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Information Representation, Processing, and Storage in the Brain: Analysis at the Single Neuron Level

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Abstract. The ways in which information is represented, processed, and stored in the nervous system of primates as shown by recording from single neurons are considered.

1) Individual stimuli, objects, or responses (termed events) are coded as the pattern of firing across a population of neurons. That is, ensemble encoding rather than "grandmother cell" encoding is used. Evidence for this from recordings in temporal cortical areas involved in face recognition is presented.

2) In order to clarify how the nervous system would function with such ensemble encoding, and to clarify how single neurons might respond in such a system, a theoretical analysis of information representation and storage in matrix memories formed by neuronal networks is presented. It is shown that such distributed information processing and storage has a number of advantages, including completion of an incomplete pattern, generalization, graceful degradation when the system is damaged or incomplete, and speed. It is also shown that these properties arise only if ensemble coding for information across subpopulations of neurons is used. It is further noted that the tuning of neurons, which is graded differentially to different events rather than being so specific that it occurs only to one event, is advantageous in making many fine discriminations. Also, it is shown that such neuronal networks allow any pattern of firing to be interfaced to any other pattern of firing, providing a basis for information transmission from sensory input through to motor output with no special "homunculus" required.

3) Through the connected stages of a processing system the representation of information becomes more sharply differentiated between events, as shown by the fineness of tuning of single neurons in different stages of the taste system and in temporal lobe visual areas.

One reason that this is necessary is to reduce interference in the transfer of information across and storage of information within matrix memories. Neuronal networks which will perform this categorization, or orthogonalization (decorrelation) of the representations of stimuli or events using learning to achieve the necessary mountain climbing, are described.

4) Evidence that neurons in the amygdala and orbitofrontal cortex of the primate are involved in association memory, for example in cross-modality associations and in stimulus-reinforcement associations, is described. It is shown that sensory information processing occurs through several areas in the primate before it is interfaced with such associational and motivational systems. This is illustrated by taste and visual information processing systems involved in the control of feeding in which modulation by hunger occurs only after several cortical stages of analysis. The theoretical significance of this is that particular stimuli, such as a particular food, can only be represented across a limited ensemble of neurons which is well differentiated from other ensembles representing non-foods or other foods after several stages of analysis; and that this differentiation is necessary so that when motivation acts, or association learning occurs, it does so with sufficient specificity for that particular food or stimulus and not for other stimuli.

5) Evidence that neurons in the hippocampus of the primate are involved in memories for combinations of events, such as where in the environment a particular object was seen or which motor response should be made to a particular stimulus, is described. Evidence on how hippocampal circuitry may be appropriate for detecting such conjunctions or combinations of events which may reach it from different areas of the temporal, parietal, and frontal cortex is described.

6) The storage of information in short-term memories is shown to usually involve short-term changes in synaptic efficacy (e.g., in the inferior temporal visual cortex in delayed matching-to-sample tasks) but in a few cases involves holding a pattern of firing during a delay period (e.g., in the dorsolateral prefrontal cortex in delayed response tasks).

INTRODUCTION

In this paper the ways in which information is represented, processed, and stored in the nervous system of primates will be considered. The evidence will be based on analysis of the activity of single neurons because this is the basic level at which information is transferred over any distance in the nervous system, so that the information being processed must be represented (at least when transferred over any distance) in the firing pattern of single neurons. The examples will be drawn from work on the nonhuman primate to make it as relevant as possible to understanding brain function in man.

Evidence will be presented to show that information is represented over ensembles of neurons. Theoretical analyses, which show how such distributed information processing occurs and which highlight its advantages for brain function, are described first in order to make the understanding of these neuronal operations involved in information processing and the types of response which are obtained from single neurons more precise. After this, the ways in which information is represented across ensembles of neurons will be described. Then the changes in information representation which take place through the sensory systems as information is categorized by cortical processing are described. Also discussed are the ways in which such information is used in different information storage and processing systems in the brain; those involved in association memory and short-term memory will be described.

MODELS OF NEURONAL INFORMATION PROCESSING AND STORAGE

Matrix models of memory (25, 33, 34, 51) provide useful insight into information processing in groups of neurons. They can be used to help understand the types of response found in single neurons in the brain by analyzing how the equivalent of single neurons in a computer simulation of a matrix memory respond. Matrix models can be modified to provide more complex models of information processing in brain regions such as the neocortex and hippocampus (66).

Consider a population of n neurons with vertically oriented dendrites intersected by a set of n horizontally running axons (see Fig. 1). At each intersection of an axon with a dendrite there is a modifiable synpase. (This situation is almost exactly what is found in the cerebellum (see (26)). The unconditioned (unlearned) response is represented by the pattern of firing of the n vertically oriented neurons in Fig. 1. The conditioned stimulus is represented by the pattern of firing of the n horizontal axons. When there is simultaneous activity in a horizontal axon and a vertical neuron, the synapse becomes modified. (This is a very simple learning rule. The modification can consist of a decrease or an increase of synaptic strength.) In such a memory information is thus stored in a correlation matrix formed by the product of a vector of n neurons representing the conditioned stimulus with a vector (perhaps also of n neurons) representing the unconditioned stimulus. Many associations can be stored in the same matrix by adding each product to the previous summed contents of the matrix. This process of storage is illustrated in Fig. 2.

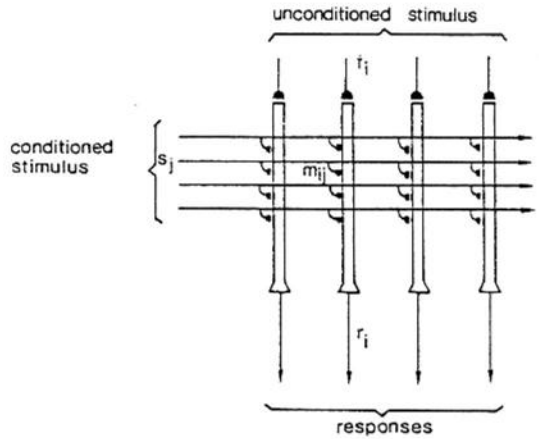

FIG. 1 – Neurons connected to form a matrix memory. The vertical rectangles represent the dendrites of the neurons which respond unconditionally to application of the unconditioned or forcing stimuli (f) to produce the responses (r). The conditioned stimuli (s) are applied to the horizontally running axons, each one of which forms a modifiable synapse with each dendrite it passes (see text).

To recall an association from the matrix memory the conditioned stimulus is applied to the horizontal axons. Each axon activates each dendrite in proportion to how much the particular synapse was modified during learning. The firing of each vertical neuron then represents the sum of effects produced through all its synapses. This is the sum over all conditioned stimulus input axons of the firing on that axon multiplied by the synaptic strength at the synapse at each axon-dendrite intersection in the matrix. An example of how this recall process functions is shown in Fig. 3.

