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Hippocampal activity, olfaction, and sniffing: an olfactory input to the dentate gyrus

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Experiments in freely moving rats showed that olfactory stimuli elicit a burst of rhythmical 15–30 Hz waves in or near the hilus of the dentate gyrus but not in adjacent regions of CA1. This fast wave burst is not elicited by visual, auditory, or somatosensory inputs and is not related to motor activity. Electrical stimulation of the olfactory bulb evokes a complex potential in the hilus of the dentate gyrus but not in adjacent regions of CA1. Experiments making use of wave-triggered averaging demonstrated that there is a degree of phase-locking between (a) hippocampal RSA and sniffing or other respiratory patterns, (b) hippocampal RSA and the initiation of jumping, and (c) respiration and the initiation of jumping. An early hypothesis that the hippocampus and dentate gyrus are part of an olfacto-motor mechanism may merit re-examination.

INTRODUCTION

In the early years of this century, neuroanatomists considered that the hippocampal formation was primarily, but not exclusively, an olfacto-motor structure. The granule cells of the dentate gyrus were considered to play a receptive role analogous to the cells of the internal granular layer of the neocortex, while the large pyramidal cells of Ammon's horn were considered to have an effectory or motor function analogous to the large, deeply located pyramidal cells of the neocortex[8,22]. However, since hippocampal ablation had little or no effect on olfactory discrimination[2,45] and since olfactory bulb efferents do not reach the hippocampus directly, these views were abandoned[8]. Instead, the hippocampus came to be regarded as being involved in emotion[37], visceral and emotional functions[29], memory[33,41] and spatial-cognitive abilities[34].

Studies in freely moving animals have shown that hippocampal slow wave activity is strongly correlated with motor activity[46,47], a finding that may be regarded as consistent with the earlier view that Ammon's horn has an effectory or motor function. Anatomical data[40] and electrophysiological studies in anesthetized animals[12,17,50,53] indicate that the olfactory bulb communicates with the dentate gyrus via the entorhinal cortex and perforant path, a pathway involving a minimum of two synapses. However, there are no data demonstrating the operation of this pathway in a behaving animal responding to odorants.

Under some circumstances there is a significant phase relation or coupling between hippocampal rhythmical slow activity (RSA) and sniffing behavior[27,30,31]. Macrides et al.[31] suggest that septal cells that act as pacemakers for RSA also influence the respiratory rhythm of sniffing. In addition, there have been reports that there is a non-random phase relation between hippocampal RSA and the occurrence of lever pressing in rats[9,42].

Many years ago, during the course of work on the behavioral correlates of RSA in freely moving rats[46], I noticed an enhancement of fast wave activity in the dentate gyrus during sniffing. In the experiments described here, this phenomenon, hitherto unreported, has been investigated more fully. The relation of RSA to olfactory input and sniffing has also been studied.

MATERIALS AND METHODS

Thirty-one male hooded rats, weighing 340–530 g, were anesthetized with pentobarbital. Using a stereotaxic instrument[11,38] elec-

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trodes were placed in the hippocampal formation and the olfactory bulb or near the olfactory mucosa. The electrodes consisted of stainless steel wire, 125 μm in diameter, insulated with Teflon except for the cross-sectional area of the tip, and soldered to subminiature gold-plated connectors. Screw-type electrodes fixed in the skull provided a ground connection (frontal bone) and an electrically quiet indifferent site (interparietal bone). Hippocampal electrodes (2–4 per rat) were placed, bilaterally or on the right side only, in or near the hilus of the dentate gyrus, in or near the hippocampal fissure, and in or near the stratum oriens of CA1. One electrode was placed in the deep layers of the olfactory bulb and one was placed on or near its dorsal surface. An electrode intended to monitor the activity of the olfactory mucosa was placed in the labyrinth of the ethmoid bone (3–4 mm rostral to the cribriform plate, 1.0 mm lateral to the midline, and 2.0 mm below the skull surface). Finally, the shortened plastic hub of a hypodermic needle (scored on the outside to improve adhesion to dental cement) was placed vertically over the left parietal bone. The entire assembly was fixed to the skull with stainless steel screws and dental cement.

Experiments began after a recovery period of at least two weeks. The activity of the olfactory mucosa, the olfactory bulb, the hippocampal formation, and the outputs from movement-sensing devices, were recorded using an ink-writing polygraph (Grass Instruments), a storage oscilloscope (Tektronix) and an averager (Neurolog, 256 sample points/sweep). The frequency bands used were 1–75 Hz in the case of the ink writer and 1–3,000 Hz (half amplitude points) in the case of the oscilloscope. The movement sensors consisted of (a) a light platform (on which the rat was placed), mounted on foam rubber pads and attached to a magnet inserted in a coil, and (b) a miniature magnet-and-coil device (10 g mass) which could be mounted in the hypodermic needle hub fixed on the rats' head. This device contained an inverted L-shaped arm made from two pieces of hypodermic tubing and a short piece of stiff nylon monofilament (fishing line) secured in the vertical part of the L, bridging a gap between the two pieces of tubing. The horizontal part of the L bore a lead weight and a tiny magnet (from a magnetic stirring bar) which was inserted in a small coil. During movement, the inertia of the lead weight resulted in torsion of the nylon filament and movement of the magnet relative to the coil.

