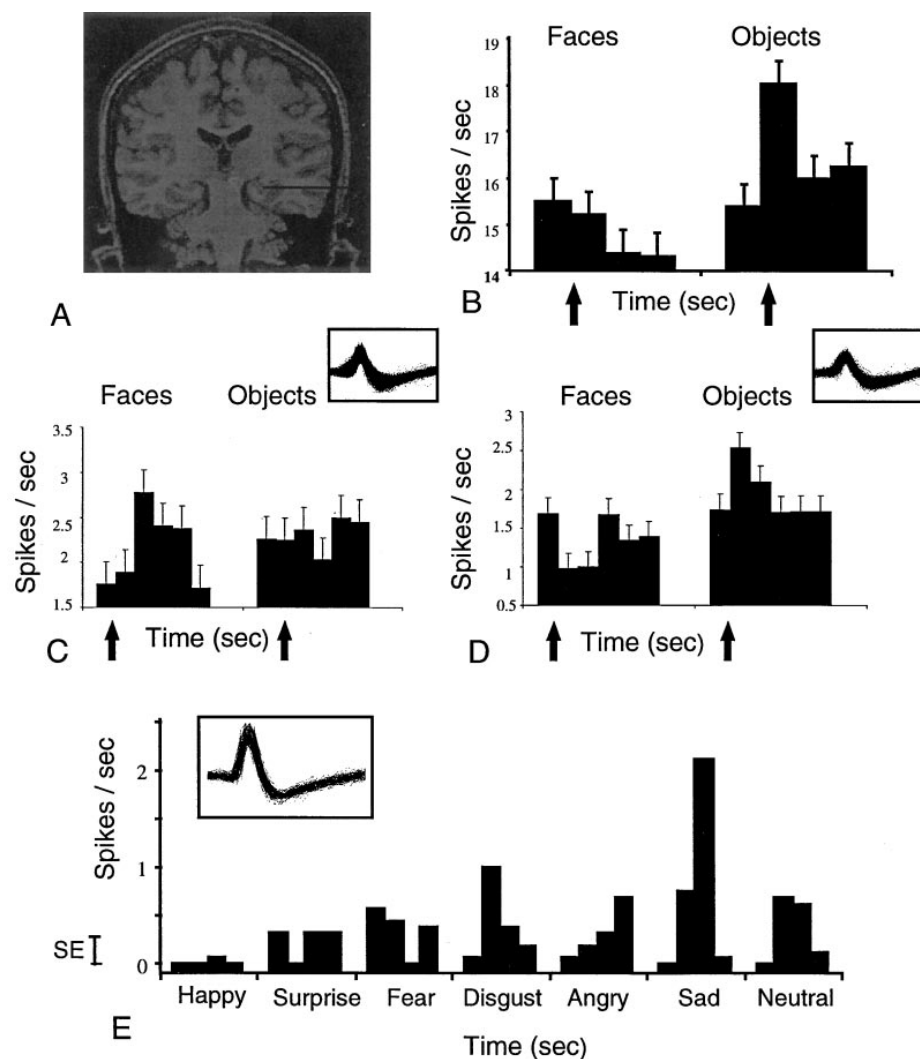


Figure 1. Electrode Placement and Histograms (1 s Bins) of Single Neuron Activity Recorded in the Medial Temporal Lobe in Relation to Presentation of Objects and Faces

Mean discharge rates (and pooled standard errors) are depicted for the second prior to stimulus onset (arrow) and the ensuing 3–5 s. The insets show consecutive action potentials recorded from each unit during 2 min of the task.

(A) Trajectory of an electrode placed in the left hippocampus, depicted on a coronal magnetic resonance image (MRI).

(B) Unit in the left entorhinal cortex during the encoding task. Note selective response to objects during the second of stimulus presentation (following arrow).

(C) Unit in the left hippocampus recorded from the electrode in (A), during the encoding task. Note increased discharge rate during the second after offset of face stimuli, persisting for another 2 s.

(D) A unit recorded from the same wire as in (C) 10 hr later, during the recognition task. Note the reversed response pattern (i.e., decrease in discharge rate for faces and increase for objects). Although the units depicted in (C) and (D) probably represent the same neuron, it is possible that these were two different units recorded from the same microwire.

(E) Unit in the left hippocampus of another patient during the encoding of faces with different expressions (SE, pooled standard error). Note selective response to expressions of sadness and disgust. The response to “sad” peaked when the stimulus was no longer present.

the activity of single neurons during two sessions. In the first session (“encoding”), pictures of faces and objects were presented to be remembered. The faces were those of eight actors, each with seven emotional expressions. One to ten hours later, subjects underwent a “recognition” session, where they were shown the previously presented faces and objects (“old”) as well as novel stimuli (“new”) and asked to indicate whether they had seen each face or object in the encoding session.

Using this design, we asked the following questions:

- (1) Are complex stimulus features reflected in the activity of single neurons in the medial temporal lobe?
- (2) Does the neuronal response persist when the stimulus is no longer present?
- (3) Can long-term traces of past exposure to a stimulus be detected in the activity of single neurons upon repeated presentation of the stimulus?
- (4) What is the relationship of these traces to conscious recollection?

Table 1. Number and Percentage of Units in Amygdala, Hippocampus, and Entorhinal Cortex with Differential Responses to the Variables: Stimulus Class (Faces versus Objects), Stimulus Novelty (Old versus New), and Subject's Recognition Response (Yes versus No)

Variables differentiated	Task	Number (%) of units in:			
		Amygdala	Hippocampus	Entorhinal cortex	Total
Faces versus objects	Encoding	3 (13.6%)	4 (12.1%)	5 (26.3%)	12 (16.2%)
	Recognition	3 (27.3%)	9 (31.0%)	4 (20.0%)	16 (26.7%)
Old versus new	Recognition	2 (18.2%)	6 (20.7%)	8 (40.0%)	16 (26.7%)
Yes versus no	Recognition	2 (18.2%)	5 (17.2%)	5 (25.0%)	12 (20.0%)

For each of the tasks (encoding and recognition), number and percentage of units significantly related by ANOVA to the relevant variable are depicted for each of the three anatomic regions.