There are many biologically desirable properties of this type of information store, including recall of a complete stimulus from the memory when only a part of a stimulus is shown, generalization to a similar stimulus if a stimulus which has never been seen before is shown (see Fig. 4), and considerable tolerance to partial destruction or absence during development of synapses or neurons in it (i.e., graceful degradation in performance as damage to the memory increases; see Fig. 5). This type of information store also shows some of the other features of biological memory such as interference. This interference can be reduced by thresholding (see Figs. 4 and 5). Anatomical and

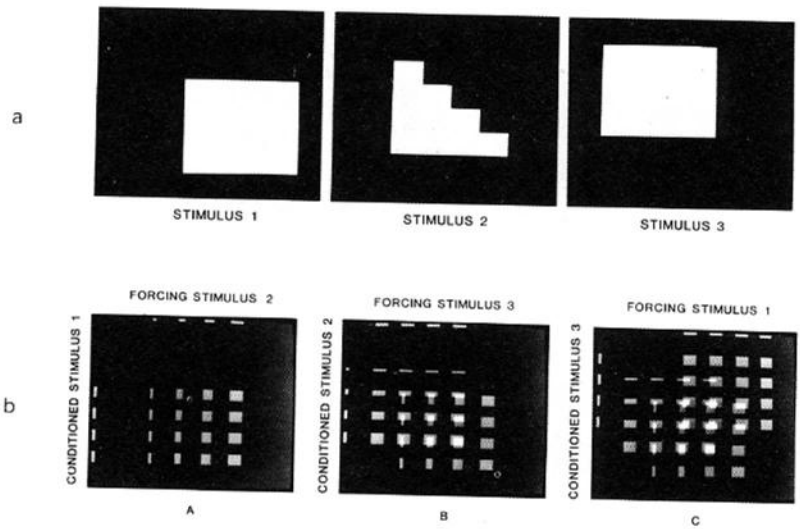

FIG. 2 – Storage of information in a matrix memory. a) The stimuli used consisted of 8 by 8 pixels and were read off by rows to form 64-element vectors applied as stimuli to the matrix memory. b) The matrix memory with three different associations being stored. In A, stimulus 1 is used as the conditioned stimulus and stimulus 2 as the unconditioned or forcing stimulus. The 64 dendrites in the matrix run as 64 vertical columns across which the unconditioned stimulus (represented as a 64-element vector and shown above the matrix) is applied. The 64 horizontal axons run as the rows of the matrix, and to these the conditioned stimulus is applied (represented as a 64-element vector and shown at the left of the matrix). The gray scale values within the matrix are proportional to synaptic strength formed by the conditioning. The gray values of the vectors are proportional to firing rate. B and C show the formation of further associations, which overlap and add to the strength of some synapses in the memory.

physiological evidence is also consistent with the idea that information storage in some parts of the brain uses such a distributed storage system (65, 66). Another useful property of this type of memory is that it is fast, with only one synaptic delay being interposed between application of the input stimulus pattern and appearance of the output pattern.

The types of response shown by single neurons and populations of neurons can be clarified by considering how a single neuron in such a memory might respond using computer simulations. These included 64 neuron (a 64 by 64 storage matrix) and 1024 neuron (a 1024 by 1024

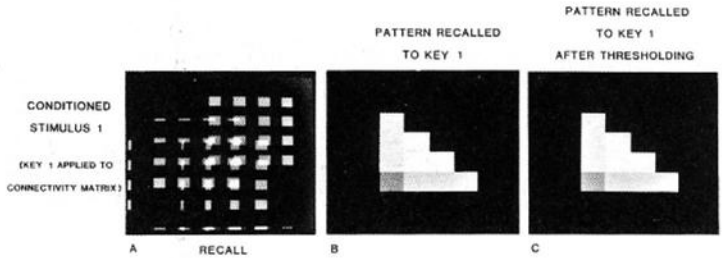

FIG. 3 – The recall of information from a matrix memory. A) Application of conditioned stimulus 1 (shown on the left of the diagram) to the matrix containing three stored associations results in the pattern of firing of the output neurons represented as a vector across the bottom of the diagram (cf. Fig. 1). B) The recalled pattern (i.e., the pattern of firing of the output neurons) represented as an 8 by 8 image (cf. Fig. 2a). C) The recalled pattern after thresholding at half the maximal firing rate (brightness level).

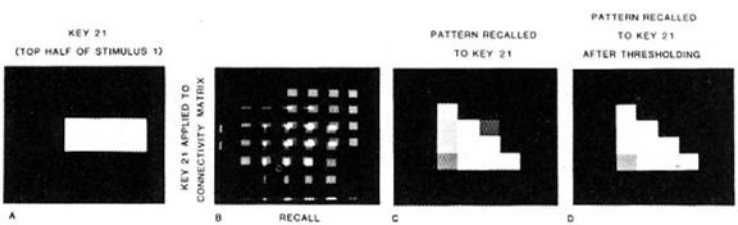

FIG. 4 – Completion and generalization in the recall from a matrix memory. The upper half of stimulus 1 (A) is applied to the connectivity matrix (B) and results in recall of the pattern in (C) shown after thresholding in (D).

storage matrix) linear associative matrix memories. In the 1024 neuron network, lateral inhibition was applied to the input stimulus vectors in order to orthogonalize the stimuli and thus improve the storage capability of the network (see Kohonen *et al.* (34)). It should be remembered that each neuron in the matrix is represented by each vertical dendrite (see Fig. 1). The information stored on such a single neuron i by modification of its synapses is the sum over every stimulus pair of the pattern of the conditioned stimulus multiplied by the firing of that (i'th) neuron to the unconditioned stimulus. Thus the i'th neuron

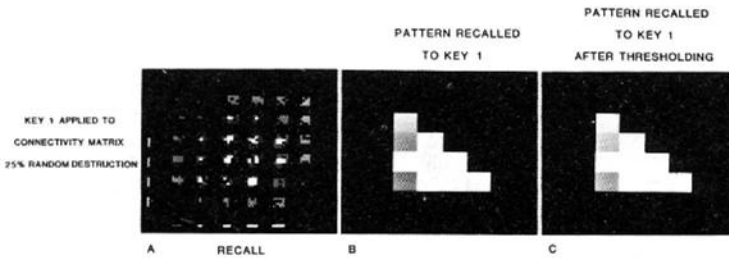

FIG. 5 – Graceful degradation of the performance of a matrix memory when it is damaged. The application of key 1 to the matrix after 25% of the synapses had been removed at random (A) resulted in the recall shown in (B) and after thresholding in (C).

responds best in such a memory to a combination of one to many of the conditioned stimuli. In one extreme condition, if neuron i fires to only one of the unconditioned stimuli, then it responds best to the conditioned stimulus associated with that unconditioned stimulus. In the other extreme condition, if neuron i fires to all the unconditioned stimuli, then it is most responsive to a combination of all the conditioned stimuli. Between these limits, neuron i will respond best to a combination of a subset of the conditioned stimuli, and will respond partly to each of the stimuli in the subset. The results of the simulation show that in some cases the neurons respond best to one of the conditioned stimuli applied to the network, and in other cases to several of the conditioned stimuli applied to the network (see Fig. 6). This is remarkably similar to what is found when recordings are made from single neurons in the cortex in the superior temporal sulcus of the monkey, for in this region each neuron typically responds to only a subset of the stimuli (which in this case are faces) which are effective for activating the different neurons in this region (see below and (4, 58)).