The extracellular field potentials of the olfactory mucosa, olfactory bulb, and hippocampal formation were studied by wave-triggered averaging. By this method, spontaneous waveforms were smoothed by passage through a band-pass filter (24 db roll-off per octave) and lead to a window discriminator. The output pulses from the discriminator, triggered from negative or positive wave peaks, triggered the averager, which processed waveforms that had not been filtered. This method permits averages to be made from (a) multiple samples of activity from a single electrode site, or (b) multiple samples of activity from one site triggered by activity at another site. These averages, presenting data as a function of time, are comparable in some respects to auto-correlation and cross-correlation, respectively, which present data as a function of frequency. However, wave-triggered averaging does not result in an average of activity following each wave in the sample. For example, if a given hippocampal RSA wave triggers the averager, the succeeding waves occurring during the sweep time of the averager are not used to trigger averages themselves.

In some experiments, the output pulses of the window discriminator, triggered by 6–12 Hz band-pass filtered hippocampal activity, were displayed on the polygraph. This provided a simple RSA detector.

Waveforms passed through the band-pass filter were also rectified, integrated by an R-C circuit, and the result displayed on the polygraph. The foregoing methods were used to study olfaction-related activity in several behavioral situations. Odorous substances were presented to the rats' nostrils directly or, in the case of odorous liquids, via a Q-tip (a small wooden stick with cotton fluff wrapped tightly around one end). Stimuli were presented when the rat stood motionless and was not already sniffing. The substances tested included: acetone, ammonia, cedarwood oil, coffee, cologne, fresh dandelion blossoms, dioxane, ethyl alcohol, ethyl ether, formaldehyde, ink, lanolin, lubricating oil, methyl butane, methyl methacrylate, orange extract, plasticene, rat food pellets, rat litter (soiled sawdust taken from under rat cages and presented in a teaspoon), rubber stoppers, toluene, vaginal swabs from estrual or non-estrual female rats, vanilla extract, and xylene. Control stimuli included: dry Q-tips, distilled water, auditory stimuli (dropping objects on the floor, firing a starter pistol), somatosensory stimuli (touching or tapping various parts of the body) and visual stimuli (flashing lights, moving objects in the visual field). Stimuli were presented in an irregular series at intervals of about 30 s. An individual item was usually presented three times before moving on to a different item, and items with interesting effects were repeated as often as 50 times on a single test day. The effect of placing a second rat on the recording platform was also observed.

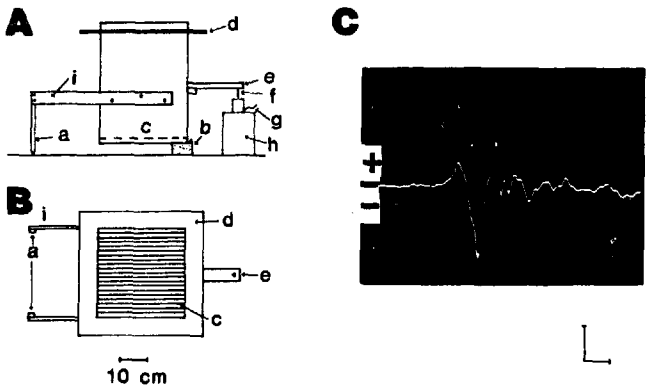

Fig. 1. A schematic drawing of the avoidance apparatus and movement sensor from the side (A) and the top (B). a, pointed wooden dowels which act as pivots; b, foam rubber blocks; c, grid floor; d, cat-walk for rat to rest on during inter-trial intervals; e, wooden support; f, round bar magnet fixed in a hole in e; g, coil from a relay with wires leading to an amplifier; h, wooden block; i, wooden support fixed to the box. During use, the block, h, was raised so that the magnet was located well inside the coil. C: oscilloscope record of movement sensor output as a rat jumps out of the box. The initial positive deflection is due to a lowering of the floor as the rat's hind feet thrust downwards; the initial negative deflection is due to the upward rebound of the box after the rat has left the floor. The dot indicates the output pulse from a window discriminator triggered by the initial negative deflection. Calibration for C, horizontal 50 ms and vertical 50 mV.

After these tests, the effect of electrical stimulation of the olfactory bulb was observed. Single pulses (0.1 ms duration) were applied (deep electrode negative, surface electrode positive) to the electrode pair in the olfactory bulb at intervals of several seconds and average evoked responses were obtained from sites in the hippocampal formation. This procedure was carried out a second time in a terminal experiment after the rats had been anesthetized with urethane (1.0–1.5 g/kg).

