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# The hippocampus as an olfacto-motor mechanism: were the classical anatomists right after all?

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**Abstract**

The relations between behavior, olfactory input (monitored by recording the activity of the olfactory mucosa), and the spontaneous field potentials of the dentate gyrus were studied in freely moving rats. Bursts of 30–80 Hz (gamma) waves were elicited in the dentate gyrus when a rat sniffed at a variety of objects but were not elicited by auditory, somesthetic, or visual inputs and were not related to the occurrence of locomotion. The presence of gamma wave activity was associated with an enhancement of the population spike elicited in the dentate gyrus by stimulation of the perforant path. Odorized air blown into a nostril via a cannula, inserted under light urethane anesthesia, elicited a gamma wave response bilaterally in the dentate gyrus. These and other data were reviewed to support the general hypothesis that the hippocampus is primarily an olfacto-motor mechanism and does not play any unique role in learning and memory, cognitive mapping, or emotion. The role of the hippocampus in the control of some forms of motor activity is supported by numerous anatomical and electrophysiological studies, studies of the effect of hippocampal lesions on behavior, and studies of the effects of electrical or chemical stimulation of the hippocampus on behavior. 

*Keywords:* Cognitive maps; Dentate gyrus; Emotion; Gamma waves; Hippocampus; Learning and memory; Motor system; Olfaction; Perforant path; Rhinencephalon

## 1. Introduction

In the early 20th century, neuroscientists were in general agreement that the function of the hippocampal formation was strongly related to olfaction. Ramon y Cajal, summarizing the results of his pioneering research in this field in 1917, stated: "Discovering, in the upper part of the olfactory or pyriform lobe of the lissencephalic and gyrencephalic mammals of a special focus, with a singular structure, to which comes an important olfactory pathway and from which emanates the principal pathway of exogenous fibres destined for Ammon's horn. By virtue of this finding, there was established the existence of three sequential olfactory foci: *the primary olfactory focus or inferior sphenoidal* cortex in which terminate the fibres of the external root of the olfactory bulb; the *secondary olfactory focus* (which we have called *angular* or *spheno-occipital*), in which terminate the fibres originating in the preceding (focus); and the *tertiary olfactory focus*, represented by Ammon's horn and the fascia dentata, the point of final arborisation of the fibres emanating from the cited angular (focus)" [40, p. 137].

In Ramon y Cajal's time, the dentate gyrus was widely regarded as the receptive part of the hippocampal formation, partly because it was believed to receive an olfactory input and partly because the small size of the dentate granule cells was reminiscent of the small granule cells observed in other sensory or receptive areas in the spinal cord, the medulla, and the neocortex [86, pp. 1419, 1561–1562]. Similarly, the large pyramidal cells of Ammon's horn, resembling as they do, cells "of the type recognised in other places as effectory or motor, strongly suggests that the hippocampus (i.e. Ammon's horn) is primarily an effectory structure" [26, p. 204]. Thus, although it was widely recognized that non-olfactory inputs could also reach the hippocampal formation, there was formerly a widespread consensus

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that the dentate gyrus and Ammon's horn constituted the afferent and efferent components, respectively, of an olfacto-motor mechanism.

Brodal [26] however, criticized the concept that the hippocampal region had an olfactory function on the grounds that: (a) there was no convincing evidence that olfactory inputs actually reached either the entorhinal cortex or the dentate gyrus–Ammon's horn region, and (b) behavioral experiments showed that olfactory conditioned responses were little affected by surgical destruction of the hippocampal region. These criticisms appear to have had a strong effect on neuroscientific opinion, opening the door to theories that the hippocampal formation is involved in other functions, especially: (a) emotion [115,140]; (b) memory [120,156], and (c) a central representation of Euclidean space [137]. Evidence relevant to each of these points of view will be discussed in this review.

## 2. The role of the hippocampal formation in olfaction

Recent anatomical studies have confirmed the view that the hippocampal formation receives a strong olfactory input. It is well established that the pyriform cortex receives a heavy input from the olfactory bulb and Ramon y Cajal's finding of projections from the pyriform cortex (Cajal's inferior sphenoidal cortex) to the entorhinal cortex (Cajal's angular or spheno-occipital cortex) has been confirmed by anterograde and retrograde transport methods [69,110]. Cajal's further discovery that the entorhinal cortex projects to the dentate gyrus and parts of Ammon's horn has been confirmed many times by a variety of methods [15]. It is also well established that the entorhinal cortex receives a direct input from the olfactory bulb [117,176] and further, that some individual entorhinal neurons that project to the hippocampus (as shown by retrograde transport) receive a direct input from the olfactory bulb (shown by the presence of degenerating terminals produced by a previous olfactory bulb lesion) [155]. Thus, the olfactory input to the dentate gyrus involves a minimum of three synapses (olfactory receptors → mitral cells in the olfactory bulb → entorhinal cortex cells → dentate granule cells) plus additional multisynaptic pathways. In comparison, the visual input to the striate cortex involves a minimum of four synapses (retinal photoreceptors → retinal bipolar cells → retinal ganglion cells → lateral geniculate nucleus cells → striate cortex cells).

Studies of slow potentials or unit activity evoked by electrical stimulation of the olfactory bulb revealed a response in the hippocampal formation with a latency of 15–22 ms in rats, cats and monkeys [17,36,188,206]. Intracellular recording from units in CA1 and CA3 in waking monkeys demonstrated excitatory post-synaptic potentials in response to stimulation of the olfactory bulb [224]. Stimulation of the pre-pyriform cortex produced a negative response in the apical dendrites of CA3 cells and in dentate granule cell dendrites coupled with a positive potential in the dentate hilus [70]. These observations indicate that the olfactory input generates excitatory post-synaptic potentials in dentate granule cells and in Ammon's horn cells [70]. The pathway from the olfactory bulb to the hippocampal formation is dependent on perforant path fibers arising in the lateral entorhinal cortex [218].

Olfactory stimulation by the odor of toluene or xylene elicits a burst of roughly 20 Hz (beta) waves in the rat olfactory bulb and dentate hilus but not in CA1 (Fig. 1) and not in the lateral part of CA3 (experiments with bilateral electrodes in two rats). Similar waves are present in the rat pyriform cortex, as well as in the olfactory bulb and dentate gyrus, and can be elicited in all three sites by the odor of: (a) most organic solvents; (b) a number of compounds which occur in the anal scent gland secretions of weasels and other mustelids (2-aminoacetophenone, 2-hydroxyacetophenone, 2-propylthietane [76,198,227]) and foxes (trimethylthiazoline, isopentenylmethyl sulfide [76,226,227]); and (c) several chemicals, such as eucalyptol and salicylaldehyde, which are derived from plants [226]. Other strong odors such as those of ammonia, butyric acid, caproic acid, cadaverine and putrescine do not appear to elicit a beta wave response in the rat rhinencephalon. Olfactory beta wave responses can also be elicited in the pyriform cortex of the meadow vole, *Microtus pennsylvanicus*, by the odors of xylene, isopentenylmethyl sulfide (a component of fox odor), and 2-propylthietane, (the main component of the odor of a weasel) [199].

The dentate gyrus beta wave response is specifically olfactory and cannot be elicited by a variety of auditory, visual, somesthetic and gustatory stimuli. Further, it has no particular relation to the occurrence of gross motor activity and the accompanying hippocampal rhythmical slow activity (RSA) [76,188]. It is interesting that the odorants that elicit a beta wave response in central olfactory structure generally do not elicit sniffing. The usual response to them involves immobility or a quick withdrawal movement, often accompanied by a brief period of apnea.

Large lesions of the entorhinal and subicular cortices, including section of the angular bundle, abolish the odor-induced beta wave response of the dentate gyrus [75], suggesting a dependence on entorhinal projections to the dentate gyrus. Lesions of the septal nuclei or the amygdala do not have this effect. Study of phase delays in the olfactory beta wave response of the olfactory bulb, pyriform cortex, entorhinal cortex and dentate gyrus also indicate the existence of a multisynaptic olfactory pathway through the pyriform lobe to the dentate gyrus [33].

Taken together, all these data suggest that rats and other small mammals have evolved a multisynaptic olfactory input to the dentate gyrus, which signals the possible presence of a predator [76]. There is an extensive behavioral literature showing that the compounds that elicit an olfactory beta wave response also elicit a behavioral avoidance response in a variety of small mammals [74,199]. On this interpretation, other compounds that elicit an olfactory beta wave response (such as organic solvents) do so by mimicking the effect of naturally occurring predator odors.

### 2.1. Gamma waves in the dentate gyrus

Mapping studies have demonstrated that an electrode placed in the hilus of the dentate gyrus detects large amplitude (1 mV or more) 30–90 Hz (gamma) waves [23]. Dentate granule cells appear to generate gamma

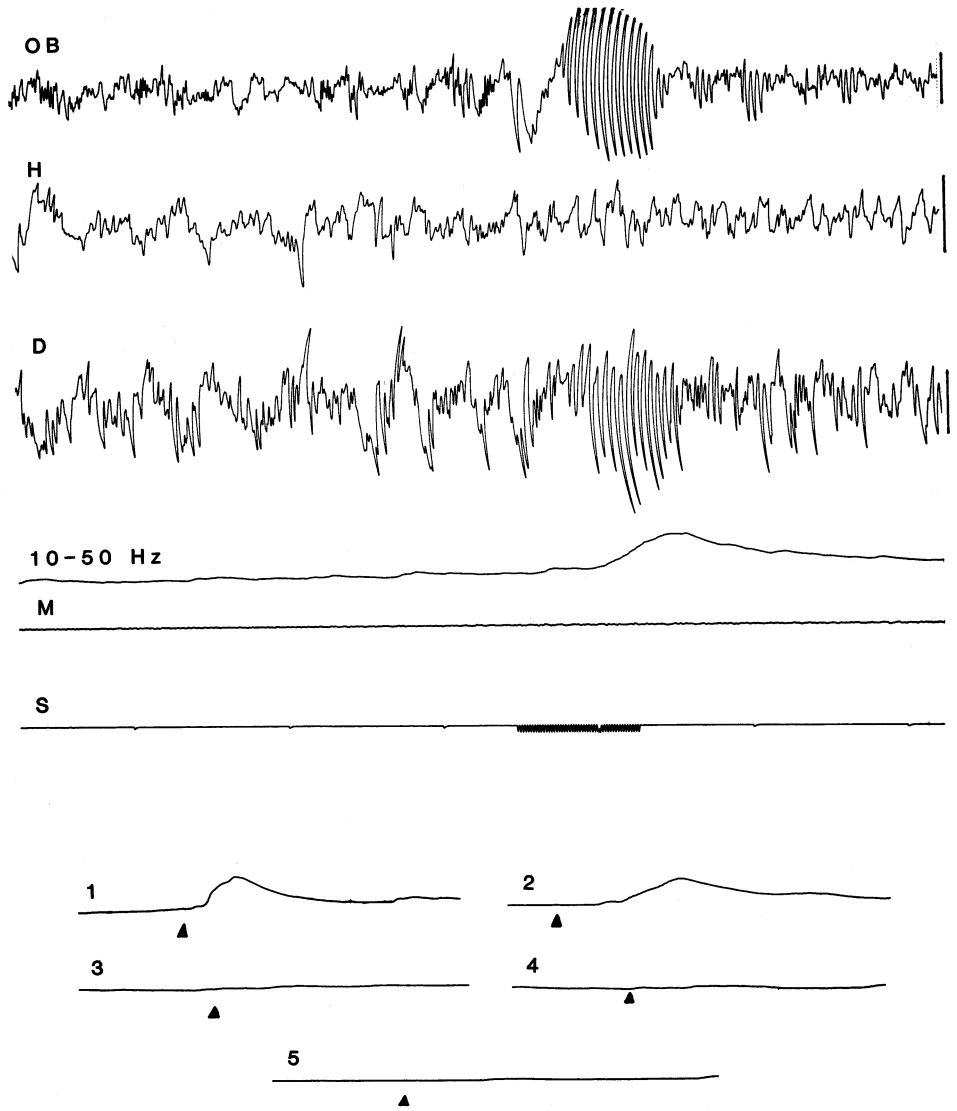


Fig. 1. Activity in the olfactory bulb and the dentate gyrus during the presentation of various sensory stimuli. OB, deep layers of olfactory bulb; H, stratum oriens of CA1; D, site in or just below the granule cell layer of the dorsal blade of the dentate gyrus; 10–50 Hz, integrated 10–50 Hz activity from the dentate record; M, motor activity recorded by the platform sensor (a magnet and coil arrangement that detected movement of the platform on which the rat stood); S, presentation of toluene by means of a Q-tip. Time is marked in seconds in the trace marked 's'. Voltage calibration, 1.0 mV. Records OB, H, and D are all monopolar, negativity up. Note that toluene produced (a) predominantly positive potentials in the olfactory bulb followed by a rhythmical wave burst of about 20 Hz, (b) no clear effect at an RSA-generating site in the hippocampus, and (c) a fast wave burst of about 20 Hz in the dentate gyrus. The rat made no visible behavioral response to the toluene on this occasion. Spontaneous activity recorded in the olfactory bulb was rather depressed as a result of repeated tests with toluene and xylene. (1–5) integrated dentate responses to various stimuli; 1, toluene on another trial; 2, xylene; 3, cedarwood oil; 4, firing a starter's pistol which produced a violent startle response followed by running; 5, room lights flicked on and off. Black triangles indicate approximate time of stimulus application (from Ref. [188] by permission of Elsevier Science Publishers, B.V.).

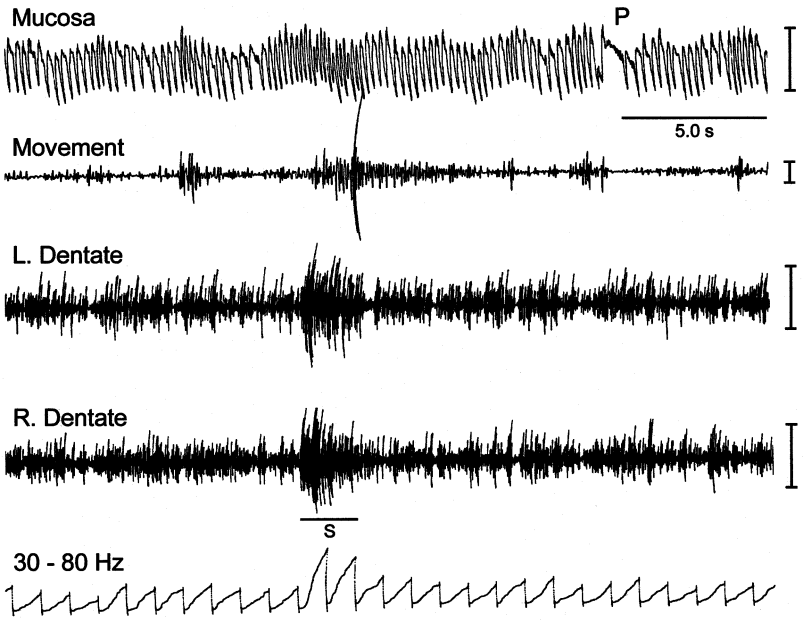


Fig. 2. Activity of the olfactory mucosa and dentate gyrus in a rat sniffing at a pencil (rat # 3971). Mucosa, left olfactory mucosa, 0.3–90 Hz frequency band; Movement, output (1–90 Hz) from a magnet-and-coil arrangement attached to a light platform on which the rat was standing; L. Dentate, R. Dentate, 30–90 Hz frequency band of activity from the left and right dentate gyrus, respectively; 30–80 Hz, 30–80 Hz activity from the left dentate gyrus rectified and integrated over 1.0 s intervals. Mucosa and dentate gyrus records are monopolar, negative up, with an indifferent placed in the skull over the cerebellum. Calibration: 1.0 mV, 5.0 s. At the heavy bar (marked S) the eraser end of a pencil was held near the rat's snout, provoking an increase in the frequency of the rhythmical respiratory potentials of the olfactory mucosa, accompanied by visible sniffing, head and vibrissae movement, plus a stepping movement (large deflection in the movement sensor record). The sniffing is associated with a bilateral high amplitude burst of gamma waves in the dentate gyrus. Note also that a brief apneic period (P) is not associated with any obvious change in dentate activity.

wave activity under the influence of an excitatory perforant path input and a probable inhibitory input from hilar interneurons [25].