This type of information storage in neuronal networks also has implications for the representation of information in the brain. In order to derive the benefits of information storage in a matrix memory noted above (such as completion, generalization, and graceful degradation) it is essential that each individual object in the environment (such as a particular grandmother) be represented by the firing pattern of an ensemble of neurons. (This pattern of firing is termed an "event.") This is because completion, generalization, and graceful degradation rely on some of the neurons which represented the original object or event being

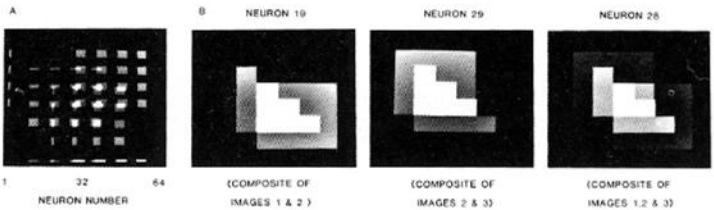

FIG. 6 – Response properties of single neurons in a matrix memory. A) The association matrix containing 3 associations. The 64 "neurons" in the matrix are 64 vertical columns, each of which has synapses modified on it which represent the patterns of none, one, or several of the conditioned stimuli. Examples of the information stored on single neurons are shown in B.

activated by the incomplete event, by the similar event, or after some of the synapses or neurons in the network have been destroyed. On the other hand, each event must not be represented over a very large population of neurons which overlaps almost completely with the population activated by a different event; if this were the case then the matrix memory would display great interference and would be a very inefficient memory storage or interfacing system. These two arguments lead to the conclusion that in a matrix memory system each event must be represented across an ensemble of neurons but that the ensemble must be of limited size. In such an ensemble, in which information represented could individuate an event (e.g., the face of a particular person), it would be expected that each neuron would be tuned to differentiate quite sharply between the different members of the set of individual stimuli represented in that matrix but would typically respond to more than one member of the set of stimuli. That is, neurons which responded only to one object or event (e.g., grandmother Smith) would not be useful in a matrix memory system. This theoretical analysis thus explains the utility of the type of information representation across the neurons in the cortex in the superior temporal sulcus of the monkey, where it is found that each neuron typically responds to a limited subset of the stimuli (which in this case are faces) which are effective for activating the different neurons in this region (see above).

Another advantage of such ensemble encoding is that if neurons are not tuned to only one stimulus, but instead each stimulus activates differentially its own set of graded filters, then fine, continuous discriminations between the members of that set are enhanced.

Potentially more discriminations are possible than with the one neuron-one stimulus type of encoding (for further discussion see Erickson (17, 18)).

Another problem which is clarified by this theoretical analysis is sensory to motor or input-output processing in the brain. The analysis shows that such neuronal nets effectively enable an input vector of n elements (represented by the firing of the conditioned stimulus axons in Fig. 1) to be connected to an output vector of (for example) n elements (represented by the firing of the unconditioned stimulus neurons in Fig. 1) in such a way that any particular pattern of firing in the input vector or population of neurons can produce any particular pattern in the output vector or population of neurons. An ensemble of neurons in this analysis is the pattern of firing in a subset of the neurons in a vector. (The ensemble which represents each stimulus is usually a subset of the whole vector or population of neurons so that interference between the stimuli or events is minimized.) These matrix operations thus provide a simple way of interfacing one population of neurons (perhaps an input population) to another population of neurons (perhaps an output population), with no need at any stage for a special "interpreter" or homunculus. In practice, in the brain, there are a series of matrix operations modified from this basic design, so that information processing proceeds through a series of specialized stages which categorize the stimulus before it is interfaced to motivational or motor systems (see below).

THE REPRESENTATION OF INFORMATION ACROSS ENSEMBLES OF NEURONS

One way in which the representation of information across ensembles of neurons in the brain is being investigated is by analyzing the responses of single neurons in the temporal lobe visual cortex which respond preferentially to faces. The question considered is whether information which could specify the face of one individual is represented by the firing of one neuron or whether the pattern of firing of an ensemble is needed to enable identification of the individual being seen.

Neurons which respond preferentially or selectively to faces are found in certain areas of the temporal lobe visual cortex which receive their inputs via a number of corticocortical stages from the primary visual cortex, the striate cortex, through prestriate visual areas ((14, 16, 83), see Fig. 7). The responses of these neurons to faces are selective in that they are 2-10 times as large to faces as to gratings, simple geometrical stimuli, or complex 3-D objects (4, 6, 52). They are probably a

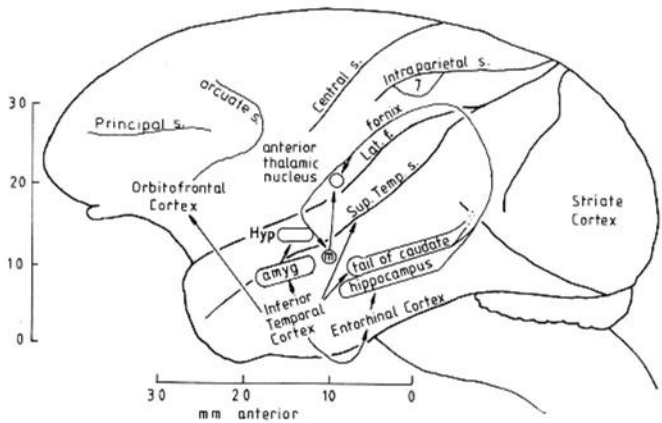

FIG. 7 - Some of the pathways described in the text are shown on this lateral view of the rhesus monkey brain. amyg = amygdala; central s = central sulcus; Hyp = hypothalamus / substantia innominata / basal forebrain; Lat f = lateral (or Sylvian) fissure; m = mammillary body; Sup Temp s = superior temporal sulcus; 7 = posterior parietal cortex, area 7.

specialized population for processing information from faces in that they are found primarily in architectonic areas TPO, TEa, and TEm and are not just the neurons with the most complex types of response found throughout the temporal lobe visual areas (6). The advantage of such a specialized system in the primate may lie in the importance of rapid and reliable recognition of other individuals using face recognition, so that appropriate social and emotional responses can be made (58).

In experiments to determine how information which could be used to specify an individual is represented by the firing of these neurons, it has been shown that in many cases (77% of one sample) these neurons are sensitive to differences between faces (4), but that each neuron does not respond to only one face. Instead, each neuron has a different pattern of responses to a set of faces, as illustrated in Fig. 8.

Such evidence shows that the responses of each of these neurons in the cortex of the superior temporal sulcus do not code uniquely for the face of a particular individual. Instead, across a population of such cells, information is conveyed which would be useful in making different behavioral responses to different faces. Thus information which specifies an individual face is present across an ensemble of such cells.

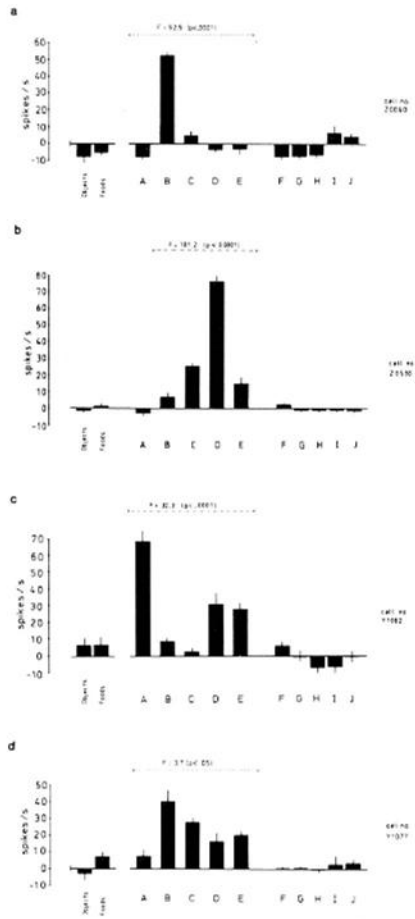

FIG. 8 – The responses of four cells (a-d) in the cortex of the superior temporal sulcus to a variety of face (A-E) and nonface (F-J) stimuli. The responses to nonface objects and to foods are shown on the left of the diagram. The bar represents the mean firing rate response above the spontaneous baseline firing rate with the standard error calculated over 4-10 presentations. The F ratio for the analysis of variance calculated over the face set indicates that the units shown range from very selective (Z0060) to relatively nonselective (Y1077) (from (4)).