Seven rats with electrodes yielding RSA of at least 1.0 mV were trained to avoid electric shock by jumping out of a box (Fig. 1). The training procedure has been described[48]. In brief, rats placed in the box were allowed 10 s to jump out to a height of 35.5 cm. Failure to jump was punished by brief shocks from an old Harvard inductorium that produced rather irregular repetitive brief potentials of 500–600 V. Recording began after the rats had received at least 100 training trials and were jumping very reliably. Average records of hippocampal activity and olfactory mucosal activity were taken during the period prior to and during the initiation of the jump response. This was achieved by triggering the averager by the potentials generated by a movement sensor attached to the avoidance apparatus (see Fig. 1) and passing the signal to be averaged through an analogue delay line. The output of the movement sensor appeared to give an accurate indication of the onset of the jump. A light tap on the apparatus (timed by recording the contact potential occurring when a piece of metal lying on the apparatus was struck by a second piece of metal) produced a response from the movement sensor in 1–3 ms.

Artifact-free records during jumping were ensured by clamping the recording leads[11] in a padded alligator clip that had been cemented to the tip of a 1.0 ml plastic syringe that, in turn, could be seated firmly in the needle hub cemented to the skull.

All rats were given avoidance testing both in the normal state and after the injection of scopolamine hydrobromide (5.0 mg/kg, s.c.).

At the conclusion of the experiments, the rats were deeply anesthetized and perfused through the heart with a saline (0.9%) and a saline plus 10% formalin solution. After several days fixation, frozen coronal sections, taken through the recording sites in the olfactory bulbs and hippocampal formation, were stained with gallocyanin.

Non-parametric statistical tests were used in the analysis of the data[43].

RESULTS

Histology

Histological data were obtained in 25 rats. In all cases the position of the deep hippocampal electrode could be determined, but sometimes the position of the shallow electrode could not be identified (Fig. 2). The deep electrode in the olfactory bulb ($n = 12$) was always located in the deep layers of the structure, usually in or between the glomerular layer and the internal granular layer. The position of the electrode placed in the labyrinth of the ethmoid bone ($n = 13$) was determined by gross dissection in 3 cases only.

Electrical activity and behavior

Electrodes placed in or near the stratum oriens in CA1 or in the region of the hippocampal fissure always yielded clear RSA during type-1 behavior, such as walking, moving the head about, or changing posture. Monopolar recordings from these sites yielded RSA of opposite phase (180° phase reversal), while bipolar recording yielded RSA with an amplitude approximately equal to the sum of the amplitudes at the individual sites (sometimes over 2.5 mV). Electrode tips placed in the hilus of the dentate gyrus, or in the granule cell layer of the dorsal blade of the dentate gyrus, yielded prominent fast activity (15–50 Hz) with an amplitude up to 1.0 mV. Electrodes located in the olfactory mucosa and the olfactory bulb yielded rhythmical waves, closely related to respiration, with some superimposed fast activity.

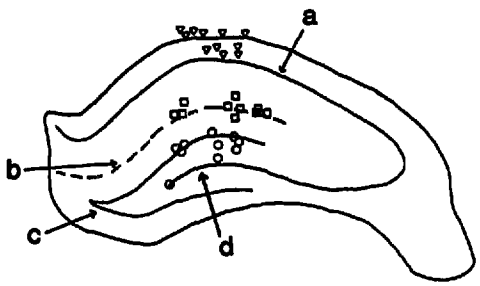

Fig. 2. Electrode sites in the dorsal hippocampal formation. Open circles, sites that yielded a fast wave response when odors were presented to the nose; open squares, sites that yielded large amplitude RSA; open triangles, sites that yielded lower amplitude RSA. The RSA recorded at sites marked with triangles was 180° out of phase with RSA recorded at sites marked with squares. a, CA1 pyramidal cell layer; b, hippocampal fissure; c, granule cell layer; d, CA3 pyramidal cell layer.

Electrical activity at all these sites was affected by olfactory input. When a rat was standing motionless on the recording platform, activity in the stratum oriens and the region of the hippocampal fissure consisted of large amplitude irregular waves, while rhythmical waves of 1–3 Hz occurred in the olfactory mucosa and bulb. If sniffing occurred in the absence of extensive head movement it was accompanied by rhythmical waves of about 6 Hz in the mucosa and bulb and by irregular activity in the hippocampus. The presentation of rat litter, rat food pellets, or Q-tips bearing rat vaginal material, all provoked head movements, vigorous sniffing and, sometimes, stepping forward and nibbling at the stimulus or attempts to grasp it with a paw. These behaviors were accompanied by rhythmical waves of 6–8 Hz in the olfactory mucosa and bulb, and by 7–8 Hz RSA in the hippocampus. Both the behavioral and the electrophysiological responses diminished and disappeared if the same stimulus was presented repeatedly.