Results

We recorded the activity of 74 units during the encoding session (33 in hippocampus, 22 in amygdala, and 19 in entorhinal cortex) and 60 units during recognition (29 in hippocampus, 11 in amygdala, and 20 in entorhinal cortex). In general, medial temporal lobe neurons exhibited a low frequency of discharge (mean = 2.9 spikes/s). A separate repeated measures analysis of variance (ANOVA) was carried out for each unit.

We first examined the stimulus specificity of neuronal activity in response to presentation of faces and objects. During the encoding session, 12 of 74 units (16.2%) differentiated faces from objects by significant changes in firing rate, whereas during the recognition task, 16 of 60 (26.7%) units did so (Table 1; Figure 1). A goodness of fit Chi-square test was applied to these data to examine the hypothesis that the number of significantly responding neurons might have been a result of chance. This hypothesis was rejected for both encoding ($\chi^2 = 30.14$; $P < 0.0001$) and recognition ($\chi^2 = 150.80$; $P < 0.0001$). Neuronal discharge rates were examined during the second of stimulus presentation (T1), the second following stimulus presentation (T2), and in succeeding seconds before the presentation of the next stimulus. Changes in neuronal firing in response to face or object stimuli were often present during T1 (Figures 1B and 1D), but in some units, the response persisted or arose during T2 or later (Figure 1C). The majority of the hippo-

campal units that discriminated faces from objects did so during both T1 and T2 (75% during encoding and 78% during recognition).

The presentation of a large number of faces with systematically altered attributes, namely identity, expression, and gender, provided us with the opportunity to examine the relationship of neuronal activity in the hippocampus and associated structures to complex stimulus attributes and their conjunctions. This analysis was limited to patients who had been presented with sufficient repetitions of face stimuli for ANOVA; that is, 50 units during encoding and 60 units during recognition (Table 2). Differential responses based on gender were observed in 12% of the units during encoding and in 15% during recognition (Table 2). However, the possibility that these findings might be due to chance could not be ruled out by a goodness of fit Chi-square test.

During encoding, 14% of medial temporal lobe neurons responded preferentially to particular facial expressions, and 11.7% responded in this fashion during recognition (Figure 1E; Table 2). During recognition, this percentage was significantly greater in the amygdala (Pearson $\chi^2 = 3.89$; $P = 0.048$) and hippocampus (Pearson $\chi^2 = 3.84$; $P = 0.05$) compared to entorhinal cortex. The number of units responding differentially to facial expression was significantly greater than expected by chance, during encoding ($\chi^2 = 13.94$; $P = 0.007$), but not during recognition ($\chi^2 = 7.50$; $P = 0.11$). However, when past exposure to the stimulus was considered

Table 2. Number and Percentage of Units in Amygdala, Hippocampus, and Entorhinal Cortex with Significant Responses to Facial Attributes and Novelty and to Their Conjunctions

Variables and conjunctions	Task	Number (%) of units in:			
		Amygdala	Hippocampus	Entorhinal cortex	Total
Expression	Encoding	2 (10.5%)	3 (21.4%)	2 (11.8%)	7 (14.0%)
	Recognition	2 (18.2%)	5 (17.2%)	0	7 (11.7%)
Gender	Encoding	2 (10.5%)	2 (14.3%)	2 (11.8%)	6 (12.0%)
	Recognition	1 (9.1%)	5 (17.2%)	3 (15.0%)	9 (15.0%)
Expression × Novelty	Recognition	2 (18.2%)	10 (34.5%)	8 (40%)	20 (33.3%)
Gender × Novelty	Recognition	2 (18.2%)	3 (10.3%)	1 (5%)	6 (10.0%)
Expression × Gender × Novelty	Recognition	1 (9.1%)	4 (13.8%)	4 (20%)	9 (15.0%)

Number and percentage of units significantly related by ANOVA to the relevant variables and conjunctions are depicted for each of the three anatomic regions. The variables were expression and gender of faces and stimulus novelty (Old-New).