Gamma wave activity is also present in the olfactory bulb and pyriform cortex where it is elicited by air currents moving past the olfactory mucosa [2,190]. Unlike the case of rhinencephalic beta waves, no specific odors appear to be involved: all that is needed to elicit pyriform gamma activity is the flow of a large volume of air, or air moving at a relatively high velocity, past the olfactory mucosa [190].

The functional correlates of dentate gamma activity have not been elucidated. Therefore, a series of rats was prepared with electrodes chronically implanted in the olfactory mucosa, hilus of the dentate gyrus in the region dorsal to the thalamus, and the white matter underlying the subiculum (to permit stimulation of perforant path fibres).

In freely moving rats, sniffing can be identified by close observation most easily by the rhythmical movements of the vibrissae [209] or by the presence of rhythmical 6–8 Hz waves in the olfactory mucosa. Quiet respiration is associated with 1–5 Hz rhythmical mucosal potentials. If an object is held near the snout for a few seconds, a rat will almost invariably sniff at it on the first presentation but if the object is presented again after a short delay, sniffing is less intense and may not occur at all. The occurrence of sniffing is almost invariably accompanied by a high amplitude burst of gamma waves in the dentate gyrus on the first presentation but the gamma wave burst is less well developed on the second or third presentations (Figs. 2 and 3).

Records taken in two rats with chronic electrodes implanted bilaterally in CA1 and CA3 revealed minimal increases in gamma wave activity during sniffing. Therefore, sniffing-related gamma wave bursts are probably generated primarily, perhaps, exclusively, in the dentate gyrus. Furthermore, an ongoing undergraduate research project (unpublished experiments by Nadia Jandali and C.H. Vanderwolf) has shown that both gamma and beta waves can be elicited in the posterior part of the dentate gyrus (adjacent to the superior colliculus) by appropriate olfactory stimulation. Therefore, it appears that olfactory inputs reach a large part of the dentate gyrus.

Sniffing-related dentate wave bursts can, apparently, be elicited by almost any object that a rat will sniff at, such as rubber stoppers, pencils, other rats, food, or the experimenter's fingers (Fig. 2). Objects that are presumably almost scentless, such as a glass beaker that has been thoroughly washed in detergent, rinsed, and air-dried, sometimes failed to elicit a dentate gamma wave response even though sniffing was elicited. Fur-

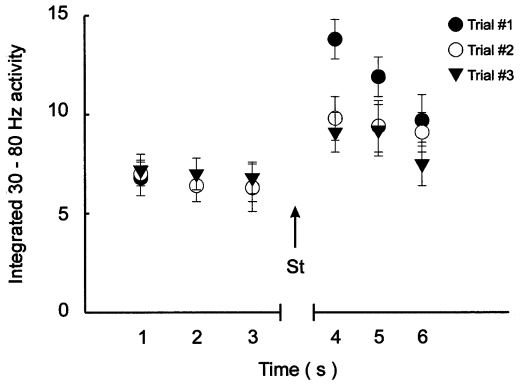


Fig. 3. Integrated dentate gyrus 30–80 Hz activity before and during the presentation of various objects that elicited sniffing in rat # 3971. Fifteen different objects were each presented to the rat's snout on three successive trials separated by an interval of about 10 s. Values are means ± S.E.M. Rectified and integrated 30–80 Hz activity was plotted for 3 s preceding and 3 s following stimulus presentation (St) on each trial. If stimulus onset occurred during the middle of an integration period (1.0 s), data from that period were excluded. The objects used to elicit sniffing were: a pencil, a rat food pellet, three types of dry breakfast cereal, a piece of sausage, a cork, a rubber stopper, a leather glove, two different pieces of foam rubber, a bar of soap, an old brush used to sweep the floor, a drain stopper, and a beaker filled with litter collected from another rat's cage. Note that the initial presentation of an object elicits a larger dentate gamma wave response than the second and third presentations.

ther, if a rat sniffed in the air with its snout some distance away from any definite object, no unusual dentate gamma activity was detected (Table 1). These observations suggest that dentate gamma activity bursts occur in response to the sensory effects of odors and have no direct relation to the motor act of sniffing.

Table 1
Integrated dentate gyrus 30–80 Hz activity under various conditions in the rat

| Conditions | Mean (± S.E.M.) 30–80 Hz activity | *N* |
|---|---|---|
| (a) Waking immobility | 5.4 ± 0.5 | 6 |
| (b) Pushing rat to induce walking | 5.5 ± 0.5 | 6 |
| (c) Sniffing in the air, not near any object | 5.7 ± 0.3 | 6 |
| (d) Walking and sniffing simultaneously | 6.6 ± 0.4 | 6 |
| (e) Lights on | 6.4 ± 0.4 | 6 |
| (f) Lights off for 5 s periods | 7.0 ± 0.7 | 6 |
| (g) First second of sniffing a new object | 10.1 ± 0.7 | 8 |
| (h) Waking immobility in the eight rats in condition 'g' above | 5.3 ± 0.5 | 8 |

Dentate gyrus activity (30–80 Hz band) was rectified and integrated over 1.0 s periods. The amplitude of this integrated activity was measured (in mm) over 10 s per condition per rat. Conditions 'a–f' do not differ significantly except that integrated 30–80 Hz activity was higher during 'lights off' than during 'lights on' in each of the six rats tested ($P<0.05$; Wilcoxon test). Sniffing a new object is always associated with higher amplitude gamma activity than quiet breathing during behavioral immobility (conditions 'g' and 'h' differ significantly according to a Wilcoxon test, $P<0.01$).

Non-olfactory sensory inputs such as loud sounds produced by dropping a heavy object, or stroking, handling or pushing the rat have very little effect on dentate gamma activity (Fig. 4, Table 1). Heale et al. [76, Fig. 3] show that gustatory stimulation (intraoral injection of solutions of quinine, acetic acid, sucrose, or sodium chloride) also does not elicit gamma activity in the dentate gyrus. Therefore, the dentate gamma wave burst seems to be elicited mainly or exclusively by an olfactory input. Switching the room lights off for 5 s produces a small but reliable increase in dentate gamma activity (Table 1) but this effect is probably an indirect accompaniment of an increase in sniffing, revealed in the olfactory mucosa records (the rats could not be observed directly in the dark).

Although an olfactory input appears to be uniquely capable of eliciting gamma wave bursts in the dentate gyrus, other evidence indicates that hippocampal activity can be affected by other sensory modalities. Virtually any type of sensory stimulus can elicit hippocampal RSA (or theta rhythm) as first pointed out by Jung and Kornmuller [85]. Studies of place cell activity in freely moving animals (Section 5) indicate that visual stimuli influence hippocampal activity [136,157].

Placing one's palm flat on a rat's back induces deep slow breathing accompanied by vocalization in many rats (but not in all). This simple manoeuvre reveals a striking difference between gamma wave activity in the dentate gyrus and in the pyriform cortex (Figs. 4 and 5). The pyriform cortex, it appears, is highly sensitive to the pattern of airflow during breathing but the dentate gyrus does not react to this. Dentate gamma bursts appear to be elicited only by definite odors. In contrast, only low-level gamma wave activity is present in the pyriform cortex during sniffing [190].

There is evidence that gamma waves in the neocortex are associated with excitatory processes in neuronal membranes [165,166]. If this is also true in the dentate gyrus, one might expect that the excitatory post-synaptic potentials and neuronal discharges elicited in the dentate gyrus by stimulation of the perforant path [8,106] might be substantially modified by the presence of a background of high amplitude gamma wave activity. Fig. 6 confirms this expectation. The population spike elicited in the dentate gyrus by stimulation of the perforant path is larger during vigorous sniffing behavior (associated with high amplitude gamma activity) than it is during quiet breathing. This effect, seen in each of the eight rats tested, was sometimes rather small but in the most extreme case the population spike during sniffing was approximately three times as large as it was during quiet breathing. Fig. 6 represents a more typical example. The enhancement of the population spike suggests that dentate granule cells are more

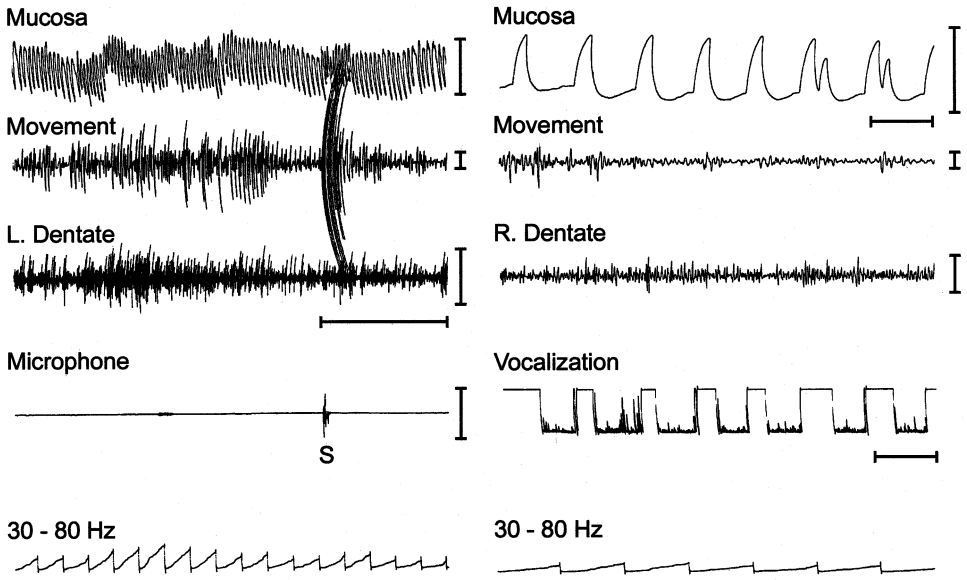


Fig. 4. Activity in the olfactory mucosa and dentate gyrus during startle and during vocalization. Left side: Rat # 3971. Mucosa, left olfactory mucosa, 0.3–90 Hz frequency band; Movement, output from a movement sensor as in Fig. 2; L. Dentate, 30–90 Hz frequency band of activity from the left dentate gyrus; 30–80 Hz, rectified and integrated 30–80 Hz activity from the left dentate gyrus; Microphone, 1–90 Hz activity from a microphone hanging near the rat. Calibration: 1.0 mV, 5.0 s. Note the occurrence of 7–8 Hz rhythmical potentials in the olfactory mucosa (characteristic of vigorous sniffing) associated with high amplitude dentate gyrus gamma activity. At 'S' a large heavy wooden plank was allowed to fall to the floor in an adjacent room. This elicited a strong startle response, running, and rapid breathing. There was no obvious change in dentate gyrus gamma activity. Right side: Rat # 3949. Mucosa, Movement, Dentate and 30–80 Hz records as on the left side. Calibration: 1.0 mV, 1.0 s. Vocalization: output pulses from a window discriminator (downward deflections) adjusted to detect rat vocalization as recorded by the microphone (this was necessary because the high frequency of rat vocalization precludes direct recording on an ink-writing oscillograph). Throughout the right-hand records, the experimenter's flat palm was pressed lightly on the rat's back, eliciting deep slow breathing with vocalization during each expiration. Dentate gyrus gamma activity does not show any obvious relation to this respiratory pattern.

excitable during sniffing and the associated gamma bursts than they are at other times.

An alternative possibility that the enhanced population spike during sniffing might be related to head movements, stepping and other behaviors which accompany sniffing and are correlated with hippocampal RSA (Section 3.1) is unlikely since the population spike elicited in the dentate gyrus by perforant path stimulation is actually slightly depressed during locomotion as compared with waking immobility [72].

A final observation made in the freely moving state is that pushing a rat to induce stepping and locomotion has no clear effect on dentate gamma wave activity (Table 1) even though it is a powerful way of inducing hippocampal RSA. Dentate gamma bursts, therefore, are unlikely to have any direct relation to the occurrence of Type 1 motor activity.

Upon completion of the foregoing experiments on dentate gamma activity in the freely moving state, all the rats ($N = 14$) were given a light anesthetic dose of urethane and a catheter was placed in one nostril. Manual injection of 5.0 ml of odorized air produced a slow potential response in the olfactory mucosa and a bilateral gamma wave burst in the dentate gyrus (Fig. 7). The gamma wave burst was usually better developed ipsilateral to the side of air injection and, on rare occasions, it was restricted to the ipsilateral side. Dentate gamma wave bursts were obtained with air scented with dirty litter from a rat cage, rat food pellets, caproic acid, cedar wood oil and breakfast cereal. Ordinary room air sometimes gave a response as well. It was noted that olfactory responses were poor or entirely absent if the walls of the airway were injured and bleeding as a result of insertion of the cannula.

Subsequent histological study of the brain in seven of the rats revealed that the recording electrodes were located in the dentate hilus in the dorsal hippocampal formation in all cases. Stimulating electrodes, present in six of the seven rats, were located in the white matter underlying the subiculum in five cases. In the remaining case, the stimulating electrode was located in the thick cellular layer of the subiculum ventral to the white matter. All of these electrodes were, therefore, located in the trajectory of perforant path fibers.

This series of experiments demonstrates that the dentate gyrus receives two kinds of olfactory inputs that can be distinguished by the frequency of the rhythmical field potentials that they elicit.

(1) Bursts of gamma frequency waves (30–90 Hz) are elicited in the dentate gyrus by almost any object that a rat will sniff. Two main lines of evidence indicate that these gamma waves are linked primarily to an olfactory input and not to the motor act of sniffing. (a) General-

ized sniffing in the air, away from any specific object produces very little gamma activity. (b) Delivery of odorized air to the olfactory mucosa in a lightly anesthetized rat will elicit dentate gamma waves even though sniffing behavior does not occur. Dentate gamma waves are specifically olfactory and cannot be elicited by a variety of visual, auditory, gustatory or somesthetic stimuli. Further, they have no particular relation to the occurrence of Type 1 behavior and hippocampal RSA (see below).

(2) Bursts of beta waves (about 20 Hz) are elicited in the rat dentate gyrus by (a) components of the scent of several rat predators; (b) most organic solvents; and (c) a few phytochemicals, but not by other strong odors. It is suggested that this olfactory pathway may play a role in the avoidance of predators.