When xylene or toluene were presented there was usually no behavioral response, apart from small head movements, on the first 1–6 applications of the stimulus. Clear-cut sniffing (identified both by rhythmical vibrissae movement and by the characteristic rhythmical waves in the olfactory mucosa or olfactory bulb) did not occur (Fig. 3). On later presentations, the rat would turn its head away and either back up or run away. It eventually became difficult to present these stimuli for more than a fraction of a second since the rat would terminate contact immediately or even attempt to avoid the Q-tip as it approached.

In the olfactory mucosa, toluene and xylene produced large negative-going potentials that were often followed by a burst of rhythmical potentials of 12–20 Hz. A positive-going potential, also often followed by a rhythmical burst, occurred in the olfactory bulb (Figs. 3 and 4). Application of toluene or xylene reduced the amplitude of the spontaneous rhythmical waves in both the olfactory mucosa and the olfactory bulb (Fig. 3) to such an extent that such waves sometimes disappeared altogether for a brief period after repeated applications. Hippocampal RSA was very prominent as the rat turned its head and walked or ran away when toluene or xylene were presented (Fig. 3). However, the elicitation of RSA was in no sense specific to olfactory stimuli. Auditory, tactile, and visual stimuli also invariably elicited RSA, provided that such stimuli would

elicit type-1 behavior, such as head movement or locomotion.

In the fast-wave generating sites in the dentate gyrus the odor of toluene or xylene usually produced a burst of fast waves with a frequency in the range of 15–30 Hz (Fig. 4). Although this fast wave response was sometimes seen on the very first application of toluene or xylene, it seemed to appear more strongly after several tests had been made and did not diminish with long continued presentations. In contrast to hippocampal RSA, which developed in rough proportionality to the intensity of the accompanying motor response, the dentate fast wave response occurred in a well-developed form even in the absence of motor activity (Fig. 4). The dentate fast wave response could not be elicited by somatosensory stimuli (picking the rat up, touching or poking various parts of the body), auditory stimuli (hand claps, dropping objects on the floor, report from a starter's pistol), or by visual stimuli (flashing lights, moving objects about in the rats' visual field). This was so even though some of these stimuli, such as picking the rat up or firing the pistol, produced vigorous motor activity (Fig. 4). Hippocampal recording sites near the hippocampal fissure, or dorsal to the CA1 pyramidal cell layer, did not yield a detectable fast wave response to odors (Fig. 4).

Toluene and xylene elicited a clear fast wave response in the dentate gyrus on 50–100% (mean = 80%) of a long series of trials in each of 12 rats with an electrode in the dentate fast wave zone (histological confirmation of this was available in 10 of these rats as shown in Fig. 2). Ethyl ether and methyl methacrylate