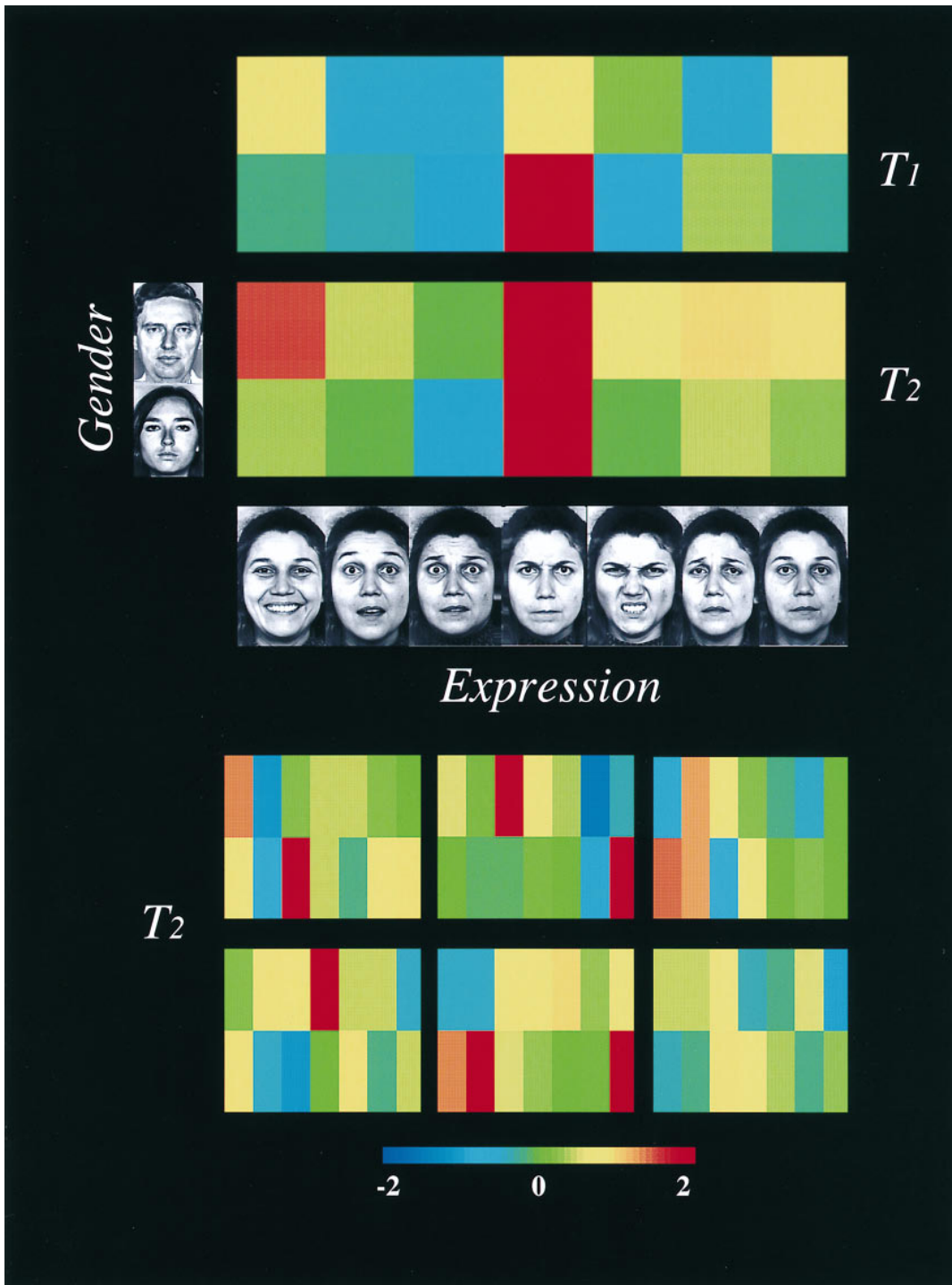


Figure 2. Single Neuron Responses to Conjunctions of Facial Expression and Gender during Encoding

(Upper section) Discharge rates of a neuron in the left hippocampus during (T_1) and following (T_2) presentation of male and female faces with different expressions during the encoding task. Neuronal activity is displayed in a two-dimensional "attribute space" defined by expression and gender. Expressions are arranged in an ordinal scale based on studies using multidimensional scaling for judgments of emotional facial expressions (Russel and Bullock, 1985; Adolphs et al., 1994). Neighboring emotions on this scale, such as happiness and surprise, reflect similar ratings in normals; the scale is circular, i.e., "neutral" (far right) is adjacent to "happy" (far left). Each rectangle represents the mean neuronal response to conjunction of a particular facial expression and gender, based on eight stimulus presentations. Mean discharge rates are expressed as pseudocolored z-score values with respect to a 1 s baseline firing rate (T_0), based on ANOVA. Red rectangles depict discharge rate increases of 2 z scores or more, and dark blue rectangles depict similar decreases (see scale). During presentation (T_1) of female faces with expressions of anger, the neuron's discharge rate increased from a mean of 0.625 spikes/s at baseline (T_0) to a mean of 4.375 spikes/s. This represents an increase of 2.15 z scores and is thus depicted in red. The red rectangles in T_2 indicate significant increase,

(Table 2), a greater number of neurons (33.3%) differentiated facial expressions during recognition (18.2% in amygdala, 34.5% in hippocampus, and 40% in entorhinal cortex). Such units, then, responded to associations of facial expression and novelty or familiarity of stimuli (Table 2). The number of these units was much greater than expected by chance alone ($\chi^2 = 88.25$; $P < 0.0001$).

Medial temporal lobe neurons also responded differentially to conjunctions of facial expression and gender: 10% during the encoding task and 11.7% during the recognition task. Examples of preferential responses to conjunctions are shown in Figure 2, which depicts the simultaneously recorded activity of seven hippocampal units from a small area, no greater than 5 mm in diameter. Neuronal activity is portrayed in an "attribute-space" defined by two dimensions: gender and expression of faces. Four units showed increases or decreases in activity at particular "places" in this space, reflecting preferential responses to particular gender-expression conjunctions. As shown in Figures 2 and 3, some units altered their discharge rates in response to "adjacent" conjunctions, i.e., to male or female faces with expressions that have been found to be similar in multidimensional scaling experiments (Russell and Bullock, 1985; Adolphs et al., 1994). While the number of units responding to conjunctions of facial expression and gender was small, and the possibility that the findings were due to chance could not be ruled out, a larger number of units (15%) responded to conjunctions of expression and gender dependent on whether the faces were "old" or "new" ($\chi^2 = 90.80$; $P < 0.0001$; Table 2). These neurons, therefore, responded to complex conjunctions involving the stimulus attributes of gender and expression as well as stimulus novelty.

Conjunctive coding was also found for associations of expression and identity of faces. For 50 neurons, sufficient repetitions were carried out during the encoding task such that interactions between the identity and expression factors could be examined in an ANOVA model. Responses to conjunctions of identity and expression occurred in 26% of the neurons (Figure 4). This number was significantly greater than would be expected by chance alone ($\chi^2 = 43$; $P < 0.0001$). In 54% of these "conjunctive" units, the neuronal response did not differ between T1 and T2.

We next examined the relation of neuronal activity to past exposure to stimuli and to conscious recollection of the same stimuli. During the recognition task, 27% of the units differentiated "old" from "new" stimuli (Table 1; Figure 5), a greater number than would be expected by chance ($\chi^2 = 11.17$; $P < 0.025$). To each stimulus, subjects made a key press response ("yes" or "no"), indicating whether they explicitly remembered having

seen the stimulus before. A total of 20% of units differentiated stimuli that were followed by a "yes" response from stimuli followed by a "no" response (Table 1); however, this number was not greater than would be expected by chance alone ($\chi^2 = 6.89$; $P = 0.14$). The discharge rate of some units was significantly related to previous exposure to the stimulus as well as to the subject's recognition response. Of all units, 11.7% were related to the subject's recognition response but not to previous exposure to the stimulus. Conversely, the discharge rate of 18.3% of the units was related to previous exposure to the stimulus but not to the subject's conscious recollection of the stimulus, as expressed by the recognition response (Figure 5). Among the units discriminating "old" from "new" stimuli, 81% did so depending on whether the stimuli were faces or objects. These units, then, responded to conjunctions of stimulus novelty and type.