The pathways subserving these different olfactory effects in the dentate gyrus have not been worked out. However, it may be significant that beta wave activity has similar functional relations in the pyriform cortex and dentate gyrus (elicitation by predator odors, organic solvents and a few phytochemicals, but not by a large number of other odors) but gamma wave activity has different functional relations in these two structures. Pyriform gamma waves are activated by high air flow rates past the olfactory mucosa but not by sniffing at various objects. Dentate gamma wave activity, in contrast, is activated by sniffing odorous objects but not by high air flow rates. These facts suggest that dentate beta waves are elicited by an output from the pyriform cortex, perhaps by the pathway from the olfactory bulb to the dentate gyrus via the pyriform and entorhinal cortices as originally described by Ramon y Cajal (Section 1). Dentate gamma waves, in contrast, do not appear to be a result of an input from the pyriform cortex. Perhaps, they are dependent on the more direct olfactory bulb input to the entorhinal cells that give rise to the perforant path.

Gamma wave activity occurs in Ammon's horn as well as in the dentate gyrus but the functional significance of the waves in the two sites may be quite different. Leung [101,102] has shown that 20–70 Hz

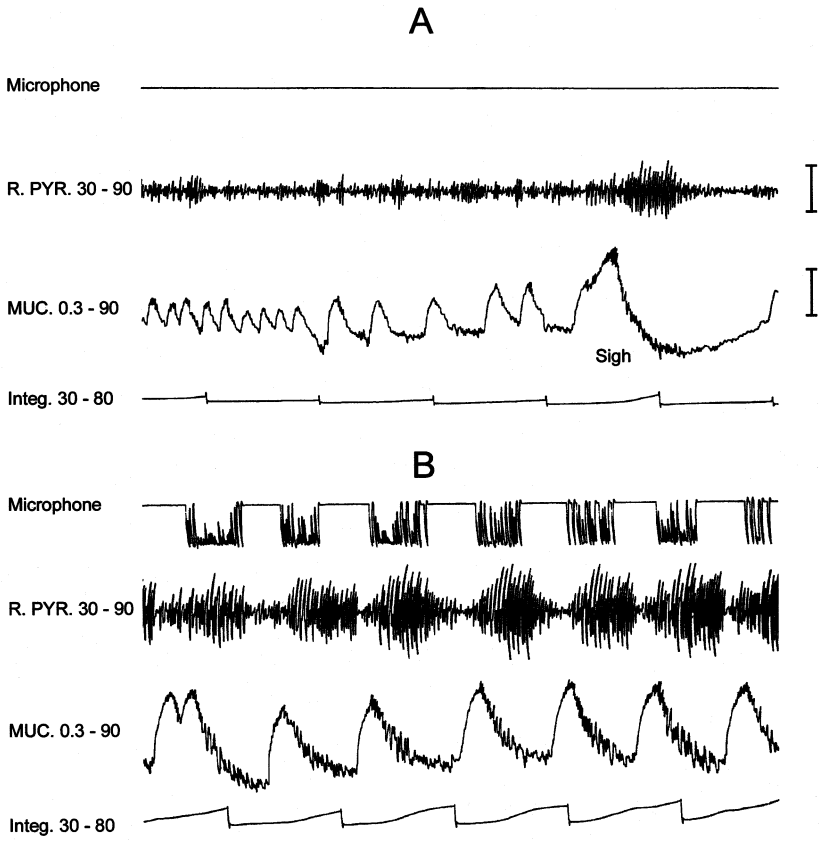


Fig. 5. Pyriform cortex gamma wave activity during undisturbed immobility and during vocalization elicited by light contact of the experimenter's hand with the back (rat # 3877). Microphone, output pulses from a window discriminator adjusted to detect audible vocalization recorded by a microphone placed near the rat's head; R. PYR 30–90, surface to depth bipolar record from the right pyriform cortex, 30–90 Hz frequency band; MUC, 0.3–90, monopolar record (negative up) from the left olfactory mucosa, 0.3–90 Hz frequency band; Integ. 30–80, right pyriform cortex activity, band pass 30–80 Hz, rectified and integrated over 1.0 s intervals. Calibration, 1.0 mV. A, rat immobile, head up, eyes open, undisturbed. Note the large gamma wave burst associated with an unusually long deep breath (sigh). B, rat breathed deeply and slowly, vocalizing at each expiration, in response to light manual pressure on the back. Note that large amplitude gamma wave bursts occur in association with each expiration-vocalization event. From Ref. [190] by permission of Elsevier Science Publishers, B.V.

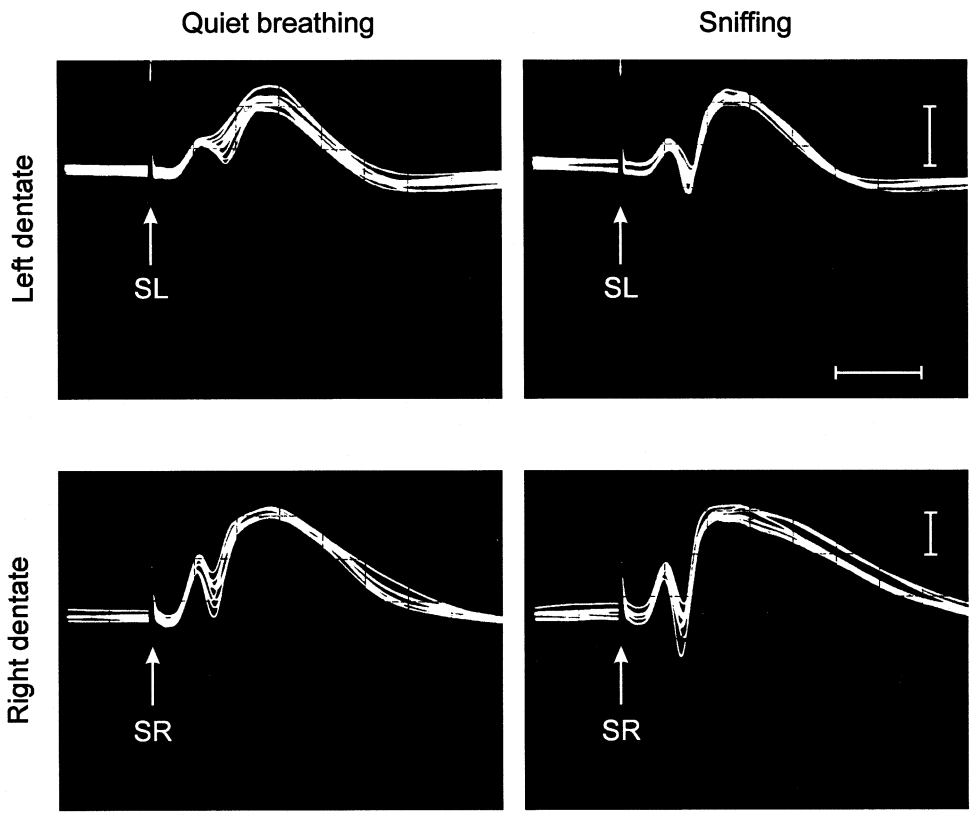


Fig. 6. Different effects of perforant pathway stimulation on the activity of the dentate gyrus during sniffing and during quiet breathing in rat # 3968. Right and left dentate records are monopolar, positive upwards, 1–10 000 Hz band pass. Calibration: 4 ms, 5.0 mV. SL, stimulate left perforant pathway, 0.1 ms negative pulse (indifferent in frontal bone), 210 μA, delivered manually at intervals of several seconds. SR, stimulate right perforant pathway using the same parameters except that the current was about 600 μA. In each case the level of current was adjusted at the start of the experiment in order to elicit a moderate-sized population spike. Eight sweeps per condition. Sniffing was elicited by manually presenting a second rat near the snout of the experimental rat. Sniffing and quiet breathing were identified by close observation of the experimental rat with subsequent confirmation by inspection of the ink-writer record which was allowed to run continuously. Note that the population spike (the short duration negative deflection) is larger during sniffing than during quiet breathing.

waves in CA1 occur in relation to RSA and Type 1 movement (see below). Dentate gamma waves occur in relation to olfactory inputs. Further, Bragin et al. [25] found that entorhinal cortex lesions suppressed dentate gamma activity but enhanced Ammon's horn gamma activity, indicating that gamma wave activity in the two structures has a different origin and significance.

### *2.2. The effect of hippocampal lesions on olfaction*

Observations made in the 19th century suggested that the pyriform lobe, hippocampal formation, and possibly even the cingulate cortex, are involved in olfaction [52] but no detailed analyses of this idea were ever carried out. More recent studies of olfaction in patients who have undergone unilateral temporal lobectomy have revealed olfactory impairments, including a diminished ability to identify common odors, via the nostril ipsilateral to the lesion. Parietal and central (Rolandic) lesions had no effect on olfactory ability but frontal lesions that included orbitofrontal cortex also impaired olfactory ability. Olfactory detection thresholds, however, were not affected by any of the lesions [50,84,225]. The patient H.M., famous for a severe amnestic syndrome produced by extensive bilateral surgical removal of medial temporal structures, also displayed normal detection thresholds for various odorants but could not identify such common odors as coconut, mint, almond, lemon, orange, cloves, or raspberry [49]. None of these studies permit any conclusions concerning the relative roles of different temporal lobe structures (hippocampal gyrus, uncus, amygdala, Ammon's horn, dentate gyrus, subicular cortex, neocortex, etc.) because the large lesions present in these patients involved many different structures.

Animal studies involving selective lesions of different olfactory structures might shed light on this problem. A classic study by Swann [173] showed that large lesions of the hippocampal formation, pyriform lobes, septal nuclei, or the amygdala did not prevent rats from discriminating the odors of anise and creosote. In contrast, Eichenbaum et al. [48] found an impairment of performance in both simultaneous and successive olfactory discriminations in rats that had lesions of the

fornix. It is important in such studies to demonstrate that the impairment observed is specifically olfactory, i.e. that the animals can perform the same task normally if it involves some other sensory modality. For example, Kimble [89] showed that successive visual discrimination performance is impaired in rats with hippocampal lesions. Therefore, some of the deficits described by Eichenbaum et al. [48] may not have been specifically olfactory.

Heale et al. [73], abandoning the learning-conditioning approach to the analysis of brain function, studied the effect of the odors of butyric acid, cadaverine, caproic acid, 2-propylthietane, and toluene on rat's preference for scented versus unscented food pellets. Normal rats prefer food scented with cadaverine (a malodorous diamine which occurs in cadavers) to unscented food (perhaps to be expected since rats normally scavenge dead decaying animals), avoid food scented with toluene (an organic solvent) or 2-propylthietane (the principle component of the anal scent gland secretions of weasels and stoats, which prey on rats) and are indifferent to food scented with butyric (rancid butter odor) or caproic (goaty odor) acids. Multiple intrahippocampal injections of colchicine, which had the effect of destroying mainly dentate gyrus and CA1 cells, produced a general tendency to avoid all the odors and the size of this effect varied with the dose of colchicine used. The effect is reminiscent of hyperosmia or dysosmia in humans, a condition in which normally neutral or even pleasant odors became strong and aversive.

Despite the effect of colchicine-induced hippocampal damage on olfactory control of feeding, there was no apparent effect on the rat's normal tendency to avoid food flavored with quinine and to prefer food flavored with sucrose [73]. Therefore, the impairment may be specifically olfactory.

These data indicate that the olfactory control of behavior can be altered by localized hippocampal damage but much more work will be necessary to delineate the nature and extent of this alteration. It is to be

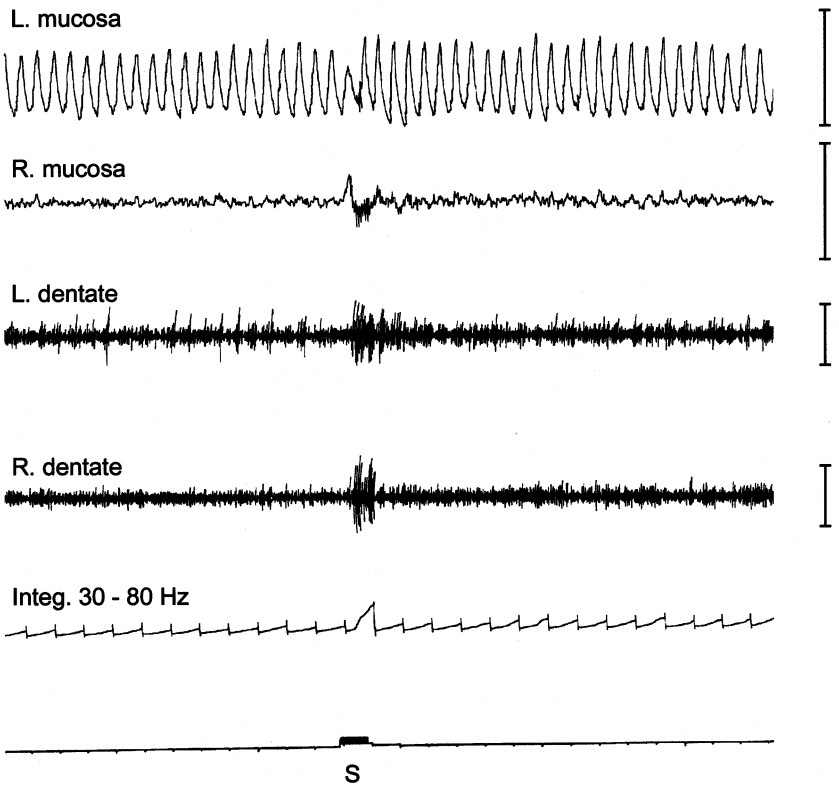


Fig. 7. Effect on the activity of the olfactory mucosa and dentate gyrus of blowing scented air into one nostril. Rat # 3969, lightly anesthetized with urethane (ethyl carbamate, 1.0 g/kg, i.p.). L. Mucosa, R. Mucosa, left and right olfactory mucosa, respectively, frequency band 0.3–90 Hz; L. Dentate, R. Dentate, left and right dentate gyri, respectively, frequency band 30–90 Hz; Integ. 30–80 Hz, rectified and integrated 30–80 Hz activity of the right dentate. All analogue records are monopolar, negative upwards. Calibration: 1.0 mV. One second intervals are marked by the integrator and by the timer on the bottom-most trace. A length of PE 60 polyethylene tubing (inner diameter, 760 μm; outer diameter, 1220 μm) was inserted in the right naris to a depth of about 1.5 cm. By blocking spontaneous airflow, this eliminated the spontaneous rhythmical respiratory potentials of the right mucosa. At 'S', 5.0 ml of air drawn from a closed glass container half filled with rat food pellets was injected manually into the right airway. This resulted in a slow negative deflection followed by a gamma wave burst in the right mucosa and a bilateral gamma wave response in the dentate gyrus. The overall pattern of breathing, as indicated by the rhythmical potentials of the left olfactory mucosa was little affected by this procedure (sniffing did not occur) except that the left mucosa potential was smaller than usual for one cycle and a tiny gamma wave burst was detected.

hoped that investigators entering this field will not confine themselves to experiments involving conditioning and olfactory discrimination. The mammalian olfactory system has multiple functions, including the control of feeding, reproduction, avoidance of predators, and social behavior [169]. The role of the hippocampal formation in the olfactory control of each of these large groupings of behaviors and physiological activities deserves careful study.