In that each neuron does not respond to only one face, and in that a particular face can activate many neurons, these are not "grandmother"

cells (2). However, because their responses are relatively specialized both for the class "faces" and within this class, they could contribute to relatively economic coding of information over relatively few cells (see Barlow, (2)). It should be noted that even if individual neurons in this population are not completely tuned to respond specifically to only face stimuli, it is nevertheless the case that the output of such an ensemble of neurons would be useful for distinguishing between different faces. The appropriateness of these neurons for such a function is enhanced by their relative constancy of response over some physical transforms, such as size, contrast, and color (52, 67). These findings lead to the hypotheses that such neurons are filters, the output of which could be used for recognition of different individuals and in emotional responses made to different individuals. Their different responses to different faces, and also their different responses to different parts of faces (52) and to different parts of the spatial frequency spectrum present in faces (5, 68), provide further evidence for understanding them as filters.

It is unlikely that there are further processing areas beyond those described where ensemble coding changes into grandmother cell encoding. Anatomically there does not appear to be a whole, further set of visual processing areas present in the brain beyond the temporal lobe visual areas such as those described, from which outputs are taken to limbic and related regions such as the amygdala and via the entorhinal cortex to the hippocampus. Indeed, tracing this pathway onwards, Leonard *et al.* (35) have found a population of neurons with face-selective responses in the amygdala, and in the majority of these neurons different responses occur to different faces with ensemble (not unique) coding still being present. After interfacing with limbic circuits in this way, there is evidence for further links which may be important in the behavioral output via the connections of the amygdala to the ventral striatum (which includes the nucleus accumbens), for in the ventral striatum a small number of neurons are found which also respond to faces (see Rolls, (64)).

INFORMATION CATEGORIZATION IN SENSORY SYSTEMS

The example of information representation described above shows that information needed to specify an individual face is represented across the population of neurons studied efficiently in terms of what is appropriate for a distributed information processing system illustrated by the properties of matrix memories. In particular, each neuron responds to only some faces and has graded responses to the faces to which it does respond. This would maintain interference at a reasonably

low level in the matrix memory, yet would allow the beneficial properties such as completion, generalization, and graceful degradation to occur. The fundamental problem which the sensory systems of the brain have is how to reduce the redundancy present in the input signals and to extract a functionally useful information representation of the type just described. It may be noted, for example, that discrimination between faces based on gray level pixel images would be extremely difficult because of the great correlation or lack of orthogonality present between such images. The way in which information changes across successive processing stages in order to achieve efficient categorization is described with an example from the taste system.

The first central synapse of the gustatory system is in the rostral part of the nucleus of the solitary tract (NTS) (7, 8). In order to investigate the tuning of neurons in the nucleus of the solitary tract, the response of single NTS neurons to the prototypical stimuli (NaCl, glucose, HCl, and quinine), to water, and to a complex stimulus (blackcurrant juice) were measured in the macaque monkey. It was found that NTS neurons are relatively broadly tuned to the prototypical taste stimuli ((80, see Fig. 9). The breadth of tuning index used was that of Smith and Travers (84). This is a measure derived from information theory of entropy, calculated as

$$H = -k \sum_{i=1}^{n} P_i \log P_i$$

where H= breadth of responsiveness, k = scaling constant (set so that H = 1.0 when the neuron responds equally well to all stimuli in the set of size n), p_i = the response to stimulus i expressed as a proportion of the total response to all the stimuli in the set.

The NTS projects via the thalamic taste area to the frontal opercular taste cortex and insula (7). In these regions gustatory areas were found, and it was discovered that the breadth of tuning of the neurons in these areas was finer than in the NTS ((81, 95), see Fig. 9). The frontal opercular taste cortex projects into a fourth order gustatory area in the caudolateral orbitofrontal cortex (77), and here it was found that the tuning of gustatory neurons was even finer ((93), see Fig. 9). This analysis shows that one change which takes place in the representation of information in the gustatory system is that entropy (in terms of breadth of tuning described above) is reduced; that is, neurons become better able to differentiate between different stimuli or, equivalently, the correlation between the responses of a given neuron to different

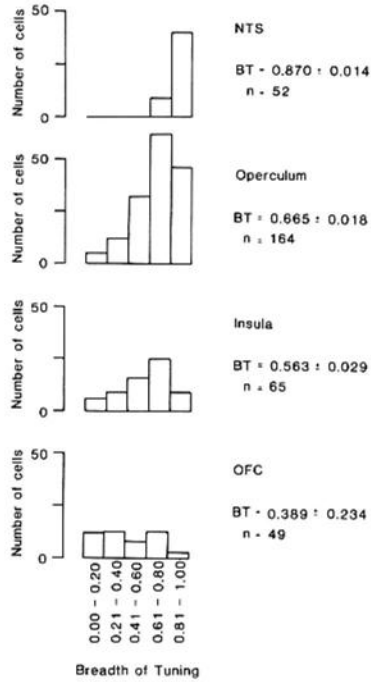

FIG. 9 – The breadths of tuning of neurons in different stages of the taste system. A value of 1 represents equal responses to all stimuli (i.e., very broad tuning) and a value of 0 represents a response to only one of the stimuli (see text). The stimuli used were 1 M glucose, 1 M NaCl, 0.01 M HCl, 0.001 M quinine HCl, water, and 20% blackcurrant juice.

stimuli becomes less. This is ideal for a distributed information processing system because it reduces interference in memories and interfacing systems, as illustrated by the properties of matrix memories described above.

Another important principle of nervous system function may be illustrated by information processing in the taste system. It is only after several or many stages of sensory information processing (which produce efficient categorization of the stimulus) that there is an interface to motivational systems, to other modalities, or to systems involved in association memory. Thus in the taste system of the primate neuronal responses to gustatory stimuli in the NTS, opercular taste cortex, and insular taste cortex are not affected by hunger (96, 97). It is

only in the orbitofrontal taste area that neuronal responses are modulated by hunger, ceasing to occur, for example, to glucose if glucose has just been eaten to satiety (75). The reason for this is probably as follows. If satiety were to operate at an early level of sensory analysis, then because of the broadness of tuning of neurons, responses to non-foods would become attentuated as well as responses to foods (and this could be dangerous if poisonous non-foods became undetectable). This argument becomes even more compelling when it is realized that satiety typically shows some specificity for the particular food eaten, with other foods not eaten in the meal remaining relatively pleasant (59). Unless tuning were relatively fine this mechanism could not operate, for reduction in neuronal firing after one food had been eaten would inevitably reduce behavioral responsiveness to other foods. Indeed, it is of interest to note that such a sensory-specific satiety mechanism can be built by arranging for tuning to particular foods to become relatively specific at one level of the nervous system (as a result of categorization processing in earlier stages), and then at this stage (but not at prior stages) to allow habituation to be a property of the synapses. This would result in a decreased response to the taste of a food which had just been eaten but not to another taste unless they were very similar. It appears that precisely this mechanism is found in the gustatory system (75).