Discussion

Coding of Multiple Attributes by Single Neurons

Neurophysiological investigations in nonhuman primates indicate that as processing of stimuli progresses from primary visual to association temporal cortex, neuronal coding shifts from elementary features to complex attributes (Gross et al., 1972; Rolls and Baylis, 1986; Baylis et al., 1987; Gochin et al., 1994). There is also evidence for segregation of different stimulus classes or features in temporal cortex. Electrophysiological and functional neuroimaging studies in humans have demonstrated specialized cortical areas for visual processing of various stimulus classes, such as faces, objects, letter strings, colors, and words (Sergent et al., 1992; Allison et al., 1994b; Nobre et al., 1994; Puce et al., 1995). Human and nonhuman primate studies have shown that attributes such as identity, expression, and gender of faces are represented in separate specialized cortical regions (Fried et al., 1982; Perrett et al., 1984; Baylis et al., 1985; Hasselmo et al., 1989; Young and Bruce, 1991; George et al., 1993; Sergent et al., 1994). Both the hippocampus (via entorhinal cortex) and amygdala receive highly convergent input from widespread uni- and polymodal neocortical areas (Van Hoesen et al., 1972; Aggleton et al., 1980; Insausti et al., 1987). Our data indicate that neuronal segregation of stimulus class and attributes, which is present in neocortex, is maintained in the hippocampus and its associated structures. This is suggested by the abundance of cells discriminating objects from faces as well as cells with selectivity to attributes such as expression of faces. However, while segregation by function is present in neocortex in widely separated regions, in the confines

following offset of both female and male faces with expressions of anger. The rise at T2 for male faces was to a mean of 3.875 spikes/s (from a baseline of 0.625 spikes/s). The rise for angry female faces noted at T1 was maintained at 4.25 spikes/s at T2.

(Lower section) Responses to the same expression-gender conjunctions at T2 are depicted for six other simultaneously recorded neurons in the left hippocampus of the same patient during the encoding task. Note significant increases (red) or decreases (blue) in neuronal activity in response to expression-gender conjunctions for four of the six units. For example, the unit on the left in the upper row has increased activity following presentation of female faces with expressions of fear. The middle unit in the lower row has increased activity following presentation of female faces with neutral, happy, and surprised expressions. These have been linked as neighboring expressions in multidimensional scaling studies (Russell and Bullock, 1985; Adolphs et al., 1994).

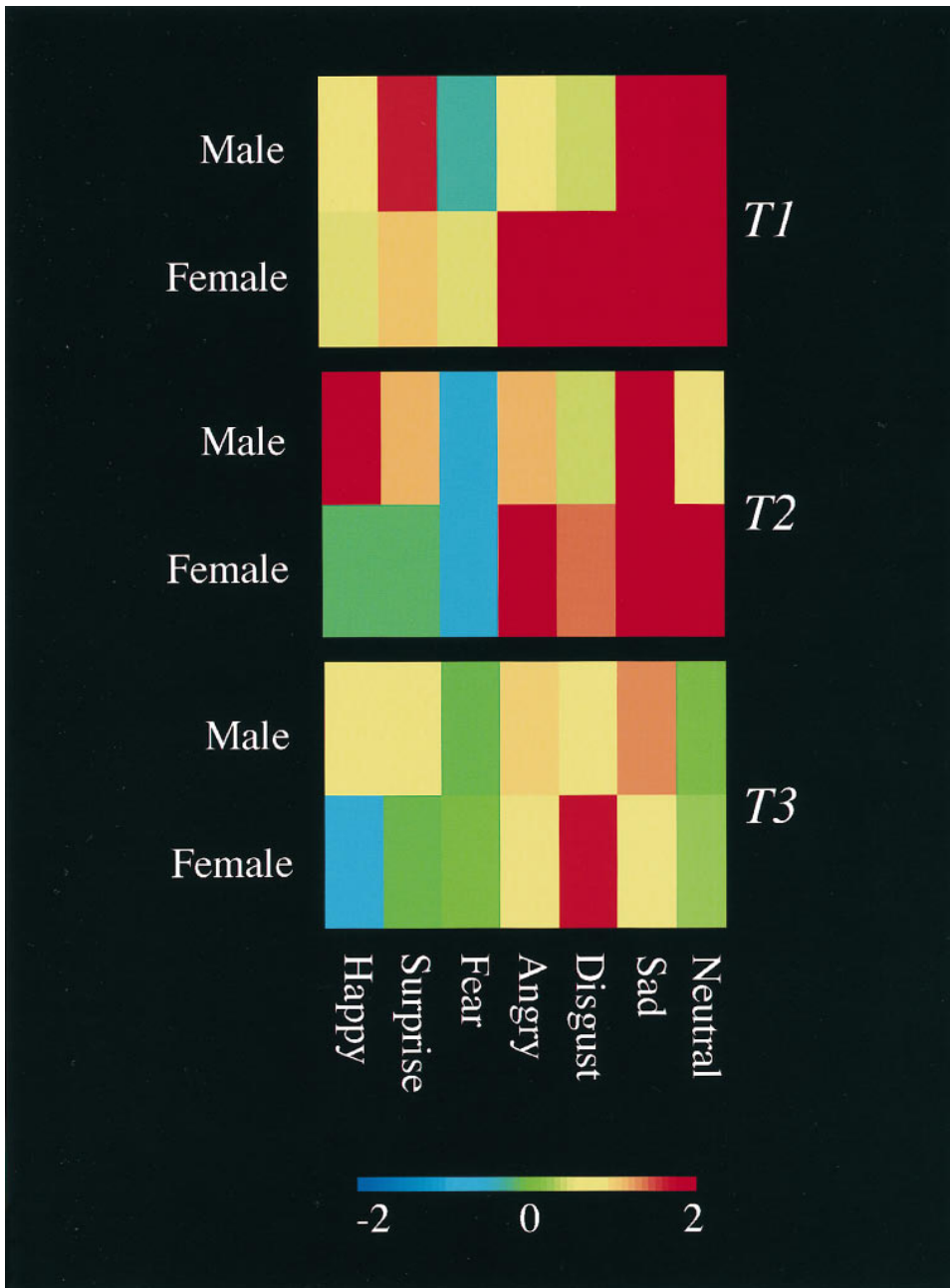


Figure 3. Single Neuron Responses to Conjunction of Facial Expression and Gender during Recognition