## 3. Control of motor activity by the hippocampus

### *3.1. Electrical activity*

The morphology and connections of the Ammon's horn pyramidal cells suggested to the classical anatomists that these cells had an effectory or motoric function analogous to the function of the large pyramidal cells of layer V of the neocortex [26,86]. Support for this view was provided by the finding that nearly sinusoidal 6–12 Hz RSA (theta rhythm) occurs in the hippocampus in rats and guinea pigs in close correlation with such motor patterns as spontaneous head movements, walking, running, jumping, digging, swimming, changes in posture, and manipulating objects with the forelimbs (e.g. handling a piece of food while eating or pressing a lever in a Skinner box). These activities have been referred to as Type 1 behavior. The RSA accompanying lever pressing or handling food is generally of a lower amplitude and frequency than the RSA accompanying a gross movement such as walking, a fact which suggests a lesser hippocampal involvement in restricted limb movements than in walking. Hippocampal RSA is not ordinarily present in rats and guinea pigs during the maintenance of a motionless waking posture or such motor acts as chewing food, licking water or licking the fur, shivering, face washing during grooming, or pelvic thrusting during copulation (Type 2 behavior) [103,150,185,194,217]. Related observations have been made in dogs and cats [11–13,18]. A theta rhythm is also present in monkeys and may be correlated with motor activity [167]. Motor potentials and increases in multiunit activity preceding a self-paced voluntary movement have been described in Ammon's horn as well as the pre-central gyrus in rhesus monkeys [9]. Halgren [71] has shown that unit activity is increased in the hippocampus in epileptic patients during the performance of voluntary movements such as skilled movements of the hands or sticking out the tongue.

If Ammon's horn is actually the site of generation of RSA then these observations suggest that the Ammonic pyramidal cells may play a role in controlling Type 1 behavior but have no role (or a different role) in controlling Type 2 behavior. Several lines of evidence do, in fact, indicate that hippocampal RSA is generated by transmembrane currents occurring synchronously in a large population of Ammon's horn pyramidal cells: (a) RSA displays a phase reversal in the apical dendrite layer of CA1 [67]; and (b) intracellular records from identified hippocampal pyramidal cells reveal rhythmical spontaneous membrane potentials (intracellular theta rhythm) which are phase-reversed with respect to the local extracellular theta rhythm [56,59,104,132] The depolarizing component of these waves is often associated with an action potential. Presumably, the transmembrane currents associated with these slow potentials are responsible for the extracellular RSA wave form. Both inhibitory and excitatory post-synaptic potentials may be involved in generating hippocampal RSA [28,104,132,161]. Although individual hippocampal pyramidal cells fire sporadically at a low rate, they do tend to fire in phase with the local extracellular RSA rhythm. A second class of hippocampal cells, which may be interneurons, fire at a much higher rate in rhythmical bursts in phase with RSA. The firing of such cells shows a strong relation to Type 1 motor activity such as locomotion or head movement [51,57,58,144].

The simple view that Ammon's horn activity is correlated with Type 1 motor activity was complicated by the discovery that dentate granule cells also fire in relation to the RSA cycle and contribute to the extracellular RSA wave form [19,20,58,147,219]. If dentate granule cells are also activated by an olfactory input, as indicated in the preceding section, one is confronted with the problem of how (or if) dentate cells and their output via the mossy fiber system can mediate olfactory control of RSA and the associated Type 1 behavior (e.g. when a rat smells food and walks toward it). This is likely to be a rather large and complex problem since the medial entorhinal cortex also generates RSA [6,7,121,168] and may receive an olfactory input from the lateral entorhinal cortex. Furthermore, the elicitation of hippocampal RSA is dependent on the activation of (at a minimum) ascending cholinergic and serotonergic inputs to the hippocampus [187]. The performance of even rather simple behaviors is associated with activation of widespread neural systems.

### *3.2. Electrical and chemical stimulation*

Current ideas about the properties of 'motor cortex' are based on experience with the pre- and post-central gyri in humans and the corresponding areas in laboratory animals. According to Penfield and Jasper [141, pp. 59–60], pioneers in the procedure of stimulating the neocortex in conscious humans, "Electrical stimulation (like local epileptic discharge) may produce movement when applied to the Rolandic motor area. At the same time, it produces paralysis of the muscles involved as far as their voluntary control is concerned. But the

result of the stimulation may occasionally be paralysis alone without any positive objective response. Thus, instead of hand movement there may be only hand paralysis. Instead of vocalization there may be inability to vocalize.'' Further, Penfield and Jasper note, the movements actually elicited by electrical stimulation of motor cortex are of a coarse infantile character, revealing nothing of the skillful function of which the motor cortex is presumably capable. ''The result (of stimulation) is the same whether the patient is an accomplished pianist or a manual laborer'' [141, p. 64].

The human motor cortex seems to be particularly concerned with the control of fine differentiated movements of the extremities. In contrast, the studies of the relations of hippocampal activity to movement suggest that this structure is related primarily to the control of gross movements such as locomotion and changes in posture. Consequently, if Ammon's horn can be compared to the motor cortex, one might expect that hippocampal stimulation would produce (a) a paralysis or suppression of spontaneous Type 1 movement; or (b) the elicitation of gross postural or locomotor responses.

Clear evidence of the first type of effect (paralysis of Type 1 movement) was obtained by Bland and Vanderwolf [22] and Whishaw and Nikkel [215] who found that stimulation of the dentate hilus in the middle of the septo-temporal extent of the hippocampal formation produced short-latency (2.5–7.0 ms) evoked potentials over an extensive septo-temporal region of CA1. This effect was presumably due to stimulation of cells which project to a wide region of the ipsilateral and contralateral dentate gyrus, Ammon's horn, and subiculum [175]. Stimulation at low frequencies had very little behavioral effect, but at higher frequencies (5–100 Hz), when each RSA wave cycle was interrupted by one or more evoked potentials (thereby disrupting normal function), there was a complete arrest of spontaneous locomotion, lever pressing, swimming, jumping out of a box (a previously established avoidance response), or struggling in response to being held. These effects were obtained in the absence of any electrographic or behavioral signs of seizure activity. The motor activities of maintaining a normal standing posture, licking movements of the tongue (drinking water) and shivering (after immersion in cold water) appeared to be quite unaffected by dentate stimulation [22,187]. Therefore, as a first approximation, dentate gyrus stimulation selectively disrupts Type 1 behavior but has little effect on Type 2 behavior.

The elicitation of active Type 1 movements by stimulation of the hippocampus has been demonstrated most clearly by the local injection of various chemicals that mimic the effects of naturally released acetylcholine and serotonin, neurotransmitters that are essential for the natural occurrence of RSA [187]. Injection of carbachol (a muscarinic agonist) into various regions of Ammon's horn and the dentate gyrus elicits RSA [148] and, in freely moving rats, an increase in walking, rearing, and poking the head into holes in a holeboard [53,122]. Electrical stimulation of the hippocampus may produce locomotor hyperactivity only following a seizure discharge [112,113]. Whether the seizure discharges are essential for the elicitation of motor activity is not entirely clear. Motles and González [125] found that carbachol or dioxolane (a selective cholinergic muscarinic agonist) injected unilaterally into the dorsal hippocampus in the cat provoked movements of the head and eyes toward the contralateral side. This effect was elicited in the absence of epileptiform activity in six of nine cats. Electrical stimulation also sometimes elicited a turning response but this was always associated with epileptiform activity. Takahashi et al. [177] reported that microinfusions of serotonin into the hippocampus produced an increase in locomotion unaccompanied by behavioral evidence of seizures or other abnormalities. Tranylcypromine (a monoamine oxidase inhibitor which would enhance local serotonergic activity) had a similar effect. Therefore, it is clear that stimulation of the hippocampus, whether it causes seizure activity or not, can elicit motor activities of the same general type that is normally associated with the occurrence of hippocampal RSA.

### 3.3. Effects of hippocampal lesions

If Ammon's horn is really to be compared with the motor cortex, there should be at least some similarity between the effects of lesions in the two sites. Is there really any evidence of such similarity?

Following unilateral surgical excision of the pre-central gyrus in humans or monkeys or a stroke involving the projections from motor cortex in humans, there is, at first, a flaccid paralysis of the contralateral limbs followed by a slow recovery. The effect is more severe for movement at distal joints (fingers, toes) than at proximal joints (shoulder, hip). Skilled movements, such as buttoning a shirt, are especially affected. With the passage of time, muscular tonus in the paralyzed limbs may increase to pathological levels and certain reflex movements may be more pronounced, or of a different character, on the paralyzed side of the body than on the normal side. Some motor patterns, including smiling, laughing, and movements of the thorax during quiet breathing may also be more pronounced on the paralyzed side [27,42,141].

John Hughlings Jackson, who was one of the first to make some of the foregoing observations [179], proposed that the central nervous system consists of a hierarchy of sensory-motor mechanisms. The activities of the lowest level, the reflex mechanisms of the spinal cord and brain stem, he suggested, are co-ordinated to form more complex adaptive patterns (such as locomo-

tion or reaching and grasping) by middle levels of sensory-motor integration. The middle levels, in turn, are controlled by still higher levels, which control the activity of the organism as a whole in relation to the environment. Destruction of a higher center was said to produce (a) *negative symptoms* owing to the loss of the part destroyed (e.g. paralysis after a cortical lesion) and (b) *positive symptoms* (e.g. hyper-reflexia, hyperactivity of various kinds) owing to the unregulated activity of lower level sensory-motor mechanisms.

The neural organization of locomotor activity illustrates well the principles of Jacksonian neurology. Animals with a high transection of the spinal cord made in adulthood cannot walk even though the spinal cord contains circuits that mediate components of locomotion such as rhythmical stepping movements [10,159]. This corresponds to Jackson's lowest level. Rats in which the brain stem has been transected at the mesencephalic–diencephalic border (high decerebration) right themselves spontaneously and walk about actively on a level surface [222]. This demonstrates a middle level of integration in which spinal locomotor reflexes are coordinated and brought under the influence of an additional relevant sensory input (from the vestibular system). The fact that high decerebrate or decorticate animals have severe behavioral impairments despite the preservation of spontaneous locomotion and head movement, as well as a wide variety of reflexive activities, is due, according to Jackson's ideas, to a loss of higher level motor control.

When the entire neocortex and hippocampal formation are surgically removed in the rat, very little spontaneous locomotion occurs in the first day or two [196] but after a recovery period of 30 days or more, decorticate rats are markedly hyperactive. When placed in running wheels, they run about ten times as far as control rats in two consecutive 24-h periods [193]. It is probable that a similar but smaller effect would be observed if the acute and chronic effects of hippocampal damage on locomotion were to be studied. Flicker and Geyer [54] reported that bilateral injection of a 1.0% lidocaine solution into the dentate gyrus (suppressing hippocampal electrical activity and creating, in effect, a temporary lesion) reduced spontaneous locomotion. Chronic hippocampal lesions, as is well known [89,180,213] are associated with locomotor hyperactivity. In terms of Jackson's ideas, the first effect, hypoactivity, is a negative symptom due to loss of higher level motor control mechanisms. The subsequent hyperactivity is a positive symptom attributable to the unregulated activity of middle and lower levels of sensory-motor integration. Positive symptoms of a lesion have traditionally been attributed to destruction of inhibitory pathways but nowadays we are aware that other factors are involved including: (a) denervation supersensitivity; (b) the growth of abnormal central projections [61,91] and (c) the growth of peripheral sympathetic fibers into denervated areas [47,108,163]. The existence of locomotor hyperactivity after hippocampal damage can be regarded as an additional indication that the normal role of the hippocampal formation includes the regulation of locomotor activity.

Glick et al. [64] have provided another type of demonstration of the role of the hippocampus in the control of locomotion. Following small unilateral hippocampal lesions, systemic injections of phencyclidine produce ipsiversive circling behavior, an effect which can be regarded as analogous to the ipsiversive circling produced by amphetamine in rats with unilateral lesions of ascending dopaminergic pathways [184]. Ma and Leung [114] have shown that activation of locomotor activity by phencyclidine is dependent on ascending septo-hippocampal pathways that are involved in the generation of gamma wave activity in CA1.

If the normal role of the hippocampal formation is really one of higher level control of Type 1 behavior, one might expect that chronic hippocampal lesions would produce a persisting impairment of the control of Type 1 behavior regardless of whether the behavior was displayed in response to a test of conditioning or learning or during the course of instinctive behavior. In contrast, theories that impute a special role to the hippocampus in memory would seem to require that hippocampal lesions affect learned behavior more than unlearned behavior. In fact, although hippocampal lesions impair numerous learned behaviors, as is well known, they also impair a variety of instinctive behavior patterns in rats and other rodents. These include maternal behavior, nest building, food hoarding, self-grooming, aggressive behavior, courtship, and general social interactions [32,88,90,92,151,160,182,210]. Grooming behavior is of special interest because of its apparent simplicity and resistance to modification by training, indicating that it is largely unlearned or instinctive [146]. Rats normally groom themselves in a cephalo–caudal sequence, beginning with paw-licking and face-washing and ending with licking of the body. A pronounced burst of hippocampal RSA occurs during postural changes such as those intervening between face-washing and body grooming but RSA is generally absent during licking, biting, or face-washing occurring in the absence of postural changes or extensive head movement [150,185]. Chronic hippocampal lesions disturb the cephalo–caudal sequence of grooming, as shown by the frequent failure of body grooming to follow face-washing in rats with hippocampal lesions [32]. This effect may be attributable to a loss of hippocampal control of the postural change intervening between face-washing and licking of the body. A recent analysis of the effects on grooming of treatment with scopolamine or scopolamine plus intracerebral injection

of 5,7-dihydroxytryptamine (this suppresses hippocampal RSA and neocortical activation) revealed that the resulting disturbance of grooming sequences could be attributed to interference with the control of changes in posture [146]. A deficit in the control of Type 1 behavior may also play a role in the much-studied effect of hippocampal lesions on swimming to a hidden platform. Whishaw et al. [212] have shown that rats with transection of the fimbria–fornix system of fibers approach a hidden platform by following looping or circling trajectories, even after extensive training. Control rats tend to swim in straight lines. The deficit produced by sectioning major hippocampal connections may "reside more in a disability in controlling movement through space rather than an inability to know the location of places in relation to ambient cues" [212, p. 5787].

Nonetheless, if the hippocampus really is primarily an olfacto-motor mechanism, as argued here, why do hippocampal lesions produce a severe impairment in animals in learned tasks that cannot possibly be dependent on olfactory cues? The impairment in the ability of rats with localized hippocampal damage to swim to the location of a platform hidden below the surface of a pool of water [123,170] illustrates the problem clearly.

An answer to this question (and a further set of problems) is suggested by the following findings. Lashley [98] trained rats in a puzzle box (an apparatus in which two levers, located on opposite sides of a small box, had to be pressed successively in a pre-determined order to reach food hidden in the box). Lesions made in the anterior one-third of the neocortex after training abolished the learned behavior but it could be re-established with additional training. Lesions of similar size elsewhere in the neocortex had no effect. Similarly, if rats were trained in a light–dark visual discrimination, subsequent lesions of the posterior (striate) cortex abolished the learned behavior, but it could be re-established with further training. Lesions of similar size in other cortical regions had no effect. These results indicated a clear localization of function. Ability to perform a previously learned puzzle box habit is dependent only on anterior cortex but the ability to perform a previously learned light–dark discrimination is dependent on the striate cortex.

Quite different results were obtained if rats were trained in a complex maze prior to receiving cortical lesions. In this case, lesions located anywhere in the neocortex produced a loss of the maze habit provided that the lesion included more than about 15% of the entire neocortex. Further, the extent of the behavioral impairment was proportional to the extent of cortical damage [98].