The point about interfacing to other modalities and to association memory can also be made with the taste system. In the rostral NTS, the frontal opercular taste cortex and the insular taste cortex, the neurons found are mainly gustatory, and other modalities are not represented. On the other hand, after these stages (that is when tuning has become fine) taste processing is interfaced to other modalities. For example, in and near to the orbitofrontal taste area, neurons with visual and somatosensory responses are found (87). Also, in the amygdala, which receives from the insular taste cortex (40), different modalities are brought together. Indeed, the visual projections to the amygdala follow the same rule in that visual projections are not found to the amygdala from early stages of sensory analysis but only from temporal lobe visual areas, that is after much earlier processing (9, 88, 89). The probable reason for this is again that it is only possible to allow modalities to interact in order to form associations (for example, after much processing in each modality), so that interference due to lack of orthogonalization of the representations of the stimuli can be minimized (see above). That is, it is only possible to form associations in distributed memory processing systems of the matrix memory type after the neuronal representations of

the stimuli have been at least partly orthogonalized in order to minimize interference.

NEURONAL MECHANISMS OF CATEGORIZATION

The neuronal mechanisms which perform the categorization or orthogonalization evident in, for example, the taste and visual systems as described above are not yet well understood, but the following ideas may be useful.

One simple neuronal mechanism of orthogonalization is lateral inhibition. It orthogonalizes in that it tends to decorrelate two signals by high-pass spatial frequency filtering them. Consider two different square wave signals represented in a sensory system. To the extent that they overlap, there will be neuronal elements which will respond to both, and this overlap will produce interference in, and reduce the capacity of, matrix memories. If, however, both signals are high-pass filtered by lateral inhibition then the signals have neural elements in common only at the edges of the square waves and most of the overlap will have been reduced. This is so important for any matrix memory or interface operation that it is probably the most important function of lateral inhibition.

A much more sophisticated computation which results in categorization appears to be performed by the neocortex (cf. Marr, (36)). Some theoretical insight into this may come from considering the neocortex as a variant of the matrix memory as described above.

Consider a matrix memory in which the probability that a horizontal axon makes a synapse with every (vertical) neuron it passes is not near 1 (as in Fig. 1) but is much lower, perhaps in the range 0.1 - 0.001. If these contacts are made randomly then different input patterns on the horizontal axons will tend to activate different neurons. (An alternative design is to form the matrix with random numbers of synapses at each intersection or with random strengths of synapses initially at each intersection.) The tendency for each pattern to select or activate different neurons can then be enhanced by a) increasing the synaptic weights at those synapses where there is both pre- and postsynaptic activity and b) providing inhibition throughout (or alternatively locally within) the matrix from neurons which are already responding to a stimulus to prevent too many neurons becoming allocated to that stimulus. An example of the operation of such a matrix with low contact probability to produce classification is shown in Fig. 10. Such a categorization process effectively selects different neurons to respond to

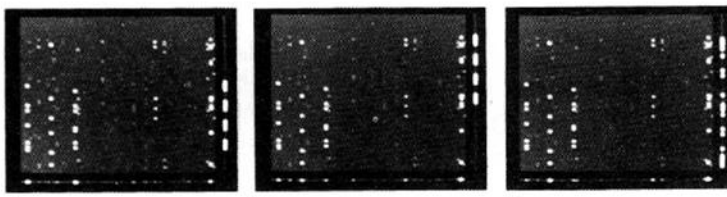

FIG. 10 – Categorization in a matrix memory with a low contact probability between a horizontal axon and a vertical dendrite (cf. Fig. 1). The contact probability was 0.13 in the 64 by 64 neuron matrix. Each panel shows the application of a stimulus (at the right of each panel) to the matrix. The resulting firing of the (vertical) neurons is shown by the output vector across the bottom of each panel. The brightness of the input and output vectors is proportional to the firing rate. The brightness of each position in the 64 by 64 connectivity matrix (with only 13% contact probability) is proportional to the strength of that synapse. Several iterations of learning with lateral inhibition to enhance the hill climbing (see text) preceded the stage shown. It is shown that after learning each complex input stimulus resulted in a different pattern of firing coded primarily across four output (vertical) neurons, the synapses of which had primarily been modified during the learning.

different combinations of active input horizontal lines. Major inputs which unconditionally activate the vertical neurons are not necessary for the operation of this system (although they may guide the mountain climbing (36, 37)). It should be noted that this categorization finds natural clusters in the input events, orthogonalizes the input events (overlap in input events can become coded onto output neurons with less overlap and many active input lines may be coded onto few active output lines), and does not allocate neurons to events which never occur (cf. Marr (36, 37)).

One way in which this theory of operation of the neocortex is being tested is by investigating whether, when completely novel faces are shown to a monkey, the neurons in the cortex of the superior temporal sulcus, which appear to be involved in the classification of different faces (4, 58), alter their responses as predicted by the theory. The theory predicts that a single neuron in such a classification system might show changes in its response to a novel stimulus within its potential classification repertoire (in this case faces) over a number of presentations of the new face and/or to familiar faces as a result of inhibition produced if other neurons in the matrix were activated by the

novel face. Some evidence for the latter form of modification is being found in experiments of Rolls and Hasselmo, now in progress.

Other theoretical approaches to categorization in neuronal networks have been described by Kohonen (32) and by Cooper *et al.* (13).

ASSOCIATION MEMORY

Pathways for the cross-model association of complex, patterned stimuli appear to require the amygdala in the primate. Some of the evidence for this is that lesions of the amygdala impair the learning of a one-trial, object-reward association (85) and of a tactual-to-visual, cross-modal association (46, 47). Also, many of the symptoms of the Kluver-Bucy syndrome (in which monkeys with amygdala damage, for example, select non-food as well as food objects) can be interpreted as a failure to make normal associations between stimuli such as the sight of food and reinforcement provided, for example, by its taste (28, 31, 53-63). Moreover, the amygdala is well placed anatomically for this function. It receives highly processed inputs from higher (but not lower) stages of the visual, auditory, and gustatory systems in the primate, as well as olfactory and visceral inputs. It has outputs to the autonomic centers of the brainstem, hypothalamus, and other limbic (as well as cortical) structures, through which autonomic (as well as behavioral) responses learned to stimuli, which have been paired with other stimuli including reinforcers, can be produced (9, 24, 29, 58, 60-62).