Discharge rates of a single neuron in the right hippocampus during recognition of male and female faces with different expressions. The activity of the unit is shown for the first second of stimulus presentation (T1) and during the following 2 s (T2 and T3). Neuronal responses are depicted in a two-dimensional "attribute space" defined by expression and gender. Expressions are arranged in an ordinal scale based on studies using multidimensional scaling for judgments of emotional facial expressions (Russel and Bullock, 1985; Adolphs et al., 1994), where neighboring emotions, such as anger and disgust, were assigned similar ratings. Each rectangle represents the mean neuronal response to conjunction of a particular facial expression and gender. Mean discharge rates are expressed as pseudocolored z-score values with respect to a 1 s baseline firing rate (T0). Note clustering of significant increases in neuronal activity (red rectangles) in this "attribute space" during T1 and T2. During T1, the discharge rate rose (from a baseline of 0–0.75 spikes/s) by >2 spikes/s (range, 2.12–3.60) for female faces with angry, disgusted, sad, or neutral expressions and for male faces with sad or neutral expressions. These rises were maintained during T2 for angry, sad, and neutral female faces and for sad male faces.

of the hippocampus and associated structures, it is restricted to a relatively small matrix. Selective responses to stimulus class or specific attributes were found in this study in different neurons recorded from a single

bundle of microelectrodes. Furthermore, the data presented here indicate that associations of attributes represented in disparate neocortical areas are formed in single neurons in the medial temporal lobe.



Figure 4. Single Neuron Responses to Conjunction of Facial Expression and Identity

Discharge rates of a unit in the left hippocampus in the second following presentation of faces of eight actors, each with seven facial expressions. Each rectangle represents mean neuronal response to conjunction of a particular facial expression and identity. Mean discharge rates are expressed as pseudocolored z scores (see Figure 2). Note the selective responses (increases in red; decreases in dark blue) to specific conjunctions; for example, the increased response to expression of anger in two individuals. (The actual rise was to 2.5 and 5.0 spikes/s, from a baseline of 0, for the two faces, respectively).

Several animal studies have reported coding of conjunctions of stimulus and task variables by single hippocampal neurons. These conjunctions often involved spatial and nonspatial variables, such as object color and position (Wible et al., 1986), two-dimensional patterns and position (Cahusac et al., 1989; Rolls et al., 1989a; Ono et al., 1991), and odor and its location in space (reviewed by Cohen and Eichenbaum, 1993). Responses of individual neurons in the hippocampus to more complex conjunctions involving stimulus and task variables have also been reported. For example, Eifuku et al. (1995) reported that 2.7% of recorded hippocampal neurons responded to specific combinations of object, place, and required behavior in a task. To our knowledge, the present study is the first demonstration of cells in the human brain that respond to conjunctions of stimulus variables. The convergence of functionally segregated inputs in close temporal contiguity into the relatively small confines of the hippocampus and associated structures, with the formation of associations in

single neurons, may be important for the constitution of memory traces (Wickelgren, 1979; Cohen and Eichenbaum, 1993; Alvarez and Squire, 1994; O'Reilly and McClelland, 1994; Treves and Rolls, 1994).

Of particular interest was the observation of a relatively large percentage of units responding to conjunctions of stimulus attributes and stimulus novelty or familiarity. During the recognition task, these units differentiated faces on the basis of expression or conjunctions of expression and gender, but differential responses depended on whether the stimulus had been seen before. Of the units recorded from the hippocampus and entorhinal cortex, 37% responded to conjunctions of facial expression and stimulus novelty or familiarity. This was a much greater percentage than responded to facial expression alone regardless of stimulus novelty (10.2%). The response of medial temporal lobe neurons to such conjunctions suggests participation of these neurons in memory function. Similarly, Rolls et al. (1989a) found that 2.4% of hippocampal neurons

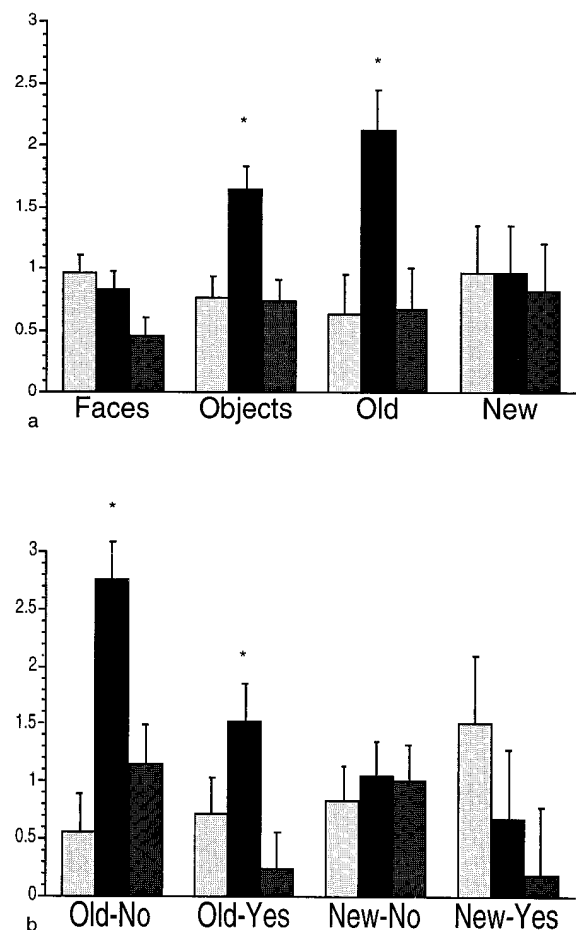


Figure 5. Selective Neuronal Responses to Novel versus Previously Presented Stimuli

Histograms of unit discharge in the left hippocampus during the recognition task (1 s bins). Mean discharge rates (and pooled SEs) are depicted for the second prior to stimulus onset (light gray bars), the second of stimulus presentation (black bars), and the following second (dark gray bars).