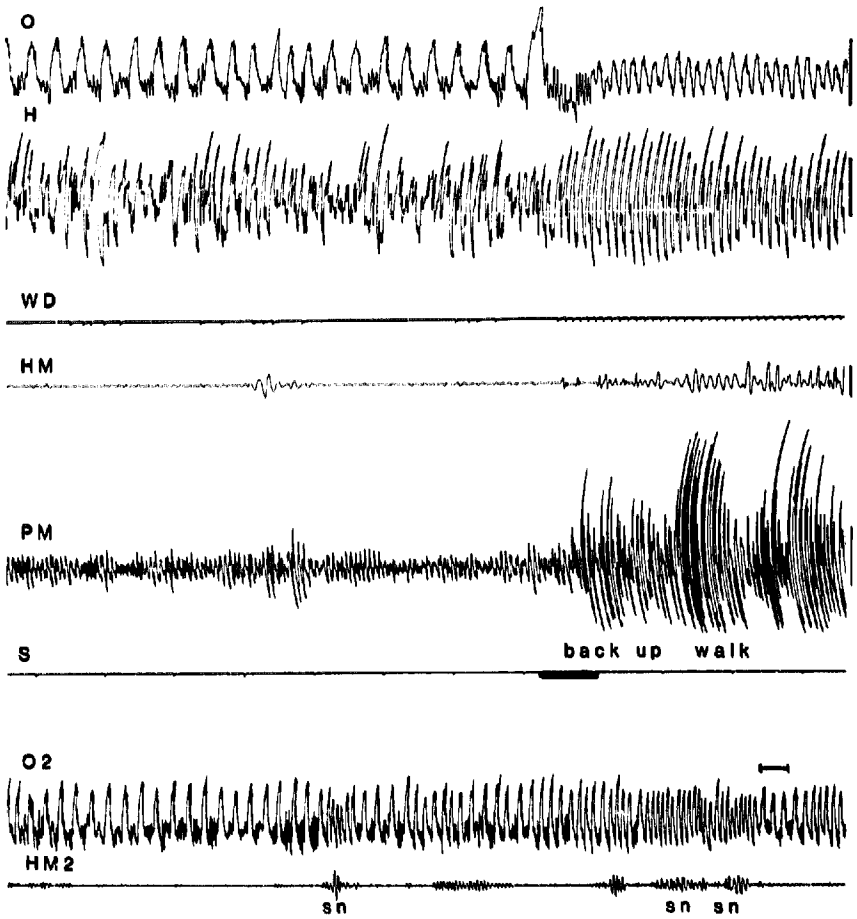

Fig. 3. Activity in the olfactory mucosa and the hippocampus during the presentation of xylene and during spontaneous sniffing. O, monopolar record from olfactory mucosa, negativity up; H, surface-to-depth bipolar record from hippocampus, deep negativity up; WD, output pulses from a window discriminator triggered by the peaks of 6–12 Hz band-pass filtered hippocampal activity; HM, head movement monitored by a sensor on the electrode cup; PM, platform movement sensor indicating the rat's movement; S, application of xylene by means of a Q-tip. Time is in seconds. O2 and HM2 are records from the olfactory mucosa and head-mounted movement sensor during quiet breathing and two episodes of spontaneous sniffing (sn). Time calibration for O2 and MH2 1.0 s. Voltage calibration (upper right): olfactory mucosa 0.5 mV; hippocampus 1.0 mV; head movement 5.0 mV; platform movement 100 mV. Note that xylene produces (1) a large negative potential followed by a burst of fast waves in the olfactory mucosa, (2) well-developed RSA, and (3) a behavior of turning the head, backing up and walking away. The spontaneous activity of the olfactory mucosa is reduced in amplitude for some time following the application of xylene, but sniffing and rhythmical vibrissae movement did not occur even though the respiratory rate rose to about 6 Hz. In the olfactory mucosa, undisturbed quiet breathing is associated with 2–4 Hz large rhythmic potentials and sniffing with 5–7 Hz rhythmical potentials of slightly reduced amplitude.

were almost equally effective (mean = 62%, range = 25–97%). A variety of other stimuli including rat food, formaldehyde, acetone, dioxane, methyl butane, cedarwood oil, lanolin, cologne, vinegar, vanilla extract, orange extract, ethyl alcohol (95% solution), rat vaginal odors, rat litter, and the experimenter's fingers produced a fast wave response on 12% of the tests (range = 2–23%). This is significantly less than the response to toluene or xylene in all cases ($P < 0.02$ or better, using Mann–Whitney or Wilcoxon tests, as appropriate). Rat food pellets were the most effective stimuli of this entire group. Ammonia was ineffective in producing a dentate fast wave response (a positive response was seen once in one rat) even though it elicited a vigorous behavioral response of eye closure, backing up and running away. Clean dry Q-tips failed to produce a fast wave response in the dentate gyrus on all tests but distilled water was effective on 3.1% (range 0–25%) of the tests.

There did not appear to be any necessary correlation between the occurrence of a fast wave response in the dentate gyrus and a fast wave response in the olfactory mucosa or the olfactory bulb. Thus, the occurrence of a fast wave response in the olfactory mucosa or bulb did not guarantee the occurrence of a fast wave response in the dentate gyrus. Further, a fast