It was therefore of interest to investigate the decoding of visual information through the inferior temporal visual cortex-amygdala-hypothalamic pathway, in order to determine at which stage visual information reflected the association of visual stimuli with reinforcement such as the taste of food. It was found that in the inferior temporal visual cortex the significance of a stimulus in terms of its association with reward or dependence on motivational state (hunger) was not a factor in determining the responses of the neurons (71). In the amygdala, neurons were found which responded to reinforcing stimuli such as food, but these neurons typically responded also to one or several neutral or even aversive stimuli, so that they did not completely code specifically for the reinforcement value of visual stimuli (79). Also, these neurons did not appear to reflect the changing reinforcement associations of stimuli during visual discrimination reversals (79). There is also a population of neurons in the basal accessory nucleus of the amygdala which responds to faces, and these neurons may be involved in emotional responses (35, 58, 60-62). This evidence thus suggests that the amygdala may be important in motivational and

emotional responses to reinforcing stimuli, but that another system (perhaps the orbitofrontal cortex, see below) may be important in the rapid and readily reversible association of visual stimuli with reinforcement in visual discrimination tasks. At a further stage of information processing, the lateral hypothalamus and substantia innominata, which receive projections from the amygdala and orbitofrontal cortex (61) (approximately 13.4% in one sample of 764 neurons), had responses to the sight and/or taste of food (53, 54, 59, 63, 79). These neurons came through learning to respond to the sight of food as opposed to non-food visual stimuli. Their responses became associated with the sight of a previously neutral stimulus which signified food in a visual discrimination task, showed extinction if a stimulus no longer signified food, and showed reversal in the reversal of a visual discrimination task (45, 74). For example, when a monkey had to choose whether to initiate feeding in the visual discrimination task, it was found that the responses of these neurons occurred to the visual stimulus which signified that a lick response could be initiated to obtain food but not to the visual stimulus which indicated that the monkey should not lick or he would obtain aversive hypertonic saline. The latency of the discriminative responses of these neurons was 140-200 ms, compared to 250-350 ms for the EMG responses associated with licks made at 350-450 ms (74). Therefore the responses of these neurons preceded and predicted the initiation of feeding responses by the monkey (74). This evidence is consistent with the hypothesis that neuronal responses, which represent the reward value of the stimulus and thus reflect an output of an association memory, are elaborated along this pathway but are not fully evident until the stage of the ventral forebrain neurons (for further discussion see (53-63, 70)). Consistent also with this hypothesis are the latencies of neuronal firings which are approximately 100 ms in the inferior temporal visual cortex, 110 ms in the amygdala, and 140 ms in the basal forebrain (53-63, 71, 74, 79). It is of interest to note that relatively simple reward-related coding is evident at the hypothalamic level. This may be because from here the interface is to autonomic and endocrine systems so that neuronal firing has to be at a level at which the outputs of a reinforcement related system (which might include, for example, salivation to the sight of food) can be realized.

It should be noted that this cortico-amygdaloid system (and the cortico-orbitofrontal cortex system, see below) is particularly appropriate for the association of complex stimuli, given the cortical areas from which the amygdala receives its inputs. Although there are changes in

neuronal responses to a tone-conditioned stimulus in the rabbit amygdala during the acquisition of an aversive Pavlovian conditioning procedure (1, 30), associations involving simple stimuli which do not require cortical processing, such as pure tones, can probably in some cases be made at an earlier stage of information processing in the brain, (e.g., in the magnocellular medial geniculate nuclei; see (92)). However, this relatively peripheral type of altered neuronal responsiveness may not be the normal mode of association formation, as this probably involves complex patterned stimuli in the natural environment. Similarly, although Berger *et al.* (10) have found neurons in the hippocampus which come to respond to the conditioned stimulus during tone-eye blink conditioning in the rabbit, these neurons must have some function other than the formation of the association because hippocampal damage does not impair the learning of this task. It is now thought that the association of a simple stimulus, such as a tone, with a simple motor response of this type involves the cerebellum because damage to this impairs the learning, and neuronal responses become modified here during the learning (86). The types of memory for which the hippocampus is crucial and the modification of neuronal activity in it during these types of learning in the primate are considered below.

Another area thought to be important in association memory in the primate is the orbitofrontal cortex. Damage to it impairs the flexible association of environmental stimuli with reinforcement. Examples of the situations in which a behavioral deficit is produced by orbitofrontal lesions include a) extinction, in that behavioral responses continue to be made to the previously reinforced stimulus; b) reversals of visual discriminations, in that the monkeys make responses to the previously reinforced stimulus or object; c) Go/Nogo tasks, in that responses are made to the stimulus which is not associated with food reward; and d) passive avoidance, in that feeding responses are made even when they are punished (11, 19, 27, 61, 78).

To investigate how the orbitofrontal cortex may be involved in the flexible association of visual stimuli with reinforcement and the reversal of such associations, recordings were made of the activity of 494 orbitofrontal cortex neurons during the performance of a Go/Nogo visual discrimination task, reversals of the visual discrimination task, extinction, and passive avoidance (87). First, neurons were found which responded a) in relation to the preparatory auditory or visual signal used before each trial (15.1%) or b) nondiscriminatively during the period in which the discriminative visual stimuli were shown (37.8%).

Thus, visual information reaches the orbitofrontal cortex, which anatomically receives connections from the inferior temporal visual cortex and the amygdala (61). Second, 8.6% of neurons had responses which occurred discriminatively during the period in which the visual stimuli were shown. It was shown using reversals of the visual discrimination that the majority of these neurons responded to whichever visual stimulus was associated with reward; the stimulus to which they responded changed during reversal. However, 6 of these neurons required a combination of a particular visual stimulus in the discrimination and reward in order to respond. Further, none of this second group of neurons responded to all the reward-related stimuli including different foods which were shown so that in general this group of neurons coded for a combination of one or several visual stimuli and reward. Thus information that particular visual stimuli were currently associated with reinforcement was represented in the responses of orbitofrontal neurons. Third, 9.7% of neurons had responses which occurred after the lick response was made in the task to obtain reward. Some of these responded independently of whether fruit juice reward was obtained. Aversive hypertonic saline was obtained on trials on which the monkey licked in error or was given saline in the first trials of a reversal. Through these neurons information that a lick had been made was represented in the orbitofrontal cortex. Other neurons in this third group responded only when fruit juice was obtained, and thus through these neurons information that reward had been given on that trial was represented in the orbitofrontal cortex. Other neurons in this group (3.6% of the total sample) responded when saline was obtained when a response was made in error, when saline was obtained on the first few trials of a reversal (but not in either case when saline was simply placed in the mouth), when reward was not given in extinction, or when food was taken away instead of being given to the monkey, but did not respond in all these situations in which reinforcement was omitted or punishment was given. Thus through these neurons task-selective information that reward had been omitted or punishment given was represented in the responses of these neurons.

These three groups of neurons found in the orbitofrontal cortex could together provide for computation of whether the reinforcement previously associated with a particular stimulus was still being obtained and generation of a signal if a match was not obtained. This signal could be partly reflected in the responses of the last subset of neurons with task-selective responses to nonreward or unexpected punishment. This signal could be used to alter the monkey's behavior

leading, for example, to reversal to one particular stimulus but not to other stimuli, to extinction to one stimulus but not to others, etc. It could also lead to the altered responses of the orbitofrontal differential neurons found as a result of learning in reversal so that their responses indicate appropriately whether a particular stimulus is now associated with reinforcement.

In another part of the primate brain, the head of the caudate nucleus, neurons are found with activity related to another form of association. These neurons come by learning to respond to significant environmental events which signal, for example, that a trial of a task is about to begin (76). It is likely that the actual site of learning is the dorsolateral prefrontal cortex, which projects into this part of the striatum, for in this part of the cortex similar neurons are found (Rolls and Baylis, unpublished observations). This is probably part of a system for ensuring that the animal switches his behavior to significant environmental events (64).