(a) Separate histograms for faces and objects as well as for objects that the subject had seen 10 hr earlier ("Old"), and objects that the subject had not seen before ("New"). Note the selective increase in neuronal discharge in response to objects but not faces, as well as the selective increase to "Old" objects.

(b) Separate histograms for correct and false responses. Histograms are depicted separately for: "Old-No," the false-negative responses, where the subject denied having seen objects that were shown before; "Old-Yes," the correct positive responses, where the subject recognized previously presented stimuli; "New-No," the correct negative responses, where the subject denied having seen newly presented stimuli; and "New-Yes," the false-positive responses, where the subject incorrectly reported recognition of novel objects. The significant (asterisk) increase in discharge rate to "Old" stimuli regardless of explicit recognition (i.e., to both "Old-No" and "Old-Yes") suggests that the selective neuronal activity is related to previous exposure to the stimulus rather than to the subject's explicit recognition of the stimulus.

in the monkey responded to conjunctions of object location and novelty. The prevalence of units combining processing of facial expression with the novelty of faces is much greater than that reported from animal studies for conjunctions of object attributes and novelty and

may reflect the enormous significance of face recognition for humans. The evaluation of conjunctions of affect and novelty of faces may be of special importance; for instance, the angry face of a stranger might elicit a different response than the happy face of a stranger or the angry face of an acquaintance.

The Hippocampus and Cognitive Mapping

Numerous studies report the presence of cells in the rodent hippocampus that increase their discharge rate when the animal is at particular locations in a spatial environment (O'Keefe, 1979). These have been called "place cells" and are the basis for a proposed "cognitive map" of the animal's environment (O'Keefe and Nadel, 1978). Like a particular location in a three-dimensional rodent's maze, a complex stimulus such as a face may be viewed as a node of intersection in a multidimensional "attribute space" (Figures 2-4). In this study, conjunctions of attributes were represented in the activity of individual cells in the medial temporal lobe. These cells may be considered "place cells" in an abstract space defined by stimulus features. In some cases, an individual cell responded to clusters of "adjacent" conjunctions, i.e., those involving similar expressions (Figure 3), which further substantiates the analogy to the place fields of neurons in the rat hippocampus (O'Keefe and Nadel, 1978). Thus, the human medial temporal lobe may constitute a cognitive map of the environment that is perhaps more general than the map of the spatial environment described in animal studies. Analogous to the rodent's navigation through the spatial environment, processing of complex stimuli may therefore be considered "cognitive navigation" in a multidimensional "attribute space."

Our data suggest that this cognitive map depends on stimulus novelty or familiarity. During recognition, 15% of the units responded to conjunctions of facial expression and gender, but the responses depended on stimulus novelty. The concept of a cognitive map combining information about stimulus attributes and novelty suggests a role for the hippocampus and its associated structures in encoding and retrieving information.

Sparsely Coded Distributed Representation

The neurons sampled in this study are a minuscule fraction of the neuronal pool in the medial temporal lobe, and the choice of stimuli represents a small repertoire of possible stimuli. The prevalence of stimulus-selective responses in such small samples suggests distributed coding in networks of broadly tuned neurons (Heit et al., 1988; Ojemann et al., 1992). The prevalence of units demonstrating attribute-dependent changes in activity for a particular set of stimuli (e.g., up to 40% of the units responding to conjunctions) agrees with the abundance of place cells in the rodent hippocampus for a particular environment (up to 50%; see O'Keefe, 1979; Muller, 1996; although for a lower estimate, see Thompson and Best, 1989). At the same time, a particular conjunction of attributes in our study elicited responses in only ~1% of the units sampled, which is consistent with estimates of sparseness of neuronal coding in the hippocampus obtained in animal studies (Jung and McNaughton, 1993; Treves and Rolls, 1994). Sparseness of representation indicates roughly the proportion of neurons

active at one time, the relevant period being 1 s (the unit of time also used for our analysis) (Jung and McNaughton, 1993; Treves and Rolls, 1994). Of the neurons recorded, ~10% responded to particular gender-expression conjunctions (typically a unit responded to 1–3 of 14 possible conjunctions), suggesting sparseness of representation of ~1%–2%, whereas 25% of units responded to particular expression-identity conjunctions (typically 2–4 of 56 possible conjunctions) (Figure 4), suggesting similar sparseness of representation of ~1%–2%. These numbers should be viewed only as general estimates since the determination of whether an individual unit was responsive was based on a selected significance threshold (i.e., $P < 0.05$). Nevertheless, these low percentages concur with estimates of sparseness derived from animal studies (Jung and McNaughton, 1993; Treves and Rolls, 1994). In a group of neurons within the confines of a few millimeters, a greater percentage may respond to particular attribute conjunctions, as demonstrated by simultaneous recordings of hippocampal neurons in this study (Figure 2). Sparseness of coding allows for increased storage capacity of associative networks such as the hippocampus (Jung and McNaughton, 1993; Treves and Rolls, 1994).

Overall then, our findings support the notion of sparsely coded, distributed representation of face stimuli in human hippocampus and associated structures. Sparsely coded, distributed representation has been suggested for spatial and nonspatial information in the rodent and primate hippocampus (Marr, 1972; Wickelgren, 1979; McNaughton and Nadel, 1990; Barnes et al., 1990; Jung and McNaughton, 1993; Alvarez and Squire, 1994; O'Reilly and McClelland, 1994; Treves and Rolls, 1994) and for processing of faces in inferotemporal cortex of the monkey (Young and Yamane, 1992).