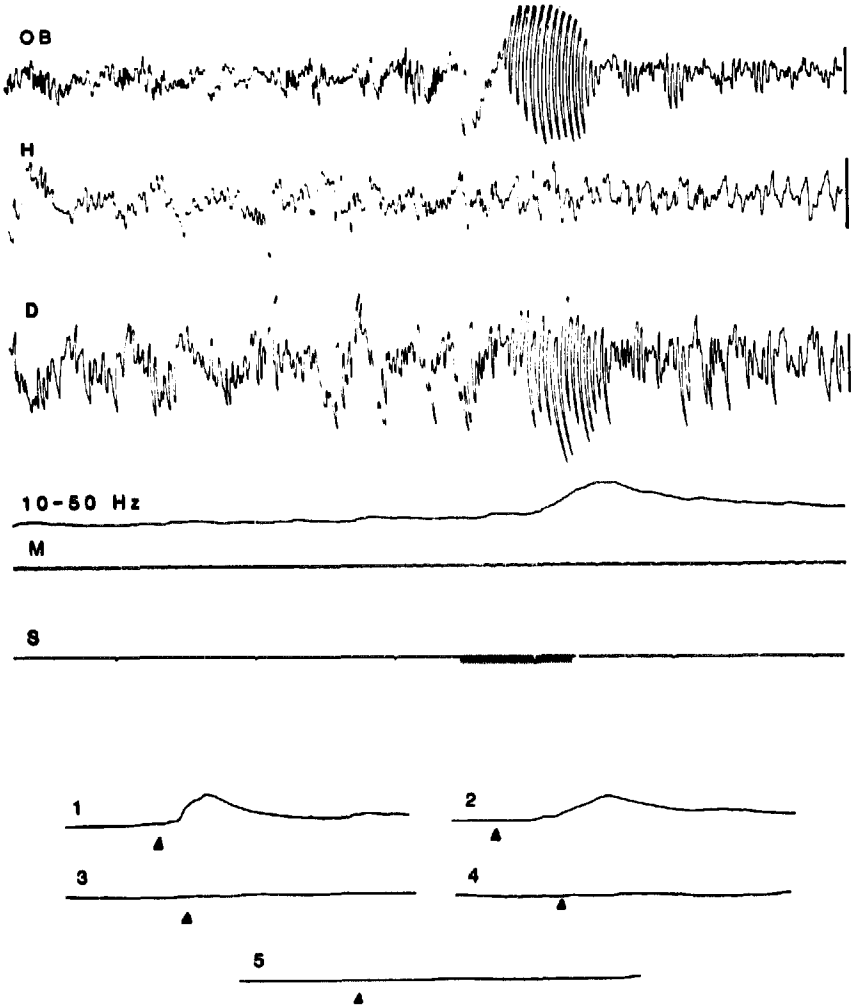

Fig. 4. Activity in the olfactory bulb and the dentate gyrus during the presentation of various sensory stimuli. OB, deep layers of olfactory bulb; H, stratum oriens of CA1; D, site in or just below the granule cell layer of the dorsal blade of the dentate gyrus; 10–50 Hz, integrated 10–50 Hz activity from the dentate record; M, motor activity recorded by the platform sensor; S, presentation of toluene by means of a Q-tip. Time is in seconds. 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.

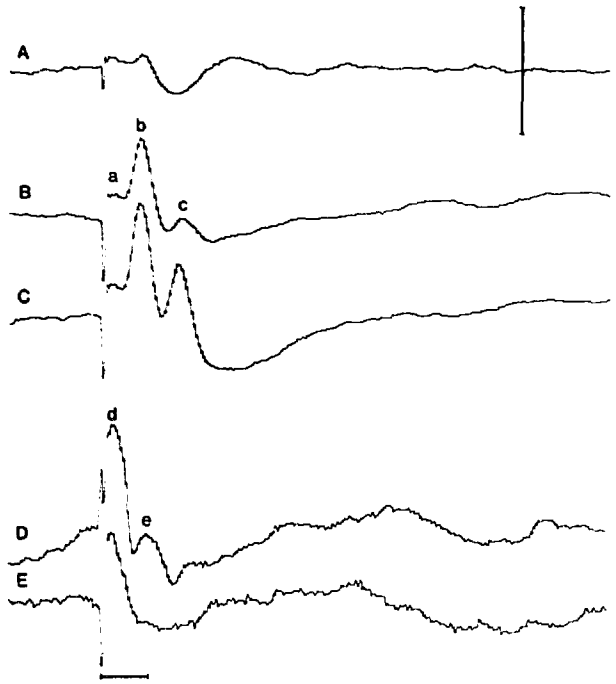

Fig. 5. Average evoked potentials in the dentate gyrus following stimulation of the ipsilateral olfactory bulb. Bulb stimulation was achieved via a bipolar electrode (one pole on the dorsal surface, one in the deep layers) which delivered 0.1 ms pulses (deep electrode negative). Records A–C were derived from a point in the granular cell layer of the dorsal blade of the dentate gyrus; records D and E were derived from the alvear surface of CA1. Initial sharp downward deflection (upwards in D) indicates stimulus artifact. Pulses were delivered manually at irregular intervals. All records are monopolar, positivity upwards, 32 sweeps/trace. Total sweep duration, 250 ms. Calibration, 20 ms, 1.0 mV. A: 15 μA stimulation. B: 82 μA. C: 210 μA. D: 210 μA. E: 41 μA. Note (1) an initial positive potential (labelled 'a' or 'd') that merges with the stimulus artifact in all records, (2) a second positive potential, in the dentate gyrus only, that peaks at a latency of about 16 ms ('b') and is followed by a negative-going potential. At high stimulus intensities, a second positive potential ('c') in the dentate gyrus peaks after a latency of about 25 ms.

wave response was sometimes seen in the dentate gyrus even though none had occurred in the olfactory mucosa or bulb.

Olfactory bulb stimulation

Single-pulse electrical stimulation of the olfactory bulb produced a large evoked potential at sites in the dentate gyrus that yielded a clear fast wave burst in response to odors. These potentials could be demonstrated either by multiple sweeps on the oscilloscope or by taking an average (Fig. 5). The stimulus threshold was usually in the range of 10–15 μA, but in one case it was about 5 μA. The evoked response, studied in 5 rats, consisted of an early phase ('a' in Fig. 5) that merged with the stimulus artifact, plus a later positive-negative potential with a latency of 16–18 ms to the positive peak ('b' in Fig. 5). At high stimulus intensities a second positive peak appeared at a latency of about 25 ms ('c' in Fig. 5). This was followed by a long-lasting negative potential.