FUNCTIONS OF THE PRIMATE HIPPOCAMPUS IN MEMORY

It is known that damage to certain regions of the temporal lobe in man produces anterograde amnesia evident as a major deficit following the damage in learning to recognize new stimuli (42, 82). The anterograde amnesia has been attributed to damage to the hippocampus, which is within the temporal lobe, and to its associated pathways such as the fornix (20, 21, 42, 50, 82). This has, however, been questioned. Alternatively, it has been suggested that damage to both the hippocampus and amygdala is crucial in producing anterograde amnesia, in that combined but not separate damage to the hippocampus and amygdala produced severe difficulty with visual and tactual recognition tasks in the monkey (43, 44, 46, 47). In investigations of the particular aspects of memory for which the hippocampus may be essential, it has been shown that monkeys with damage to the hippocampo-fornical system have a learning deficit on memory tasks which require them to make associations between a stimulus (e.g., a picture) and a motor response, such as touching one part of a screen (22). Impairment is also seen on memory tasks which require complex combinations of stimulus attributes to be processed together, such as memory not only for which object was shown but where it was shown (23).

In order to analyze the functions being performed by the hippocampus in these tasks requiring complex conjuctions of stimulus attributes or of

stimuli with motor responses, the activity of 1510 single hippocampal neurons was recorded in rhesus monkeys learning and performing these memory tasks, which are known to be impaired by damage to the hippocampus or fornix (72).

In an object-place memory task in which the monkey had to remember not only which object had been seen in the previous 7-15 trials but also the position where it had appeared on a video monitor, neurons were found which responded differentially depending on which place on the screen the objects were shown. These neurons comprised 5.7% of the population recorded. It is notable that these neurons responded to particular positions in space (whereas "place" cells in the rat respond when the rat is in a particular place, (49)). In addition, 1.0% of neurons responded to a combination of place and novelty; they responded more to a stimulus the first time it was shown in a particular position than the second time. Most of these neurons had response latencies in the range 100-200 ms compared to typical behavioral response latencies of 300 ms.

In tasks in which the monkeys had to acquire associations between visual stimuli and spatial motor responses, 10.6% of neurons responded to particular combinations of stimuli and responses. For example, in a task in which the monkey had to perform an approach response (touching a screen 3 times) when one visual stimulus was shown to obtain reward, but had to perform a withholding response for 3 s to obtain reward when a different stimulus was shown (22), 9.2% of neurons responded to one of the stimuli if it was linked to one of the responses in this task. The same neurons typically did not respond if the same stimuli or the same responses were used in different tasks or if other stimuli were associated with the same responses in this task.

It was possible to study the activity of 41 hippocampal neurons while the monkeys learned new associations between visual stimuli and motor responses. In some cases it was possible to show that the activity of these neurons became modified during this learning. This is consistent with the hypothesis that the new learned associations are represented by the changed responses of an ensemble of hippocampal neurons.

In recognition memory tasks, a small proportion of neurons (0.7%) responded differently to novel, as compared to familiar, stimuli. In addition, some further neurons responded to novel stimuli in other memory tasks such as a delayed match to sample.

These results show that hippocampal neurons in the primate have responses related to certain types of memory. One type of memory

involves complex conjunctions of environmental information, for example when information about position in space (perhaps reflecting information from the parietal cortex) must be memorized in conjunction with what that objects is (perhaps reflecting information from the temporal lobe visual areas), so that where a particular object was seen in space can be remembered. The hippocampus is ideally placed anatomically for detecting such conjunctions in that it receives highly processed information from association areas such as the parietal cortex (conveying information about position in space), the inferior temporal visual cortex (conveying a visual specification of an object), and the superior temporal cortex (conveying an auditory specification of a stimulus) (90). The positions of stimuli in space may be represented by the firing of hippocampal neurons as described above so that conjunctions of, for example, objects and their position can be formed. It may also be that conjunctions between sets of stimuli in different parts of space can be formed onto hippocampal neurons to provide a map of space (cf. O'Keefe (49)).

A second type of memory to which the activity of hippocampal neurons appears to be related is the learning of which spatial responses should be made to particular stimuli. It is important to note that these tasks involve symmetrical reinforcement (e.g., response A to stimulus 1 to obtain reward, and response B to stimulus 2 to obtain reward); if a task can be solved by stimulus-reinforcement associations it can then be learned without the hippocampus (22). The activity of hippocampal neurons often reflects a combination or conjunction of a particular stimulus and motor response in these tasks so that in this case also conjunction or combination learning appears to be an important aspect of hippocampal function. It is suggested that if the hippocampus is involved in determining which locomotor response must be made to which stimulus, then this provides a way of implementing a spatial map of the environment in which the readout might involve appropriate locomotor responses to conjunctions of stimuli in the environment. In this context it is of interest that the "place" cells in the rat hippocampus fire much more when a rat is actively moving in space that when it is passive in one position (O'Keefe, personal communication), that is when stimulus to bodily response conjunctions are being processed.

A possible theoretical basis for these results, and in particular how the hippocampus may perform the conjunction or combination learning just described, is now considered (cf. Marr (37)). The proposal is that the hippocampus is another modification of the basic design of a matrix

memory as described below. A diagram to show some of the features of the connections of the hippocampus is shown in Fig. 11. It consists of a cascade of stages in each of which axons run orthogonally across dendrites, and the probability of contact of each axon with a dendrite is low – perhaps in the range 0.1-0.001. These synapses are modifiable. The modification rule is that when many inputs to a particular dendrite (or neuron) are active (which may produce postsynaptic effects important in the modification), those synapses increase in strength. As in the neocortex, with suitable inhibition from the neurons most active to a given stimulus, this tends to produce classification of clusters of information onto single neurons, when then tend to respond in the future only to such complex conjunctions or combinations of stimuli. An example of this is illustrated in Fig. 12. An additional feature of the hippocampus (particularly of the CA3 pyramidal cells) is the presence of strong recurrent collaterals which return from the output of the matrix to cross over the neurons of the matrix, as shown in Fig. 11. These synapses are also modifiable by the same learning rule. The effect of such recurrent collaterals is to make that part of the matrix into an autocorrelation matrix. The autocorrelation arises because the output of the matrix, expressed as the firing rate of the CA3 pyramidal cells, is fed back along the horizontally running axons so that the pattern of activity in this part of the matrix (the CA3 pyramidal cells) is autocorrelated with itself (see Kohonen *et al.* (34)). The importance of the autocorrelation performed by this part of the matrix is that it forms a recognition memory with all the advantageous properties of a matrix memory. The property which is particularly relevant here is completion in that if part of a stimulus (or event) occurs then the autocorrelation part of the matrix completes that event. It should be noted that the results of long-term potentiation experiments are consistent with the proposed operation of the hippocampus (39).

Taken together, these properties of each stage of hippocampal circuitry result in complex conjunctions or combinations of events being coded onto (i.e., resulting in the firing of) hippocampal neurons, with completion being possible with only a fraction of the original pattern. That is, recall of the whole of a complex event is achieved when only a part of it occurs later. One reason for the several cascades of hippocampal circuitry may be that early stages (such as the dentate granule cells) must be broken up into a number of separate parallel substages, each of which receives from only a part of the total afferent barrage received by the hippocampus. This may be necessary in order to keep the proportion of neurons firing at any one time in the matrix low,

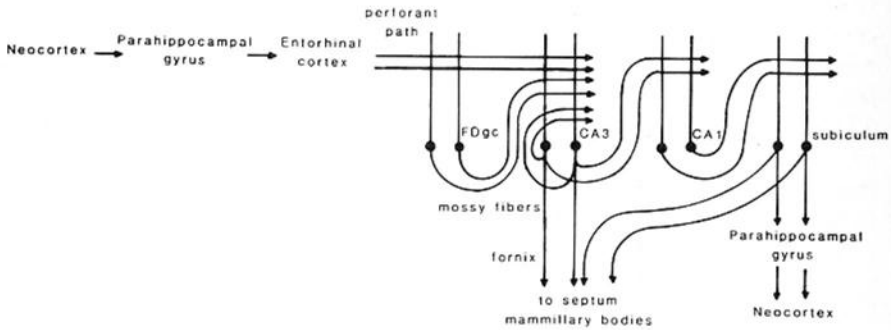

FIG. 11 – Schematic diagram of hippocampal connections. FDgc - dentate granule cells; CA3 and CA1 - pyramidal cells.