Amygdala and Facial Expressions

Neurophysiological studies of nonhuman primates have shown selective responses of amygdalar neurons to faces (Rolls, 1981, 1984; Leonard et al., 1985; Nakamura et al., 1992). In addition, there is growing evidence from human lesion data and recent functional MRI and PET studies of normal subjects that the amygdala is involved in the recognition of facial emotion, particularly fear (Adolphs et al., 1994, 1995; Breiter et al., 1996; Calder et al., 1996; Morris et al., 1996). We found units in the amygdala responding to particular emotional expressions, although not to fear exclusively. The prevalence of such units during recognition was equally high in the amygdala and hippocampus (Table 2). This may reflect the importance of both the amygdala and hippocampus in the processing of facial expressions. The fact that amygdala units were not exclusively involved in discriminating facial expression concurs with the finding that the amygdala may not be critical for processing facial expressions in adults (Hamann et al., 1996). Alternatively, more rapid habituation of amygdalar responses may have masked statistically significant face-selective effects, which depend on repetition of the stimulus. Such habituation is suggested by single unit studies of animals and recent functional MRI studies of humans (Bordi and LeDoux, 1992; Wilson and Rolls, 1993; Bordi

et al., 1993; Breiter et al., 1996). Overall, given the number of units sampled in this study, it is difficult to draw definitive conclusions about regional differences within the medial temporal lobe.

Maintenance of the Memory Trace

The effect of stimulus attributes on neuronal activity sometimes lingered after the stimulus was removed, or arose when the stimulus was no longer present (Figures 1C, 1E, and 3), suggesting a neuronal correlate for maintenance of the memory trace. Sustained activity during delay periods of memory tasks has been demonstrated in the prefrontal and temporal cortices in primate studies (Fuster and Alexander, 1971; Kubota and Niki, 1971; Fuster and Jervey, 1981; Miyashita and Chang, 1988; Funahashi et al., 1989; Wilson et al., 1993; Haglund et al., 1994; Miller et al., 1996). In contrast to cortical areas, there have been fewer reports of such delay neurons in the hippocampus. Watanabe and Niki (1985), Cahusac et al. (1989), and Otto and Eichenbaum (1992) found selective firing of hippocampal neurons during the delay phase of a delayed nonmatch-to-sample task. Nakamura et al. (1992) reported similar findings in the amygdala. However, Saltzman et al. (1993) did not find such neurons in the hippocampus. Colombo and Gross (1994) found single unit activity changes in both inferotemporal cortex and hippocampus during the delay phase of a match-to-sample task. They reported that while the inferotemporal cortex delay activity was usually selective to a particular stimulus, the hippocampal delay activity was nonselective. This raises the possibility that during the delay, hippocampal neurons may respond to conjunctions of stimuli, either spatial or nonspatial, rather than to single stimuli. Our data suggest that activity following stimulus removal is related to either stimulus attributes or conjunctions of attributes. However, our task differed from the delayed match- or nonmatch-to-sample paradigms used in most of the above studies. Since we did not record from inferotemporal cortex, comparison between this region and the hippocampus was not possible.

Neuronal Responses Related to Long-Term Recognition

Response decrements to repeated presentations of stimuli have been found in the inferotemporal cortex by several investigators and interpreted as neuronal correlates of memory. Typically, these responses were measured within a single session, and the familiarity effect did not always last long (Baylis and Rolls, 1987; Miller et al., 1991; Riches et al., 1991; Rolls et al., 1993). Units in the anteroventral inferotemporal cortex, including perirhinal and entorhinal cortices, are a possible exception. Several studies reported units in these regions responding to familiarity following long retention periods and multiple intervening stimuli (Fahy et al., 1993; Li et al., 1993). With regard to the hippocampus, Riches et al. (1991) did not find units that differentiated novel from familiar stimuli in the monkey, and Heit et al. (1988) did not find such neurons in humans. In contrast, Rolls et al. (1993) found hippocampal neurons in the macaque,

which responded differently to novel and familiar presentations of stimuli separated by a median of 21 intervening stimuli. These conflicting results may be due to methodological issues such as the particular task used and the sample size (see Rolls et al., 1993).

In our study, differential responses to “new” or “old” stimuli were observed as long as 10 hr after stimulus presentation, far longer than in most of the above studies. Whereas in the monkey hippocampus almost all neuronal responses to familiar stimuli were decremental, in our study, some units increased their discharge rate to “old” faces or objects (Figure 5), while others responded with decreased firing rates. The presence of both responses to familiar faces was also reported by Rolls et al. (1989b) in the superior temporal sulcus of the monkey.

A central question in memory research concerns the contribution of medial temporal lobe structures to retrieval compared to encoding of information (Haxby et al., 1996; Nyberg et al., 1996). Our data indicate that medial temporal lobe neurons are involved in both. When stimuli were presented for explicit retrieval as long as 10 hr after initial presentation, neurons exhibited attribute-dependent responses. Units responding to facial expression and to conjunctions of expression and gender were more prevalent during recognition than during encoding, but the responses depended on whether the stimuli were “old” or “new.” These findings suggest that the responses of many medial temporal lobe neurons, especially in the hippocampus and entorhinal cortex, are determined by both the sensory attributes and the novelty or familiarity of stimuli. These neurons therefore do not respond only to sensory features, nor are they merely “novelty–familiarity detectors,” responding to any novel or familiar stimulus. Similar units, responding to conjunctions of object novelty and features such as color and shape, have been reported in the anteroventral part of the inferotemporal cortex in the monkey (Li et al., 1993). In the monkey hippocampus, Rolls et al. (1989a) found cells responding to combinations of familiarity of objects and their spatial locations.

Single Neurons and Conscious Recollection

The relationship between neuronal activity and conscious recollection is an intriguing question. Does neuronal activity in the medial temporal lobe reflect conscious memory, or does it follow exposure to previously seen stimuli, regardless of what the subject remembers? This question cannot be examined in animals and is difficult to study in humans. Recent studies using PET and functional MRI have shown increased blood flow in the medial temporal lobe during encoding and/or explicit retrieval of information. Nyberg et al. (1996) reported increased blood flow in the left medial temporal lobe during retrieval of words. This increase appeared to be related to the success of the retrieval. Schacter et al. (1996b) found significant medial temporal lobe blood flow increases for both veridical and illusory recognition of words, suggesting that conscious recognition, rather than repeated exposure to the stimulus, is associated with the increase in medial temporal lobe blood flow. In

the present study, 20% of the units in the medial temporal lobe differentiated stimuli explicitly remembered by the subject from stimuli accorded a negative recognition response. However, changes in the activity of 18% of the units recorded in this study were related to past exposure to the stimulus rather than to the subject’s recognition response (Figure 5); i.e., the subject may deny having seen the stimulus, yet the firing rate of an individual neuron indicates the opposite. In this sense, an individual neuron appears to maintain a record of past experience that may be more accurate than the subject’s conscious recollection.