It appears that performance of some learned tasks (the puzzle box, light–dark discrimination) is dependent on a restricted region of the cortex while other learned tasks (the complex maze) are dependent on widespread cortical regions. Similar effects occur in the human brain. In a series of head-injured war veterans, it was shown that performance of some tests (block design, spatial rotation) was impaired by injuries in specific regions while performance on other tests (verbal and performance intelligence tests) was impaired by lesions in many locations and lesion volume was more important than lesion location [66]. Similarly, the occurrence of dementia after ischemic lesions in humans is more related to lesion size than to lesion location [183]. These results confirm Lashley's findings.

The ability of rats to swim to a platform in a pool of water is impaired by lesions of the hippocampal formation [123,170,171]; the thalamus [197], the caudate-putamen [214], the basal forebrain [46,216]; medial frontal and orbitofrontal neocortex [93,94,170]; parietal cortex [43]; and cingulate cortex [172]. Clearly, good performance in this type of task is dependent on neural mechanisms in almost any part of the forebrain: it certainly cannot be localized to a particular region such as the hippocampus.

The general question of why some behavioral performances depend on rather localized neural systems while others depend on widespread neural systems is unlikely to have any simple unitary answer. For the present, it suffices to point out that it does not relate exclusively to the hippocampus but also to neocortical areas, including the classical sensory-motor cortex.

It seems clear that classical sensory cortex has functions in addition to the analysis of immediate sensory input. Lashley [99] was the first to show that striate cortex lesions produced a severe impairment in maze performance in blind rats. This type of effect has been confirmed in monkeys and cats [109,138]. Presumably, the hippocampus, too, has a role in behavior that extends beyond the analysis of olfaction, even though this may be its principal sensory input.

### *3.4. Descending hippocampal projections*

The descending pathways by which the hippocampus might control motor activity were never specified by the classical anatomists, but Herrick [78, p. 10] suggested an influence via the mammillary bodies "into the apparatus of mass movement (locomotion and the like)". This is excellent, but lacking in detail.

It has been known for more than a century that the pyramidal cells of Ammon's horn project massively to the septal nuclei [128,129,174] where synaptic contacts may occur with cells that contribute descending projections to the lateral and posterior hypothalamic areas via the medial forebrain bundle [131,201]. Parallel descending pathways from the subiculum (which receives an extensive input from Ammon's horn) also reach the septal nuclei and hypothalamus [174]. Nauta [128,129]

had previously shown that direct projections from the hippocampal formation and septal nuclei reach the pre-optic area and hypothalamus as well as parts of the thalamus, the central grey and medial parts of the midbrain and pontine tegmentum.

It appears that an important target of descending hippocampal pathways, the posterior hypothalamic–subthalamic region, is of special importance in locomotion. Hinsey et al. [79] were the first to demonstrate that cats acutely decerebrated by a brain stem transection passing just rostral to this region are much more active than cats in which the plane of transection passed just caudal to this region. Electrical stimulation of the posterior hypothalamic–subthalamic area is a powerful elicitor of locomotor activity in high decerebrate animals [10]. This indicates a descending influence from this basal diencephalic region on locomotor mechanisms in the lower brain stem and spinal cord. Holstege [80] has summarized anatomical evidence of descending pathways from the lateral and posterior hypothalamus to the lower brain stem and spinal cord, which may be responsible for such descending influences.

In intact rats, electrical stimulation of the lateral or posterior hypothalamus can produce walking, rearing, running or digging (in sawdust), accompanied by hippocampal RSA [21,211,215]. Large lesions of the posterior or lateral hypothalamus produce akinesia, together with a loss of the 7–12 Hz RSA that normally accompanies Type 1 movement [105,145]. This suggests that ascending influences from the hypothalamus (or fibers of passage in the hypothalamus) may play a role in the normal correlation of hippocampal RSA with gross motor activity. In confirmation of this, Oddie et al. [133] have recently demonstrated that intraseptal injections of procaine abolish both hippocampal RSA and wheel running elicited by electrical stimulation of the posterior hypothalamus. The role of ascending septal connections in the mediation of hippocampal motor control has been confirmed by Ma and Leung [113] who showed that the increased CA1 gamma activity and the associated locomotor activity which follow an electrical stimulation-induced hippocampal afterdischarge are both abolished by injection of muscimol (an agonist of gamma-amino butyric acid) into the medial septal area. Therefore, it is probable that both ascending and descending effects contribute to hypothalamic control of gross motor activity.

The subicular projection to the nucleus accumbens [107,143a] can be regarded as analogous to the well-known neocortical projections to the dorsal striatum [77], and like the latter pathway, it probably plays a role in the control of motor activity. This conclusion is indicated by experiments showing that gross motoric effects elicited from the hippocampal formation can be reduced or abolished by injection of glutamate antagonists, gamma aminobutyric acid or a selective dopamine $D_2$ antagonist into the nucleus accumbens or the subpallidal region [112,122].

Neafsey [130] has suggested that hippocampal control of head and eye movements may be mediated by Ammon's horn projections to medial frontal cortex which, in turn, projects strongly to the superior colliculus, placing it in a position to affect tectospinal output.

Another pathway by which descending hippocampal projections might influence motor activity has been described by Allen and Hopkins [4,5]. Descending fibers from the subiculum terminate in topographical fashion in the mammillary nuclei, in a position to influence mammillo-tegmental projections to the dorsal and ventral tegmental nuclei and pontine nuclei that project to the cerebellar cortex. The existence of such pathways has been supported by evidence that electrical stimulation of the hippocampus or fornix produces short-latency evoked responses in the cerebellar cortex [68,152,153]. Therefore, descending hippocampal pathways may control motor activity, in part, via a ponto-cerebellar circuit. This pathway can be considered analogous to the massive neocorticopontine projections [207,208], which undoubtedly play a major role in motor control [139].

## 4. The role of the hippocampus in learning and memory

Gross destruction of medial temporal lobe structures in humans can produce a severe impairment of subsequent ability to learn (anterograde amnesia) together with a more moderate effect on previously acquired learned behavior (retrograde amnesia). There may also be a preservation of the ability to repeat verbal material (such as a series of digits) for a short period after presentation and a normal ability to learn certain skills such as tracing accurately around a figure visible only in a mirror. These effects, first described by Scoville and Milner [156], Penfield and Milner [142], and Milner [120], are well established [162] and have been widely attributed to destruction of the hippocampal formation.

However, the hypothesis that the hippocampal formation plays a key role in many forms of learning and memory has been severely criticized [81,82,191]. A brief summary of some of these criticisms is presented here.

(a) Amnestic effects have been reported following injury to a variety of brain structures, not only the medial temporal region. These include the thalamus, the internal capsule, the basal ganglia, the basal forebrain region, and the frontal lobe [1,3,14,31,38,41,83,95,116,119,154,178,181,202,203,205]. Lesions in each of these areas produce their own unique constellation of effects, including the presence or absence of confabulation, but the fact that all have an amnestic component suggests that many brain struc-

tures play a role in the acquisition of a new behavior. Studies in animals corroborate this. Lesions in many structures in the brain stem, cerebellum, diencephalon, and telencephalon impair some form of learned behavior, usually having a greater effect on post-operative acquisition than on pre-operatively acquired behavior [191]. Even purely peripheral manipulations can do this. Thus, peripheral sympathectomy impairs post-operative shock avoidance learning in dogs but has little effect on pre-operatively acquired shock avoidance behavior [223].

(b) It has not been established that isolated destruction of the hippocampus results in an amnestic syndrome in man. The famous patient H.M. developed a particularly severe amnestic disorder [156] following surgical removal of medial temporal polar cortex, most of the amygdala and entorhinal cortex, and about half of the hippocampus (Ammon's horn, dentate gyrus, and subicular cortex) [35]. However, Gol and Faibish [65, p. 397] who made use of a stereotaxic surgical technique to create unilateral or bilateral hippocampal lesions for the relief of chronic pain, concluded that "Certainly, bilaterally extensive hippocampal lesions did not produce the extreme memory deficits described by Penfield, Scoville and Milner". This suggests that extrahippocampal lesions, or lesions involving the hippocampus together with other structures, produced the amnestic disorder suffered by H.M.

Severe cell loss in the CA1–CA2 region of the hippocampus following prolonged cerebral ischemia [37,87,228] does not necessarily mean that the hippocampal damage was solely responsible for the ensuing amnestic syndrome. It is well known that cerebral ischemia can lead to widespread cell loss which may not be obvious owing to shrinkage of the affected tissue [183]. The hippocampal lesions studied by Gol and Faibish, which did not produce gross amnesia, are more valuable from the point of view of localization of function since they were made surgically by a stereotaxic technique. One must conclude that the proposition that lesions restricted to the human hippocampal formation can produce a full-blown amnestic syndrome has not been adequately demonstrated [81,82,191].

Finally, it should be mentioned that brain imaging studies also provide scant support for the theory that the hippocampus is specifically activated by learning and memory tasks. Lepage et al. [100], in a meta-analysis of 52 studies using positron emission tomography during the performance of various learning and memory tasks in normal human subjects, mention that significant hippocampal activation was observed in only 21 studies (13 times during 'retrieval', eight times during 'encoding'). Two recent reviews of brain imaging studies of learning in normal humans do not suggest a specific role for the hippocampus in memory [143b,200].

(c) If hippocampal function were specialized in relation to learned behavior one would expect that unlearned or instinctive behavior in animals would be relatively unaffected by hippocampal damage. This is clearly not the case. There are numerous reports of impairments in instinctive behavior in various animals following injury to the hippocampus (Section 3.3).

(d) It is unlikely that any single large structure in the brain (such as the hippocampus) is uniquely responsible for memory. Experience-dependent changes in synaptic connectivity occur widely from the olfactory bulb [221] to the spinal cord [220]. The learning of any complex behavior is probably associated with changes in the connectivity of the pre-existing circuitry at many different brain sites, the actual sites varying in relation to the sensori-motor requirements of the task [191].

(e) One might suppose that the question of the role of the hippocampus in learning and memory could easily be settled by a series of well-designed experiments in animals. Why has this not happened? From a neuroscientific point of view, learning must consist primarily of a long-term modification of synaptic connectivity as a result of experience. However, studies of the behavioral effect of brain lesions or drug treatments do not distinguish plastic from non-plastic synapses. Therefore, studies of the effect of hippocampal lesions on maze performance, for example, have only a marginal relevance to memory in a neuroscientific sense. At best, such work provides evidence relevant to the question of the role of different anatomical structures or of different neurotransmitters in the overall mediation of the behavioral performance under study. This point requires emphasis. Behavioral studies of learning in drugged or brain damaged animals are generally based on an implicit assumption that there is a brain process called 'memory' which can be distinguished from other processes such as 'perception' or 'motivation'. Not only do these psychological concepts have little in common with the neuroscientific concept of experience-dependent synaptic plasticity, but they are in themselves of very dubious validity [189,191] (Section 7).

Although electrophysiological studies are certainly capable of distinguishing between plastic and non-plastic synapses [195], extensive investigations have led to few clear conclusions. In part, this is due to a confounding of the changes expected from training with changes due to altered motor performance, changes in brain temperature [29,30,124,191] or other factors. For example, Sharp et al. [158] reported that exposure of rats to a complex novel environment increased the amplitude of the population spike elicited in the dentate gyrus by stimulation of the perforant path. This effect, although it was related by Sharp et al. to long-term potentiation and learning, may, in reality, have been related to the occurrence of sniffing of odorous objects which (as shown here) is associated with dentate popu-

lation spike enhancement. Sharp et al., being unaware of this possibility, did not monitor olfactory input even though a novel environment is almost certain to elicit sniffing in a rat.

## 5. Does the hippocampus contain a cognitive map?

O'Keefe [135] and Ranck [144] demonstrated the existence of two main classes of units in the hippocampus of the freely moving rat. One group, the complex spike cells, sometimes generate single action potentials, but at other times they generate short high frequency bursts of action potentials (complex spikes). The second group of cells fire only single spikes but at a higher frequency and with a shorter spike duration than the complex spike cells. Since firing in these cells occurs at a high frequency if, and only if, RSA or theta rhythm is concurrently present in the slow wave record, they are commonly known as 'theta cells'. The complex spike cells in Ammon's horn appear to be mainly pyramidal cells while the theta cells are mainly interneurons [57].

O'Keefe and Dostrovsky [136] and O'Keefe [134] were the first to show that if hippocampal records were taken in rats moving about freely in an extended open area, complex spike cells fire at higher rates in one part of the environment than in other parts (place cells). The firing rate seems to depend on a complex array of stimuli (especially the more distant visual stimuli) rather than on any local cues, such as a specific odor in one part of the apparatus [135,157]. O'Keefe and Nadel [137] proposed that hippocampal place cells provide a rat with an internal representation of Euclidean space, a cognitive map, which provides the animal with the information needed to navigate from one location to another. Theta cells were considered to be 'displace cells' by O'Keefe and Nadel [137] on the assumption that their activity is related to changes in spatial position.

The idea that the hippocampus is a cognitive map appears to have little in common with the hypothesis that the hippocampus is primarily an olfacto-motor mechanism. Can these ideas be reconciled or can one of them be rejected?

Foster et al. [55] first habituated rats to physical restraint (produced by wrapping the body and limbs in a towel fastened with clips) then compared the effects of placing the rats passively in various places in an open field in either the restrained or the unrestrained (no towel) conditions. It is important to note that distance receptors (for olfaction, vision, and audition) were fully functional in both conditions. Complex spike cells that displayed clear place fields in the unrestrained condition lost all trace of place-related activity in the restrained condition. Although the rats were rather quiet in both restrained and unrestrained conditions (mostly head movements and sniffing), Foster et al. noted a decreased level of 7–12 Hz RSA in the restrained condition indicating less Type 1 movement in the restrained condition than in the unrestrained condition. These data indicate that place cells do not signal a rat's location in space; rather, place cell firing is related to concurrent or potential motor activity. One can think of place cells as neurons that play a role in directing a rat's movements (i.e. walking to one point rather than another) in an extended area. In support of this, it is well established that the presence of hippocampal RSA elevates the frequency of place cell firing within a firing field and depresses firing outside the firing field [97,127]. According to McNaughton et al. [118], "Most spikes from complex spike cells occurred when the animal was located within a particular place on the maze and moving in a particular direction" (p. 41). These observations appear to be more readily compatible with the idea that hippocampal complex spike cells play a role in directing locomotion then with the idea that they signal a location in Euclidean space. Furthermore, theta cells, whose firing is related primarily to the occurrence of Type 1 behavior, also display place fields [96]. Perhaps, the activity of both types of cells is related to potential or concurrent motor activity. If theta cells are mainly interneurons whose function is to regulate the firing of projection cells, then it seems likely that the behavioral correlates of the two types of cell would have a great deal in common.

It may also be noted that a purely passive movement (translation in space without motor activity on the part of the animal) does not produce RSA and that Type 1 movement occurring without moving an animal outside an area the size of the firing field of a complex spike cell (e.g. during head movements and postural shifts, digging in sawdust, handling food while eating, pressing the lever of a Skinner box, or walking on a type of treadmill while the head is held rigidly immobile in a stereotaxic frame) is always associated with RSA [186]. Therefore, the RSA or theta systems are not activated only in association with moving from place to place in the sense intended by O'Keefe and Nadel [137].