Electrode sites in the RSA-generating zones near the hippocampal fissure and just dorsal to the CA1 pyramidal cell layer (15 sites in 10 rats) always yielded a clear 'a' potential but the later potentials could be detected only if very large stimulus currents were used (potential 'e' in Fig. 5). The 'a' potential was always positive, both dorsal to the CA1 pyramidal layer and in

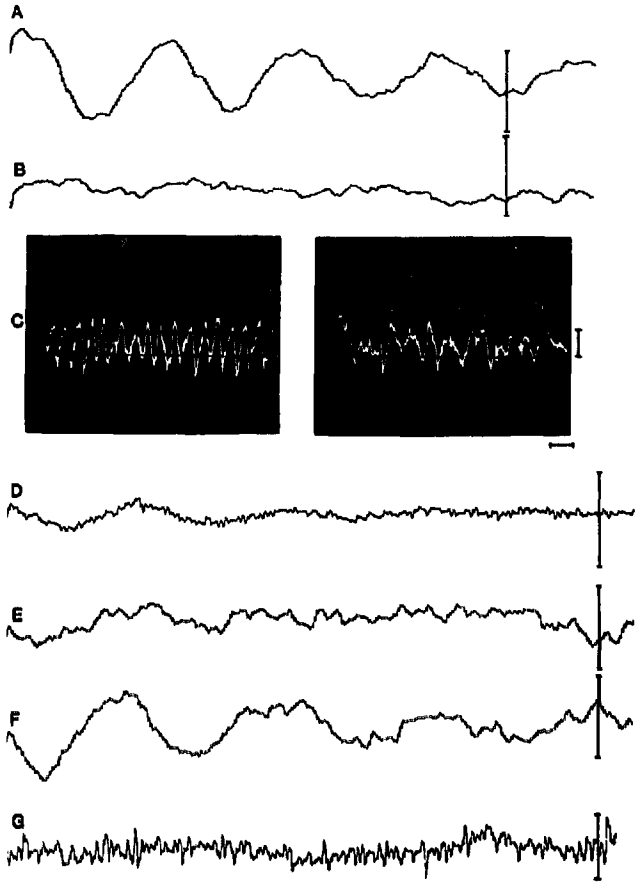

Fig. 6. Wave-triggered averages of activity in the rat hippocampus, olfactory mucosa and olfactory bulb. A: average from right hippocampal bipolar record (one electrode just dorsal to CA1 pyramidal layer and one near hippocampal fissure) triggered from 6–12 Hz-filtered slow wave activity from the right hippocampus during movement elicited by pushing the rat. B: similar average from the same electrode sites taken during immobility. C (left): bipolar hippocampal record during type-1 movement, as in A: C (right): record from the same electrode site during immobility, as in B. Dots in C are output pulses from the window discriminator triggered by 6–12 Hz-filtered hippocampal activity. D: average from the right olfactory mucosa, triggered by 6–12 Hz-filtered activity of right mucosa, during the sniffing of an unfamiliar rat. E: average activity of the right hippocampus (bipolar electrode as in A) triggered by 6–12 Hz-filtered activity from the olfactory mucosa. F: average activity of the right hippocampus triggered as in E but during locomotion elicited by pushing the rat. G: averaged activity from the right olfactory bulb triggered by 6–12 Hz-filtered activity from a bipolar hippocampal derivation during the sniffing of an unfamiliar rat. Voltage calibration: for A, B, D, E, F and G, 0.5 mV; for C, 1.0 mV. Time calibration: for C, 200 ms; for A, B, D, E, F and G, total duration equals 500 ms. A and B, 128 sweeps/trace; D, E, F and G, 32 sweeps/trace.

the region of the hippocampal fissure, even though RSA recorded from these same sites displayed a phase reversal of 180° (observed in 4 rats). Further, monopolar records from the surface of the olfactory bulb, taken during the application of negative stimulus pulses to the deep bulb electrode, revealed a response that resembled the trace in Fig. 5E. It is, therefore, possible that the 'a' and 'd' potentials in Fig. 5 are a result of volume conduction from the olfactory bulb.

When all other experiments were complete, the effects of toluene application and olfactory bulb stimulation were repeated during urethane anaesthesia. A dentate fast wave response could usually be demonstrated following application of toluene to the nostrils under light anesthesia, but if anesthesia was deepened to the point of producing a burst-suppression pattern of activity in the hippocampus and dentate, the fast wave response disappeared. The evoked potentials seen under urethane resembled those seen in the waking state except that response latency was increased by 2–4 ms.