Experimental Procedures

Subjects

The subjects were nine patients with epilepsy resistant to pharmacological treatment. They underwent implantation of intracranial electrodes in order to identify the seizure focus for potential surgical resection.

Electrode Placement

Based on clinical criteria, and following patients’ informed consent, electrodes containing microwires were stereotactically implanted, using MRI and angiographic guidance, in hippocampus, amygdala, and entorhinal cortex bilaterally as well as in other temporal and/or extratemporal sites. Each electrode consisted of a flexible polyurethane probe containing nine 40 mm platinum–iridium microwires protruding ~4 mm into the tissue beyond the tip of the probes. Patients were then monitored for up to 2 weeks until a sufficient number of seizures was recorded. MRI confirmed the position of the electrodes.

Behavioral Paradigm

The subjects participated in two recording sessions. In the first session (“encoding”), black and white two-dimensional pictures of faces and objects were presented to be remembered. The faces were those of eight actors, four males and four females, each with seven expressions, obtained from a battery of faces by Eckman and Friesen (1976). Objects were single common household items such as appliances, furniture, sports equipment, or vehicles. Whereas each face was categorized by expression, gender, or identity, objects were not divided into categories. There were altogether 98 different stimuli—56 faces and 42 objects, and each stimulus was presented once (during recordings from 24 units in four patients) or twice (during recordings from 50 units in five patients). Each stimulus was presented for 1 s, followed by a 3–5 s delay before presentation of the next stimulus. One to ten hours later, subjects underwent a “recognition” session, where they were presented with a series of 165 stimuli (94 faces and 71 objects) that included all of the previously presented stimuli as well as novel faces and objects. Novel faces were those of six additional actors, each depicting various emotional expressions, as well as additional household-related objects. Each stimulus was presented for 1 s before a question mark appeared below the picture, signaling the patient to respond with a key press (“yes” or “no”) whether they had seen the face or object in the encoding session.

Recordings

At the time of unit recording, up to six bundles of microwires were connected to a miniature jack panel attached to a 16 channel preamplifier module providing a gain of 5000 over a band pass of 0.3 Hz–6 kHz. Unit activity was recorded on FM tape. Wideband EEG activity (0.1 Hz–10 kHz) from each microwire was high pass filtered (300 Hz–10 kHz) to allow stable triggering of action potentials above background noise. Using Data Wave Experimenter’s Workbench software, 2.0 ms of electrophysiological activity surrounding each triggered action potential was digitized at 20 kHz, and multiple units were separated based on action potential amplitude, duration, slope, and other parameters of waveform morphology (McNaughton et al., 1983).

It should be pointed out that generalization about neuronal function from recordings in patients with seizure disorders is a potential limitation. Since the location of the seizure focus is unknown a priori, electrodes were also placed in regions that were eventually found to be distant from the epileptic focus. Furthermore, in many cases, a hypothesis concerning the location of the seizure focus could be formulated early during monitoring, thus enabling choice of a montage of microelectrodes that avoided the focus for recording during memory tasks. In this study, most of the units recorded (93%) were contralateral to the seizure focus or outside the vicinity of the focus.

Data Analysis

Spike counts were obtained for 100 ms bins and collapsed across 1 s epochs: the second preceding stimulus onset (T0), the second of stimulus presentation (T1), and the following second (T2). The arguments for relevance of the 1 s period are based on long-term potentiation (LTP) and episode formation timescales as discussed by Treves and Rolls (1994). A separate repeated measures ANOVA was carried out for each unit. The repeated measures were the discharge rates at T1 and T2 corrected for baseline (i.e., T0 subtracted). The factors were stimulus class (faces versus objects) and, for the recognition session, included stimulus novelty, i.e., whether the stimulus had been presented previously during the encoding task (old) or was seen for the first time during the recognition task (new). The subject's recognition key press response (yes versus no) was also introduced as a factor. A separate ANOVA was performed for faces using expression, identity, and gender (nested in identity). This analysis was limited to patients who had been presented with sufficient repetitions of face stimuli for ANOVA; that is, 50 units during encoding (19 in amygdala, 14 in hippocampus, and 17 in entorhinal cortex) and 60 units during recognition (11 in amygdala, 29 in hippocampus, and 20 in entorhinal cortex). We considered a unit as having a differential response to a factor when the factor or its interaction with time was significant ($P < 0.05$). The same rule was applied to interaction (conjunction) of factors.

For many of the cells described here with differential responses, there were significant results at P values < 0.01 . Given the number of cells and the number of ANOVA tests, a few such significant results might be expected by chance among the population of neurons from which recordings were made. To address this concern, we followed a procedure used by Rolls et al. (1989a, 1993), computing the number of cells with significant results at each level (i.e., $P = 0.05$ – 0.01 ; $P = 0.01$ – 0.005 ; $P = 0.005$ – 0.001 ; and $P < 0.001$) found in the ANOVA and comparing it, using a goodness of fit Chi-square test, with the number that would be expected by chance. Rejection of the "fit" implies that the number of cells with significant results is not merely due to chance. In computing the expected number of significant units by chance alone, we took into account the fact that a factor was considered significant if its main effect or interaction with time were significant. Thus, the expected number of "chance" units was accordingly increased.

For visual presentation of data, mean discharge rates of individual units were expressed as standardized z-score values with respect to a 1 s baseline firing rate (T0) based on ANOVA. The z-score values are mean rates in standard error (SE) units ($z = \text{mean rate}/\text{SE}$). These z values were then pseudocolored and are presented in Figures 2–4 for particular conjunctions. Each z-score value was based on the mean of six to eight stimulus presentations (two presentations in Figure 4).

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