Further, introducing a barrier into a place field modifies it profoundly regardless of whether the barrier is opaque fiberboard or a transparent sheet of Plexiglas [97,126]. A low barrier over which the rat can easily climb has very little effect on spatial fields. These observations, together with those of Foster et al. [55], suggest that place cells fire in relation to the behavioral possibilities at a particular location rather than the specific stimulus characteristics or position in space.

Another line of evidence which indicates that both complex spike and theta cells can be readily activated under conditions in which spatial translation is impossi-

ble is provided by the report that the great majority of hippocampal neurons are activated by a classical nictitating membrane conditioning procedure in restrained rabbits [16]. Perhaps, the activity of the neurons was related to motor activity: the rabbits could move their limbs and the conditioning procedure might well activate limb and trunk movement (although this was not studied by Berger et al. [16]).

In conclusion, studies of place cells can be regarded as supporting the general view that the hippocampus plays a role in the control of motor activity. The theory that the hippocampus is a cognitive map is not only contradicted by a variety of experimental findings but is also problematic in a more philosophical sense. Cognitive map theory, in common with all theories that posit representations of the outside world in the brain, appears to require the assumption of an 'inner man' who perceives the representation [164]. As Gibson [62, p. 61] points out, such theories "carry the implication of a mind that is separate from a body".

## 6. The hippocampus and emotion

The theory that intellectual or cognitive processes are associated with the neocortex while emotional processes are associated with the limbic system [115,140] has enjoyed wide support. Papez [140] suggested that the hippocampus, a key component of the limbic system, was involved in emotion on the basis of the fact that Negri bodies (virus particles) occur abundantly in Ammon's horn pyramidal cells in cases of rabies, a disorder associated with 'intense emotional, convulsive, and paralytic symptoms'. Although Papez's conclusion is, perhaps, not entirely convincing given the widespread distribution of rabies virus in the brain and the multiplicity of symptoms in rabies, no better evidence has ever been presented. Douglas [44] pointed out that hippocampal lesions in rats, cats, and monkeys do not produce behavioral changes of a type that would ordinarily be considered emotional. More recent studies have confirmed this. For example, anti-anxiety drugs such as buspirone reduce the tendency of rats to spend more time in a dark compartment than in an adjacent light compartment in a two compartment box but hippocampal lesions do not have this effect [45]. Lesions of the septal nuclei or of the fimbria–fornix pathways do not interfere with the acquisition of an autonomic conditioned response (conditioned defecation) based on the administration of a painful electric shock [192]. Studies of spontaneous hippocampal field potentials, evoked potentials, or unit activity in freely moving animals have not suggested any relation to emotion. It is true that hippocampal stimulation may result in cardiovascular and respiratory changes [149] but such effects are not necessarily related to emotion. Stimulation of the pre-central gyrus tends to elevate or depress systemic blood pressure and to produce a shift in blood flow from the visceral to the muscular vascular beds [60,204], but no one supposes that the pre-central gyrus is directly involved in emotion. The autonomic effects elicited from both the classical motor cortex and the hippocampus can, perhaps, be regarded as due to blockade or excitation of a mechanism that normally activates movement together with autonomic and respiratory functions designed to provide metabolic support for active muscles.

## 7. Are psychological concepts relevant to brain function?

Attempts to relate one or another aspect of brain structure or function to such concepts as emotion, cognition or memory raise a fundamental question. How do we know that these concepts reflect natural subdivisions of brain function? These psychological concepts did not arise from any kind of scientific investigation: their origin lies in the speculations of the philosophers of ancient Greece, transmitted to us chiefly via the teachings of Aristotle [189]. The findings of ethnopsychology demonstrate clearly that the psychological systems developed by the Indian and Chinese civilizations categorize human experience in ways that differ fundamentally from the system developed by the Graeco-Roman-Christian civilization [39]. Therefore, the possibility must be considered that the familiar concepts of conventional psychology are cultural artifacts with no greater validity than many other ideas also found in Aristotle's writings, such as the idea that fire, water, earth, and air are the fundamental material elements, or the idea that falling bodies move at a constant velocity.

Continued adherence to psychological concepts of ancient origin may have had a detrimental effect on the development of the behavioral and neural sciences. There is a growing recognition that psychological research has made little fundamental progress in a long period of time [24,34,63,111]. Attempts to investigate the mind by neuroscientific methods have fared no better. The entire brain-behavioral field now seems to be tip-toeing quietly away from the long and widely held belief that the hippocampus is a major site of mnemonic processes. Attention, a major concept in the brain-behavior field in the past half-century, has been variously related to the frontal lobes, the parietal lobes, the hippocampal formation, long-term potentiation in the hippocampal formation, the cingulate cortex, the ascending cholinergic projections from the basal forebrain, the ascending nor-adrenergic projections from the locus coeruleus, the ascending brain stem reticular formation, the intralaminar nuclei of the thalamus, and

efferent pathways that regulate activity in sensory systems. None of these ideas are generally accepted. After half a century of failure in the search for a specific neural mechanism corresponding to the concept of attention, one must consider the possibility that no such mechanism exists.

The conventional conceptual basis of brain-behavior research appears to be in need of rethinking and reorientation. There is no need to classify behavior in terms of psychological concepts such as cognition, emotion, or memory. Animal behaviorists generally classify behavior according to its functions, leading to such groupings as feeding behavior or predator avoidance behavior. Each of these categories could be said to include 'mnemonic', 'cognitive' and 'emotional' elements. How the brain categorizes behavior is an empirical question. In order to make advances in the brain-behavior field, it is essential to disentangle the study of behavior from ancient speculations about the psyche and to proceed in a rational empirical manner [189,191].

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## References

[1] Abe K, Inokawa M, Kashiwagi A, Yanagihara T. Amnesia after a discrete basal forebrain lesion. J Neurol Neurosurg Psychiat 1998;65:126–30.
[2] Adrian ED. Olfactory reactions in the brain of the hedgehog. J Physiol 1942;100:459–73.
[3] Alexander MP, Freedman M. Amnesia after anterior communicating artery aneurysm rupture. Neurology 1984;34:752–7.
[4] Allen GV, Hopkins DA. Mamillary body in the rat: topography and synaptology of projections from the subicular complex, prefrontal cortex, and midbrain tegmentum. J Comp Neurol 1989;286:311–36.
[5] Allen GV, Hopkins DA. Topography and synaptology of mamillary body projections to the mesencephalon and pons in the rat. J Comp Neurol 1990;301:214–31.
[6] Alonso A, Garcia-Austt E. Neuronal sources of theta rhythm in the entorhinal cortex of the rat. I. Laminar distribution of theta field potentials. Exp Brain Res 1987;67:493–501.
[7] Alonso A, Garcia-Austt E. Neuronal sources of theta rhythm in the entorhinal cortex of the rat: II. Phase relations between unit discharges and theta field potentials. Exp Brain Res 1987;67:502–9.
[8] Anderson P, Bliss TVP, Skrede KK. Unit analysis of hippocampal population spikes. Exp Brain Res 1971;13:208–21.
[9] Arezzo JC, Tenke CE, Vaughan HG Jr. Movement-related potentials within the hippocampal formation of the monkey. Brain Res 1987;401:79–86.
[10] Armstrong DM. The supraspinal control of mammalian locomotion. J Physiol (London) 1988;405:1–37.
[11] Arnolds DEAT, Lopes da Silva FH, Aitink JW, Kamp A. Hippocampal EEG and behaviour in dog. I. Hippocampal EEG correlates of gross motor behaviour. Electroenceph Clin Neurophysiol 1979;46:552–70.
[12] Arnolds DEAT, Lopes da Silva FH, Aitink JW, Kamp A. Hippocampal EEG and behaviour in dog. II. Hippocampal EEG correlates with elementary motor acts. Electroenceph Clin Neurophysiol 1979;46:571–80.
[13] Arnolds DEAT, Lopes da Silva FH, Boeijinga P, Kamp A, Aitink W. Hippocampal EEG and motor activity in the cat: the role of eye movements and body acceleration. Behav Brain Res 1984;12:121–35.
[14] Baddeley A, Wilson B. Frontal amnesia and the dysexecutive syndrome. Brain Cog 1988;7:212–30.
[15] Bayer SA. Hippocampal region. In: Paxinos G, editor. The rat nervous system, forebrain and midbrain, vol. 1. Sydney: Academic Press, 1985:335–52.
[16] Berger TW, Rinaldi PC, Weisz DJ, Thompson RF. Single-unit analysis of different hippocampal cell types during classical conditioning of rabbit nictitating membrane response. J Neurophysiol 1983;5:1197–219.
[17] Berry CM, Hagamen WD, Hinsey JC. Distribution of potentials following stimulation of olfactory bulb in cat. J Neurophysiol 1952;15:139–45.
[18] Black AH. Hippocampal electrical activity and behavior. In: Isaacson RL, Pribram KH, editors. The hippocampus, neurophysiology and behavior, vol. 2. New York: Plenum Press, 1975:129–67.
[19] Bland BH, Andersen P, Ganes T. Two generators of hippocampal theta activity in rabbits. Brain Res 1975;94:199–218.
[20] Bland BH, Andersen P, Ganes T, Sveen O. Automated analysis of rhythmicity of physiologically identified hippocampal formation neurons. Exp Brain Res 1980;38:205–19.
[21] Bland BH, Vanderwolf CH. Diencephalic and hippocampal mechanisms of motor activity in the rat: effects of posterior hypothalamic stimulation on behavior and hippocampal slow wave activity. Brain Res 1972;43:67–88.
[22] Bland BH, Vanderwolf CH. Electrical stimulation of the hippocampal formation: behavioral and bioelectrical effects. Brain Res 1972;43:89–106.
[23] Bland BH, Whishaw IQ. Generators and topography of hippocampal theta (RSA) in the anesthetized and freely moving rat. Brain Res 1976;118:259–80.
[24] Boneau CA. Observations on psychology's past and future. Am Psychol 1992;47:1586–96.
[25] Bragin A, Jandó G, Nádasdy Z, Hetke J, Wise K, Buzsáki G. Gamma (40–100 Hz) oscillation in the hippocampus of the behaving rat. J Neurosci 1995;15:47–60.
[26] Brodal A. The hippocampus and the sense of smell: a review. Brain 1947;70:179–222.
[27] Brodal A. Neurological anatomy in relation to clinical medicine, 3rd ed. New York: Oxford University Press, 1981.
[28] Buzsáki G, Leung L-WS, Vanderwolf CH. Cellular basis of hippocampal EEG in the behaving rat. Brain Res Rev 1983;6:139–71.
[29] Cain DP. Testing the NMDA, long-term potentiation, and cholinergic hypotheses of spatial learning. Neurosci Biobehav Rev 1998;22:181–93.

[30] Cain DP, Hargreaves EL, Boon F. Brain temperature- and behavior-related changes in the dentate gyrus field potential during sleep, cold water immersion, radiant heating, and urethane anesthesia. Brain Res 1994;658:135–44.
[31] Caine ED, Ebert MH, Weingartner H. An outline for the analysis of dementia: the memory disorder of Huntington's disease. Neurology 1977;27:1087–92.
[32] Cannon RL, Paul DJ, Baisden RH, Woodruff ML. Alterations in self-grooming sequences in the rat as a consequence of hippocampal damage. Psychobiology 1992;20:205–18.
[33] Chapman CA, Xu Y, Haykin S, Racine RJ. Beta-frequency (15–35 Hz) electroencephalogram activities elicited by toluene and electrical stimulation in the behaving rat. Neuroscience 1998;86:1307–19.
[34] Cooper RM. The passing of psychology. Canad J Psychol 1982;23:264–7.
[35] Corkin S, Amaral DG, Gonzalez RG, Johnson KA, Hyman BT. H.M.'s medial temporal lobe lesion: findings from magnetic resonance imaging. J Neurosci 1997;17:3964–79.
[36] Cragg BG. Responses of the hippocampus to stimulation of the olfactory bulb and of various nerves in five mammals. Exp Neurol 1960;2:547–72.
[37] Cummings JL, Tomiyasu U, Read S, Benson DF. Amnesia with hippocampal lesions after cardiopulmonary arrest. Neurology 1984;34:679–81.
[38] Damasio A, Graff-Radford N, Eslinger P, Damasio H, Kassell N. Amnesia following basal forebrain lesions. Arch Neurol 1985;42:263–71.
[39] Danziger K. Naming the mind: how psychology found its language. London: Sage, 1997.
[40] DeFelipe J, Jones EG. Cajal on the cerebral cortex: an annotated translation of the complete writings. New York: Oxford University Press, 1988.
[41] Dennis M, Spiegler BJ, Fitz CR, Hoffman HJ, Hendrick EB, Humphreys RP, et al. Brain tumors in children and adolescents – II. The neuroanatomy of deficits in working, associative and serial-order memory. Neuropsychologia 1991;29:829–47.
[42] Denny-Brown D. The cerebral control of movement. Springfield, Ill: Thomas, 1966.
[43] DiMattia BD, Kesner RP. Spatial cognitive maps: differential role of parietal cortex and hippocampal formation. Behav Neurosci 1988;102:471–80.
[44] Douglas RJ. The hippocampus and behavior. Psychol Bull 1967;67:416–22.
[45] Dringenberg HC, Kornelsen RA, Pacelli R, Petersen K, Vanderwolf CH. Effects of amygdaloid lesions, hippocampal lesions, and buspirone on black–white exploration and food carrying in rats. Behav Brain Res 1998;96:161–72.
[46] Dunnett SB, Whishaw IQ, Jones GH, Bunch ST. Behavioral, biochemical, and histochemical effects of different neurotoxic amino acids injected into nucleus basalis magnocellularis of rats. Neuroscience 1987;20:653–69.
[47] Dyon-Laurent C, Hervé A, Sara SJ. Noradrenergic hyperactivity in hippocampus after partial denervation: pharmocological, behavioral, and electrophysiological studies. Exp Brain Res 1994;99:259–66.
[48] Eichenbaum H, Fagan A, Mathews P, Cohen NJ. Hippocampal system dysfunction and odor discrimination learning in rats: impairment or facilitation depending on representational demands. Behav Neurosci 1988;102:331–9.
[49] Eichenbaum H, Morton TH, Potter H, Corkin S. Selective olfactory deficits in case H.M. Brain 1983;106:459–72.
[50] Eskenazi B, Cain WS, Novelly RA, Friend KB. Olfactory functioning in temporal lobectomy patients. Neuropsychologia 1983;21:365–74.
[51] Feder R, Ranck JB Jr. Studies on single neurons in dorsal hippocampal formation and septum in unrestrained rats. Part II. Hippocampal slow waves and theta cell firing during bar pressing and other behaviors. Exp Neurol 1973;41:532–55.
[52] Finger S. Origins of neuroscience: a history of explorations into brain function. New York: Oxford University Press, 1994.
[53] Flicker CI, Geyer MA. Behavior during hippocampal microinfusions. II. Muscarinic locomotor activation. Brain Res Rev 1982;4:105–27.
[54] Flicker C, Geyer MA. Behavior during hippocampal microinfusions. III. Lidocaine versus picrotoxin. Brain Res Rev 1982;4:129–36.
[55] Foster TC, Castro CA, McNaughten BL. Spatial selectivity of rat hippocampal neurons: dependence on preparedness for movement. Science 1989;244:1580–2.
[56] Fox SE. Membrane potential and impedance changes in hippocampal pyramidal cells during theta rhythm. Exp Brain Res 1989;77:283–94.
[57] Fox SE, Ranck JB Jr. Electrophysiological characteristics of hippocampal complex—spike cells and theta cells. Exp Brain Res 1981;41:399–410.
[58] Fox SE, Wolfson S, Ranck JB Jr. Hippocampal theta rhythm and the firing of neurons in walking and urethane anesthetized rats. Exp Brain Res 1986;62:495–508.
[59] Fujita Y, Sato T. Intracellular records from hippocampal pyramidal cells in rabbit during theta rhythm activity. J Neurophysiol 1964;27:1011–25.
[60] Fulton JF. Physiology of the nervous system. New York: Oxford University Press, 1949.
[61] Gage FH, Bjorklund A, Stenevi U, Dunnett SB. Functional correlates of compensatory collateral sprouting by aminergic and cholinergic afferents in the hippocampal formation. Brain Res 1983;268:39–47.
[62] Gibson JJ. The ecological approach to visual perception. Boston: Houghton-Mifflin Co, 1979.
[63] Giorgi A. Toward the articulation of psychology as a coherent discipline. In: Koch S, Leary DE, editors. A century of psychology as science. New York: McGraw-Hill, 1985:46–59.
[64] Glick SD, Meibach RC, Cox RD, Maayani S. Phencyclidine-induced rotation and hippocampal modulation of nigrostriatal asymmetry. Brain Res 1980;196:99–107.
[65] Gol A, Faibish GM. Effects of human hippocampal ablation. J Neurosurg 1967;26:390–8.
[66] Grafman J, Salazar A, Weingartner H, Vance S, Amin D. The relationship of brain–tissue loss volume and lesion location to cognitive deficit. J Neurosci 1986;6:301–7.
[67] Green JD, Maxwell DS, Schindler WJ, Stumpf C. Rabbit EEG "theta" rhythm: its anatomical source and relation to activity in single neurons. J Neurophysiol 1960;23:403–20.
[68] Green JD, Morin F. Hypothalamic electrical activity and hypothalamo–cortical relationships. Am J Physiol 1953;172:175–86.
[69] Haberly LB, Price JL. Association and commissural fiber systems of the olfactory cortex of the rat. I. Systems originating in the pyriform cortex and adjacent areas. J Comp Neurol 1978;178:711–40.
[70] Habets AMMC, Lopes da Silva FH, Mollevanger WJ. An olfactory input to the hippocampus of the cat: field potential analysis. Brain Res 1980;182:47–64.
[71] Halgren E. Firing of human hippocampal units in relation to voluntary movements. Hippocampus 1991;1:153–62.
[72] Hargreaves EL, Cain DP, Vanderwolf CH. Learning and behavioral—long-term potentiation: importance of controlling for motor activity. J Neurosci 1990;10:1472–8.
[73] Heale VR, Petersen K, Vanderwolf CH. Effects of colchicine-induced cell loss in the dentate gyrus and Ammon's horn on the olfactory control of feeding in rats. Brain Res 1996;712:213–20.