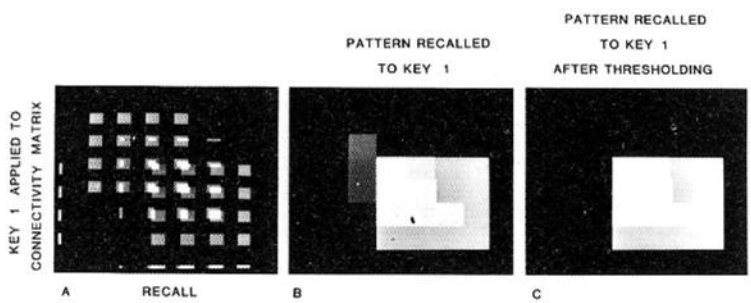

FIG. 12 – The recall of information from a recognition memory. The three stimuli shown in Fig. 2a were first stored in the matrix by applying each of the stimuli simultaneously to the vertical neurons and the horizontal axons to form an autocorrelation matrix. (Collaterals would perform this in a neuronal network.) Then, as shown in Fig. 12A, stimulus 1 was applied to the matrix. Stimulus 1 was recalled from the matrix, as shown before and after thresholding in B and C.

so as to keep interference down. After some classification has been performed by early stages, and the number of active neurons necessary to represent the input information has been reduced, all information may be brought together in the final stage of this hippocampal circuitry in the CA1 pyramids. This final bringing together of inputs received originally by the whole of the hippocampus, and thus representing highly processed neocortical information received from every sensory modality, may thus be a feature of what the hippocampus can achieve.

For example, it can detect, and classify onto a few specifically responding neurons, complex conjunctions of complex (cortically processed) events, such as that a particular object (presumably reflecting temporal lobe visual processing) has appeared in a particular position in space (probably reflecting parietal input). Another example might be that a particular stimulus should be associated with a particular body response. One should remember that this is the type of specific information which comes to activate different hippocampal neurons, as described above.

It should be noted that this computation involves recoding of the original input event into an information rich pattern of firing of a few hippocampal neurons. The exact ways in which this information is used by the rest of the brain are not quite understood. The recoding may take place over several trials, as shown by the neurophysiological experiments described above. The information represented may thus indicate what information should be stored in the neocortex. A path back from the hippocampal formation (through the subiculum and parahippocampal gyrus) to the neocortex (90) might perform this function. The evidence that the hippocampus may be involved in the storage process, but is not itself the location where the information is stored, is that hippocampal damage may impair the learning but not necessarily the retention of memory tasks of the type described above. Another important output of the hippocampus is via the fornix to the anterior thalamic nuclei and thus via the cingulate cortex to the supplementary motor area.

SHORT-TERM MEMORIES

The simplest way to build a short-term memory is to use an ordinary matrix memory (of the autocorrelation type if recognition is required), but to make it a property of the synapses that their strength decays with the required time constant. One example of such a memory is provided by some neurons in the inferior temporal visual cortex. This population has the property that after a stimulus is shown, that stimulus produces a smaller response (or for other neurons a larger response) the next time it is shown (41). To test whether these neurons could take part in a longer term form of recency memory, Baylis and Rolls (3) measured their responses when monkeys had to remember lists of visual stimuli with up to 17 stimuli intervening between the first and second presentations of a given stimulus. It was found that the majority of the neurons would remember the stimulus only providing that there were no intervening stimuli, with just a few neurons remembering over 1 or 2

intervening stimuli. Thus these neuron in the inferior temporal visual cortex do provide a short-term sensory memory but this particular memory has little resistance to disruption by intervening stimuli.

In a region which receives inputs from the inferior temporal visual cortex, the tail of the caudate nucleus, visual responses are found to the types of visual stimuli effective in exciting inferior temporal cortex neurons, but the majority of neurons in the tail of the caudate nucleus show rapid pattern-specific habituation which can be dishabituated by presentation of another visual stimulus. This thus provides a short-term visual memory system suitable for detecting changes in patterned visual stimuli (12).

In longer term recency memory, for whether a stimulus has been seen in the preceding 10-100 trials, a system with inputs to neurons at the rostral border of the thalamus is implicated (73). The inputs which drive these neurons may come from the amygdala and the hippocampus, in both of which there is a small proportion of neurons with responses which occur differently to novel and familiar stimuli in a serial recognition task (Wilson and Rolls, unpublished observations; (72)).

There is another way in which some parts of the brain provide a short-term memory suitable for bridging a delay with no intervening stimuli. This is by holding a particular pattern of firing in the delay period. For example, neurons in the dorsolateral prefrontal cortex fire in a 2-5 s delay in which a monkey must remember a position to which he must respond (i.e., in a delayed response task) (19, 48). Some of these neurons code in the delay for the position in which the stimulus has been seen and others for the response which the monkey has to make at the end of the interval (48). In the hippocampus, neurons with responses in the delay period of a delayed response task have also been found (91). It has been shown that some of these neurons reflect holding information in memory about the response required in that the same neurons do not fire when the monkey has to remember the same stimulus in a delayed matching-to-sample task (72).

NEURONAL ACTIVITY IN THE BASAL NUCLEUS OF MEYNERT DURING MOTIVATIONAL BEHAVIOR AND LEARNING

It is known that the neural changes in Alzheimer's disease include degeneration of neurons in the basal nucleus of Meynert (15, 38). In order to investigate the functions of these neurons their activity has been analyzed during a recognition memory task (in which the monkey

must remember which stimuli he has seen in the previous 17 presentations) as well as in a visual discrimination task which requires association memory. It is shown in Table 1 that some neurons in these memory tasks responded only to novel stimuli and were thus influenced by recognition memory, and that others were activated by rewarding visual stimuli in the visual discrimination task. Another large proportion of these neurons responded to the tone cue signal which preceded each trial in these tasks to enable the monkey to pay attention to the video screen (94).

TABLE 1 – Neuronal populations in the basal forebrain during memory tasks.

	No. of cells	%
Responses to novel visual stimuli (recognition memory)	39	2.0
Responses to rewarding visual stimuli (association memory)	104	5.2
Nondiscriminating visual responses	623	31.1
Responses during tone signal	257	12.8
Responses during licking or reaching	37	1.8
Unresponsive neurons	944	47.1
Total number of neurons recorded	2004	100

These results show that the basal nucleus projects to the neocortex signals which depend on whether a new visual stimulus is shown, whether a rewarding visual stimulus is shown, or whether a stimulus which informs the monkey that he should pay attention has occurred. These signals are tightly time-locked to the onset of these stimuli with latencies for the visual responses of 140-180 ms. It is suggested that a function of this signal, and of these neurons, is to enhance activation or consolidation in the neocortex at an appropriate time (that is when new, rewarding, or significant environmental stimuli occur) and that failure of this function could contribute to some of the symptoms of Alzheimer's disease.

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