[74] Heale VR, Vanderwolf CH. Toluene and weasel (2-propylthietane) odors suppress feeding in the rat. J Chem Ecol 1994;20:2953–8.
[75] Heale VR, Vanderwolf CH. Odor-induced fast waves in the dentate gyrus depend on a pathway through posterior cerebral cortex: effects of limbic lesions and trimethyltin. Brain Res Bull 1999;50:291–9.
[76] Heale VR, Vanderwolf CH, Kavaliers M. Components of weasel and fox odors elicit fast wave bursts in the dentate gyrus of rats. Behav Brain Res 1994;63:159–65.
[77] Heimer L, Alheid GF, Zaborsky L. Basal ganglia. In: Paxinos G, editor. The rat nervous system, forebrain and midbrain, vol. 1. Sydney: Academic Press, 1985:37–86.
[78] Herrick CJ. The functions of the olfactory parts of the cerebral cortex. Proc Nat Acad Sci 1933;19:7–14.
[79] Hinsey JC, Ranson SW, McNattin RF. The role of the hypothalamus and mesencephalon in locomotion. Arch Neurol Psychiatr 1930;23:1–43.
[80] Holstege G. Descending motor pathways and the spinal motor system: limbic and non-limbic components. Progr Brain Res 1991;87:307–421.
[81] Horel JA. The neuroanatomy of amnesia: a critique of the hippocampal memory hypothesis. Brain 1978;101:403–45.
[82] Horel JA. Some comments on the special cognitive functions claimed for the hippocampus. Cortex 1994;30:269–80.
[83] Irle E, Wowra B, Kunert HJ, Hampl J, Kunze S. Memory disturbances following anterior communicating artery rupture. Ann Neurol 1992;31:473–80.
[84] Jones-Gotman M, Zatorre RJ. Olfactory identification deficits in patients with focal cerebral excision. Neuropsychologia 1988;26:387–400.
[85] Jung R, Kornmuller AE. Eine methodik der ableitung lokalisierter potentialschwankungen aus subcorticalen hirngebieten. Archiv Psychiat Nervenkrankh 1938;109:1–30.
[86] Kappers CUA, Huber GC, Crosby EC. The comparative anatomy of the nervous system of vertebrates including man. New York: Hafner, 1936 reprinted in 1965.
[87] Kartsounis LD, Rudge P, Stevens JM. Bilateral lesions of CA1 and CA2 fields of the hippocampus are sufficient to cause a severe amnesic syndrome in humans. J Neurol Neurosurg Psychiat 1995;59:95–8.
[88] Kim C. Nest building, general activity and salt preference of rats following hippocampal ablation. J Comp Physiol Psychol 1960;53:11–6.
[89] Kimble DP. The effects of bilateral hippocampal lesions in rats. J Comp Physiol Psychol 1963;56:273–83.
[90] Kimble DP, Rogers L, Hendrickson CW. Hippocamal lesions disrupt maternal, not sexual, behavior in the albino rat. J Comp Physiol Psychol 1967;63:401–7.
[91] Kolb B. Brain plasticity and behavior. Mahwah, NJ: Lawrence Erlbaum, 1995.
[92] Kolb B, Nonneman AJ. Frontolimbic lesions and social behavior in the rat. Physiol Behav 1974;13:637–43.
[93] Kolb B, Pittman K, Sutherland RJ, Whishaw IQ. Dissociation of the contributions of the prefrontal cortex and the dorsomedial thalamic nucleus to spatially guided behavior in the rat. Behav Brain Res 1982;6:365–78.
[94] Kolb B, Sutherland RJ, Whishaw IQ. A comparison of the contributions of the frontal and parietal association cortex to spatial localization in rats. Behav Neurosci 1983;97:13–27.
[95] Kooistra CA, Heilman KM. Memory loss from a subcortical white matter infarct. J Neurol Neurosurg Psychiat 1988;51:866–9.
[96] Kubie JL, Muller RU, Bostock E. Spatial firing properties of hippocampal theta cells. J Neurosci 1990;10:1110–23.
[97] Kubie JL, Muller RU, Fox SE. Firing fields of hippocampal place cells: interim report. In: Buzsáki G, Vanderwolf CH, editors. Electrical activity of the archicortex. Budapest: Akademiai Kiadó, 1985:221–31.
[98] Lashley KS. Brain mechanisms and intelligence: a quantitative study of injuries to the brain. IL: University of Chicago Press, 1929.
[99] Lashley KS. Studies of cerebral function in learning. XII. Loss of the maze habit after occipital lesions in blind rats. J Comp Neurol 1943;79:431–62.
[100] Lepage M, Habib R, Tulving E. Hippocampal PET activations of memory encoding and retrieval: the HIPER model. Hippocampus 1998;8:313–22.
[101] Leung LS. Fast (beta) rhythms in the hippocampus: a review. Hippocampus 1992;2:93–8.
[102] Leung LS. Generation of theta and gamma rhythms in the hippocampus. Neurosci Biobehav Rev 1998;22:275–90.
[103] Leung LS, Lopes da Silva FH, Wadman WJ. Spectral characteristics of the hippocampal EEG in the freely moving rat. Electroenceph Clin Neurophysiol 1982;54:203–19.
[104] Leung L-WS, Yim CY. Intracellular records of theta rhythm in hippocampal CA1 cells of the rat. Brain Res 1986;367:323–7.
[105] Levitt DR, Teitelbaum P. Somnolence, akinesia, and sensory activation of motivated behavior in the lateral hypothalamic syndrome. Proc Natl Acad Sci USA 1975;72:2819–23.
[106] Lomo T. Patterns of activation in a monosynaptic cortical pathway: the perforant path input to the dentate area of the hippocampal formation. Exp Brain Res 1971;12:18–45.
[107] Lopes de Siva FH, Arnolds DEAT, Neijt HC. A functional link between the limbic cortex and ventral striatum: physiology of the subiculum accumbens pathway. Exp Brain Res 1984;55:205–14.
[108] Loy R, Moore RY. Anomalous innervation of the hippocampal formation by peripheral sympathetic axons following mechanical injury. Exp Neurol 1977;57:645–50.
[109] Lubar JF, Middaugh LD. Avoidance conditioning in cats with striate and auditory cortex lesions and contrasting effects of peripheral blindness. J Comp Physiol Psychol 1971;76:26–30.
[110] Luskin MB, Price JL. The topographic organization of associational fibers of the olfactory system in the rat including centrifugal fibers to the olfactory bulb. J Comp Neurol 1983;216:264–91.
[111] Lykken DT. What's wrong with psychology anyway? In: Cicchetti JD, Grove WM, editors. Thinking clearly about psychology: matters of public interest, vol. 1. Minneapolis: University of Minnesota Press, 1991:3–39.
[112] Ma J, Brudzynski SM, Leung L-WS. A role of subicular and hippocampal after discharges in initiation of locomotor activity in rats. Brain Res 1998;793:112–8.
[113] Ma J, Leung L-WS. Medial septum mediates the increase in post-ictal behaviors and hippocampal gamma waves after an electrically induced seizure. Brain Res 1999;833:51–7.
[114] Ma J, Leung L-WS. Relation between hippocampal $\gamma$ waves and behavioral disturbances induced by phencyclidine and methamphetamine. Behav Brain Res 2000;111:1–11.
[115] MacLean PD. Psychosomatic disease and the "visceral brain": recent developments bearing on the Papez theory of emotion. Psychosomat Med 1949;11:338–53.
[116] Markowitsch HJ, Calabrese P, Liess J, Haupts M, Darwen HF, Gehlen W. Retrograde amnesia after traumatic injury of the fronto–temporal cortex. J Neurol Neurosurg Psychiat 1993;56:988–92.
[117] McLean JH, Shipley MT. Neuroanatomical substrates of olfaction. In: Serby MJ, Chobor KL, editors. Science of olfaction. New York: Springer, 1992:126–71.
[118] McNaughton BL, Barnes CA, O'Keefe J. The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. Exp Brain Res 1983;52:41–9.

[119] Meudell P, Butters N, Montgomery K. The role of rehearsal in the short-term memory performance of patients with Korsakoff's and Huntington's disease. Neuropsychologia 1978;16:507–10.
[120] Milner B. Amnesia following operation on the temporal lobes. In: Whitty CWM, Zangwill OL, editors. Amnesia. New York: Appleton-Century-Crofts, 1966:109–33.
[121] Mitchell SJ, Ranck JB Jr. Generation of theta rhythm in medial entorhinal cortex of freely moving rats. Brain Res 1980;189:49–66.
[122] Mogenson GJ, Nielsen M. A study of the contribution of hippocampal-accumbens-subpallidal projections to locomotor activity. Behav Neural Biol 1984;42:38–51.
[123] Morris RGM, Garrud P, Rawlings N, O'Keefe J. Place navigation impaired in rats with hippocampal lesions. Nature 1982;297:681–3.
[124] Moser E, Mathiesen I, Andersen P. Association between brain temperature and dentate field potentials in exploring and swimming rats. Science 1993;259:1324–6.
[125] Motles E, González M. Motor effects of electrical and cholinergic stimulation of the cat's dorsal hippocampus. Arch Ital Biol 1984;122:225–36.
[126] Muller RU, Kubie JL. The effect of changes in the environment on the spatial firing of hippocampal complex-spike cells. J Neurosci 1987;7:1951–68.
[127] Muller RU, Kubie JL, Ranck JB Jr. Spatial firing patterns of hippocampal complex-spike cells in a fixed environment. J Neurosci 1987;7:1935–50.
[128] Nauta WJH. An experimental study of the fornix system in the rat. J Comp Neurol 1956;104:247–71.
[129] Nauta WJH. Hippocampal projections and related neural pathways to the mid-brain in the cat. Brain 1958;80:319–41.
[130] Neafsey EJ. The complete ratunculus: output organization of layer V of the cerebral cortex. In: Kolb B, Tees RC, editors. The cerebral cortex of the rat. Cambridge, MA: MIT Press, 1990:197–212.
[131] Nieuwenhuys R, Geeraedts LMG, Veening JG. The medial forebrain bundle of the rat. I. General introduction. J Comp Neurol 1982;206:49–81.
[132] Nunez A, Garcia-Austt E, Buno W Jr. Intracellular Ø-rhythm generation in identified hippocampal pyramids. Brain Res 1987;416:287–300.
[133] Oddie S, Stefanek W, Kirk IJ, Bland BH. Intraseptal procaine abolishes hypothalamic stimulation-induced wheel-running and hippocampal theta field activity in rats. J Neurosci 1996;16:1948–56.
[134] O'Keefe J. Place units in the hippocampus of the freely moving rat. Exp Neurol 1976;51:78–109.
[135] O'Keefe J. A review of the hippocampal place cells. Progr Neurobiol 1979;13:419–39.
[136] O'Keefe J, Dostrovsky J. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely moving rat. Brain Res 1971;34:171–5.
[137] O'Keefe J, Nadel L. The hippocampus as a cognitive map. Oxford: Clarendon Press, 1978.
[138] Orbach J. Disturbance of the maze habit following occipital cortex removals in blind monkeys. Arch Neurol Psychiat 1959;81:49–541.
[139] Øverby SE, Bjaalie JG, Brodal P. Uneven densities of corticopontine neurons in the somatosensory cortex: a quantitative experimental study in the cat. Exp Brain Res 1989;77:653–65.
[140] Papez JW. A proposed mechanism of emotion. Arch Neurol Psychiat 1937;38:725–44.
[141] Penfield W, Jasper H. Epilepsy and the functional anatomy of the human brain. Boston: Little, Brown, 1954.
[142] Penfield W, Milner B. Memory deficit produced by bilateral lesions in the hippocampal zone. AMA Arch Neurol Psychiat 1958;79:475–97.
[143a] Pennartz CMA, Groenenwegen HJ, Lopes da Silva FH. The nucleus accumbens as a complex of functionally distinct neuronal ensembles: an integration of behavioral, electrophysiological and anatomical data. Progr Neurobiol 1994;42:719–61.
[143b] Petrides M. Mapping prefrontal cortical systems for the control of cognition. In: Toga AW, Mazziota JC, editors. Brain mapping: the systems. San Diego: Academic Press, 2000:159–76.
[144] Ranck JB Jr. Studies on single neurons in dorsal hippocampal formation and septum in unrestrained rats. Part 1. Behavioral correlates and firing repertoires. Exp Neurol 1973;41:461–531.
[145] Robinson TE, Whishaw IQ. Effects of posterior hypothalamic lesions on voluntary behavior and hippocampal electroencephalograms in the rat. J Comp Physiol Psychol 1974;86:768–86.
[146] Robertson BJ, Boon F, Cain DP, Vanderwolf CH. Behavioral effects of anti-muscarinic anti-serotonergic, and anti-NMDA treatments: hippocampal and neocortical slow wave electrophysiology predict the effects on grooming in the rat. Brain Res 1999;838:234–40.
[147] Rose G. Physiological and behavioral characteristics of dentate granule cells. In: Seifert W, editor. Neurobiology of the hippocampus. London: Academic Press, 1983:449–72.
[148] Rowntree CI, Bland BH. An analysis of cholinoceptive neurons in the hippocampal formation by direct microinfusion. Brain Res 1986;362:98–113.
[149] Ruit KG, Neafsey EJ. Cardiovascular and respiratory responses to electrical and chemical stimulation of the hippocampus in anesthetized and awake rats. Brain Res 1988;457:310–21.
[150] Sainsbury RS. Hippocampal activity during natural behavior in the guinea pig. Physiol Behav 1970;5:317–24.
[151] Sainsbury RS, Jason GW. Fimbria–fornix lesions and sexual-social behavior of the guinea pig. Physiol Behav 1976;17:963–7.
[152] Saint-Cyr JA, Woodward DJ. Activation of mossy and climbing fibers to the cerebellar cortex by stimulation of the fornix in the rat. Exp Brain Res 1980;40:1–12.
[153] Saint-Cyr JA, Woodward DJ. A topographic analysis of limbic and somatic inputs to the cerebellar cortex in the rat. Exp Brain Res 1980;40:13–22.
[154] Schnider A, Gutbrod K, Hess CW, Schroth G. Memory without context: amnesia with confabulations after infarction of the right capsular genu. J Neurol Neurosurg Psychiat 1996;61:186–93.
[155] Schwerdtfeger WK, Buhl EH, Germroth P. Disynaptic olfactory input to the hippocampus mediated by stellate cells in the entorhinal cortex. JComp Neurol 1990;292:163–77.
[156] Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiat 1957;20:11–21.
[157] Sharp PE, Kubie JL, Muller RU. Firing properties of hippocampal neurons in a visually symmetrical environment: contributions of multiple sensory areas and mnemonic processes. J Neurosci 1990;10:3093–105.
[158] Sharp PE, McNaughton BL, Barnes CA. Enhancement of hippocampal field potentials in rats exposed to a novel complex environment. Brain Res 1985;339:361–5.
[159] Sherrington C. The integrative action of the nervous system. New Haven: Yale University Press, 1906 republished 1961.
[160] Shipley JE, Kolb B. Neural correlates of species-typical behavior in the Syrian golden hamster. J Comp Physiol Psychol 1977;91:1056–73.
[161] Soltesz I, Deschênes M. Low and high-frequency membrane potential oscillations during theta activity in CA1 and CA3 pyramidal neurons of the rat hippocampus under ketamine-xylazine anesthesia. J Neurophysiol 1993;70:1–20.

[162] Stefanacci L, Buffalo EA, Schmolck H, Squire LR. Profound amnesia after damage to the medial temporal lobe: a neuroanatomical and neuropsychological profile of patient, E.P. J Neurosci 2000;20:7024–36.
[163] Stenevi U, Bjorklund A. Growth of vascular sympathetic axons into the hippocampus after lesions of the septo-hippocampal pathway: a pitfall in brain lesion studies. Neurosci Lett 1978;7:219–24.
[164] Stent GS. Limits to the scientific understanding of man: human sciences face an impasse since their central concept of the self is transcendental. Science 1975;187:1052–7.
[165] Steriade M, Amzica F, Contreras D. Synchronization of fast (30–40 Hz) spontaneous cortical rhythms during brain activation. J Neurosci 1996;16:392–417.
[166] Steriade M, Contreras D, Amzica F, Timofeev I. Synchronization of fast spontaneous oscillations in intrathalamic and thalamocortical networks. J Neurosci 1996;16:2788–808.
[167] Stewart M, Fox SE. Hippocampal theta activity in monkeys. Brain Res 1991;538:59–63.
[168] Stewart M, Quirk GJ, Barry M, Fox SE. Firing relations of medial entorhinal neurons to the hippocampal theta rhythm in urethane anesthetized and walking rats. Exp Brain Res 1992;90:21–8.
[169] Stoddart DM. The ecology of vertebrate olfaction. London: Chapman and Hall, 1980.
[170] Sutherland RJ, Kolb B, Whishaw IQ. Spatial mapping: definitive disruption by hippocampal or medial frontal cortical damage in the rat. Neurosci Lett 1982;31:271–6.
[171] Sutherland RJ, Whishaw IQ, Kolb B. A behavioral analysis of spatial localization following electrolytic, kainate- or colchicine-induced damage to the hippocampal formation in the rat. Behav Brain Res 1983;7:133–53.
[172] Sutherland RJ, Whishaw IQ, Kolb B. Contributions of cingulate cortex to two forms of spatial learning and memory. J Neurosci 1988;8:1863–72.
[173] Swann HG. The function of the brain in olfaction. II. The results of destruction of olfactory and other nervous structures upon the discrimination of odors. J Comp Neurol 1934;59:175–201.
[174] Swanson LW, Cowan WM. An autoradiographic study of the organization of the efferent connections of the hippocampal formation in the rat. J Comp Neurol 1977;172:49–84.
[175] Swanson LW, Wyss JM, Cowan WM. An autoradiographic study of the organization of intra hippocampal association pathways in the rat. J Comp Neurol 1978;181:681–715.
[176] Switzer RC, DeOlmos J, Heimer L. Olfactory system. In: Paxinos G, editor. The rat nervous system, forebrain and midbrain, vol. 1. Sydney: Academic Press, 1985:1–36.
[177] Takahashi H, Takada Y, Nagai N, Urano T, Takada A. Serotonergic neurons projecting to hippocampus activate locomotion. Brain Res 2000;869:194–202.
[178] Talland GA, Sweet WH, Ballantine HT. Amnesic syndrome with anterior communicating artery aneurysm. J Nerv Ment Dis 1967;145:179–92.
[179] Taylor J. Selected writings of John Hughlings Jackson, vols. 1–2. London: Staples Press, 1958.
[180] Teitelbaum H, Milner P. Activity changes following partial hippocampal lesions in rats. J Comp Physiol Psychol 1963;56:284–9.
[181] Terao Y, Bandou M, Nagura H, Yamanouchi H, Ishikawa T. Persistent amnestic syndrome due to infraction of the genu of the left internal capsule. Rinsho-Shinkeigaku 1991;31(9):1002–6 Japanese, English abstract.
[182] Terlecki LJ, Sainsbury RS. Effects of fimbria lesions on maternal behavior in the rat. Physiol Behav 1978;21:89–97.
[183] Tomlinson BE, Henderson G. Some quantitative cerebral findings in normal and demented old people. In: Terry RD, Gershon S, editors. Neurobiology of aging. New York: Raven Press, 1976:183–204.
[184] Ungerstedt U. Central dopamine mechanisms and unconditioned behavior. In: Horn AS, Korf J, Westerink BHC, editors. The neurobiology of dopamine. London: Academic Press, 1979:577–96.
[185] Vanderwolf CH. Hippocampal electrical activity and voluntary movement in the rat. Electroenceph Clin Neurophysiol 1969;26:407–18.
[186] Vanderwolf CH. Is hippocampal rhythmical slow activity specifically related to movement through space? Behav Brain Sci 1979;2:518–9.
[187] Vanderwolf CH. Cerebral activity and behavior: control by central cholinergic and serotonergic systems. Int Rev Neurobiol 1988;30:225–340.
[188] Vanderwolf CH. Hippocampal activity, olfaction, and sniffing: an olfactory input to the dentate gyrus. Brain Res 1992;593:197–208.
[189] Vanderwolf CH. Brain, behavior, and mind; what do we know and what can we know? Neurosci Biobehav Rev 1998;22:125–42.
[190] Vanderwolf CH. What is the significance of gamma wave activity in the pyriform cortex? Brain Res 2000;877:125–33.
[191] Vanderwolf CH, Cain DP. The behavioral neurobiology of learning and memory: a conceptual reorientation. Brain Res Rev 1994;19:264–97.
[192] Vanderwolf CH, Kelly ME, Kraemer P, Streather A. Are emotion and motivation localized in the limbic system and nucleus accumbens? Behav Brain Res 1988;27:45–58.
[193] Vanderwolf CH, Kolb B, Cooley RK. Behavior of the rat after removal of the neocortex and hippocampal formation. J Comp Physiol Psychol 1978;92:156–75.
[194] Vanderwolf CH, Kramis R, Gillespie LA, Bland BH. Hippocampal rhythmical slow activity and neocortical low voltage fast activity: relations to behavior. In: Isaacson RL, Pribram KH, editors. The hippocampus: neurophysiology and behavior, vol. 2. New York: Plenum Press, 1975:101–28.
[195] Vanderwolf CH, Leung L-WS. The relation of brain electrical activity to behavior. In: Boulton AA, Baker GB, Bateson AN, editors. In vivo neuromethods: neuromethods, vol. 32. Totowa, NJ: Humana Press, 1998:325–57.
[196] Vanderwolf CH, McLauchlin M, Dringenberg HC, Baker GB. Brain structures involved in the behavioral stimulant effect of central serotonin release. Brain Res 1997;772:121–34.
[197] Vanderwolf CH, Penava D. Potentiation of the effects of antimuscarinic drugs on behavior by serotonin depletion: specificity and relation to learning and memory. In: Levin ED, Decker MW, Butcher LL, editors. Neurotransmitters and cognitive function. Boston: Birkhauser, 1992:257–76.
[198] Vanderwolf CH, Zibrowski EM. Pyriform cortex β-waves: odor-specific sensitization following repeated olfactory stimulation. Brain Res 2001;892:301–8.
[199] Vanderwolf CH, Zibrowski EM, Wakarchuk D. The ability of various chemicals to elicit olfactory β-waves in the pyriform cortex of meadow voles (*Microtus pennsylvanicus*) and laboratory rats (*Rattus norvegicus*), unpublished manuscript.
[200] Van Mier H. Human learning. In: Toga AW, Mazziota JC, editors. Brain mapping: the systems. San Diego: Academic Press, 2000:605–20.
[201] Veening JG, Swanson LW, Cowan WM, Nieuwenhuys R, Geeraedts LMG. The medial forebrain bundle of the rat. II. An autoradiographic study of the topography of the major descending and ascending components. J Comp Neurol 1982;206:82–108.
[202] Victor M, Adams RD, Collins GH. The Wernicke-Korsakoff syndrome and related neurologic disorders due to alcoholism and malnutrition, 2nd ed. Philadelphia: Davis, 1989.

[203] Wade DT, Parker V, Langton Hewer R. Memory disturbance after stroke: frequency and associated losses. Int Rehabil Med 1986;8:60–4.
[204] Wall PD, Davis GD. Three cerebral cortical systems affecting autonomic function. J Neurophysiol 1951;14:507–17.
[205] Waxman SG. Thalamic amnesia: clinical and experimental aspects. Int Rev Neurobiol 1988;29:245–57.
[206] Way JS. An oscillographic study of afferent connections to the hippocampus in the cat (*Felis domesticus*). Electroenceph Clin Neurophysiol 1962;14:78–89.
[207] Weisendanger R, Wiesendanger M. The corticopontine system in the rat. I. Mapping of corticopontine neurons. J Comp Neurol 1982;208:215–26.
[208] Weisendanger R, Wiesendanger M. The corticopontine system in the rat. II. The projection pattern. J Comp Neurol 1982;208:227–38.
[209] Welker WI. Analysis of sniffing of the albino rat. Behaviour 1964;22:223–44.
[210] Whishaw IQ. Activation, travel distance, and environmental change influence food carrying in rats with hippocampal, medial thalamic and septal lesions: implications for studies on hoarding and theories of hippocampal function. Hippocampus 1993;3:373–85.
[211] Whishaw IQ, Bland BH, Vanderwolf CH. Hippocampal activity, behavior, self-stimulation, and heart rate during electrical stimulation of the lateral hypothalamus. J Comp Physiol Psychol 1972;79:115–27.
[212] Whishaw IQ, Cassel J-C, Jarrard LE. Rats with fimbria–fornix lesions display a place response in a swimming pool: a dissociation between getting there and knowing where. J Neurosci 1995;15:5779–88.
[213] Whishaw IQ, Cassel J-C, Majchrzak M, Cassel S, Will B. "Short-stops" in rats with fimbria–fornix lesions: evidence for change in the mobility gradient. Hippocampus 1994;4:577–82.
[214] Whishaw IQ, Mittleman G, Bunch ST, Dunnett SB. Impairments in the acquisition, retention, and selection of spatial strategies after medial caudate-putamen lesions in rats. Behav Brain Res 1987;24:125–38.
[215] Whishaw IQ, Nikkel RW. Anterior hypothalamic electrical stimulation and hippocampal EEG in the rat: suppressed EEG, locomotion, self-stimulation and inhibition of shock avoidance. Behav Biol 1975;13:1–20.
[216] Whishaw IQ, O'Connor WT, Dunnett SB. Disruption of central cholinergic systems in the rat by basal forebrain lesions or atropine: effects on feeding, sensorimotor behavior, locomotor activity and spatial navigation. Behav Brain Res 1985;17:103–15.
[217] Whishaw IQ, Vanderwolf CH. Hippocampal EEG and behavior: changes in amplitude and frequency of RSA (theta rhythm) associated with spontaneous and learned movement patterns in rats and cats. Behav Biol 1973;8:461–84.
[218] Wilson RC, Steward O. Polysynaptic activation of the dentate gyrus of the hippocampal formation: an olfactory input via the lateral entorhinal cortex. Exp Brain Res 1978;33:523–34.
[219] Winson J. Patterns of hippocampal theta rhythm in the freely moving rat. Electrenceph Clin Neurophysiol 1974;36:291–301.
[220] Wolpaw JR, Lee CL. Memory traces in primate spinal cord produced by operant conditioning of H-reflex. J Neurophysiol 1989;61:563–72.
[221] Woo CC, Coopersmith R, Leon M. Localized changes in olfactory bulb morphology associated with early olfactory learning. J Comp Neurol 1987;263:113–25.
[222] Woods JW. Behavior of chronic decerebrate rats. J Neurophysiol 1964;27:635–44.
[223] Wynne LC, Solomon RL. Traumatic avoidance learning: acquisition and extinction in dogs deprived of normal peripheral autonomic function. Genet Psychol Monogr 1955;52:241–84.
[224] Yokota T, Reeves AG, MacLean PD. Differential effect of septal and olfactory volleys on intracellular responses of hippocampal neurons in awake, sitting monkeys. J Neurophysiol 1970;33:96–107.
[225] Zatorre RJ, Jones-Gotman M. Human olfactory discrimination after unilateral frontal or temporal lobectomy. Brain 1991;114:71–84.
[226] Zibrowski EM, Hoh TE, Vanderwolf CH. Fast wave activity in the rat rhinencephalon: elicitation by the odors of phytochemicals, organic solvents, and a rodent predator. Brain Res 1998;800:207–15.
[227] Zibrowski EM, Vanderwolf CH. Oscillatory fast wave activity in the rat pyriform cortex: relations to olfaction and behavior. Brain Res 1997;766:39–49.
[228] Zola-Morgan S, Squire LR, Amaral DG. Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. J Neurosci 1986;6:2950–67.