Olfactory potentials, RSA, and motor activity: phase relations

Wave-triggered averages of hippocampal activity, triggered from the hippocampus and taken during spontaneous locomotion, or locomotion elicited by pushing the rat, invariably revealed a strongly rhythmical waveform. The amplitude of such averages was never more than about half the amplitude of the raw activity being averaged, and declined progressively across the duration of the sweep (Fig. 6). Identical averages from the same electrode sites, but taken during immobility, approximated to a flat line, usually with an initial deflection representing the triggering event (Fig. 6). Results were similar if averaging and triggering were from the same hippocampal site, or if activity from one hippocampal RSA-producing site was used to trigger averages from an RSA-producing site in the opposite hippocampus.

Long bouts of intense sniffing could be elicited in an experimental rat if an unfamiliar rat (preferably smaller than the experimental rat, but either male or female would do) was placed on the recording platform with it. Averages of olfactory mucosal activity triggered by 6–12 Hz filtered mucosal activity during sustained sniffing were invariably rhythmical, as in the case of observations of averaged hippocampal RSA (Fig. 6). It was important in obtaining such averages that sniffing was maintained almost continuously during the recording of an average response. Sometimes the sniffing and investigation of the unfamiliar rat was interrupted by a bout of face washing, which was associated with non-sniffing respiratory waves of 1–6 Hz. If such activity was averaged together with the rhythmical 6–8 Hz waves characteristic of sniffing, the resulting average was usually a flat line. Consequently, activity taken during all averages was monitored on the polygraph to ensure that the required activity was continuously present and that no electrical artifacts were present. Continuous sniffing for periods of 30 s or longer was quite common.

In 9 rats with RSA-yielding electrodes (RSA of at least 1.0 mV, peak-to-peak), wave-triggered averages of hippocampal activity were taken while triggering from the olfactory mucosa or olfactory bulb or vice versa (i.e. averaging mucosa or bulb activity while triggering from the hippocampus). This was done during sniffing (unfamiliar smaller rat present) and during locomotion elicited by touching or pushing the rat. In both cases the averages obtained were usually somewhat rhythmical, indicating that hippocampal RSA and the rhythms of the olfactory mucosa and bulb are coupled to some degree. However, the phase relation obtained was not constant, i.e. the olfactory mucosa might be either negative or positive when the RSA in stratum oriens

TABLE I

Instantaneous frequency (Hz) of rhythmical waves in the hippocampal formation and the olfactory mucosa before and during the initiation of a jump response in rats

Note that rhythmical slow activity in the hippocampal formation rises in frequency prior to and during jump initiation ($P < 0.001$, Friedman non-parametric analysis of variance[43]) but that the respiratory waves in the olfactory mucosa do not change significantly in frequency. Data (mean ± S.E.M.) were obtained from a sample of 10 trials in each of 7 rats. The jump response occurred during a period of rhythmical breathing in all the trials that were included.

	Waves preceding jump (rank order)					*Wave during jump initiation*
	5	*4*	*3*	*2*	*1*	*0*
Hippocampal formation	8.2 ± 0.4	8.2 ± 0.4	8.5 ± 0.3	8.3 ± 0.3	9.1 ± 0.3	10.7 ± 0.3
Olfactory mucosa	4.3 ± 0.3	4.2 ± 0.4	4.5 ± 0.5	4.2 ± 0.4	4.2 ± 0.3	4.2 ± 0.4

was negative. In 4 of the 9 rats, rather flat averages were obtained on at least some occasions, indicating no consistent phase relation between RSA and the rhythmical waveforms of the olfactory mucosa and olfactory bulb.

The rats trained in the avoidance apparatus all performed reliably, requiring only an occasional 'reminder' shock during the recording experiments. When a rat was placed on the grid floor, it would usually stand motionless in a rearing posture for several seconds prior to jumping. The actual jump was immediately preceded by a brief flexion of the hind limbs and trunk, followed by a sudden extension which propelled the rat upwards. Sometimes stepping or locomotion preceded jumping. Clear RSA was always present in the hippocampus during handling as long as the rat moved its head, trunk or limbs, even when such movement was accompanied by a period of apnea which often lasted several seconds as the rat was held. Clear RSA was also present prior to and during a jump response, and increased in frequency just before and during a jump response. This effect was very reliable in all 7 rats. The rhythmical respiratory waves of the olfactory mucosa, however, did not change in frequency in relation to jumping (Table I).

Averages of hippocampal activity were taken repeatedly in each rat during several 2–3 h sessions in which up to 190 trials were given. Initially the averager was triggered off the early positive wave produced by the movement sensor as the rat thrust its hind legs downward against the grid. However, this method sometimes resulted in averages being triggered by stepping or other movements. A more satisfactory solution was to trigger the averager off the negative wave produced by the upward rebound of the box after the rat had left the floor (Fig. 1). This resulted in the averager being triggered 40–50 ms after the beginning of the downward thrust of the hind limbs (moment of jump initiation). Since the activity being averaged was delayed for 470 ms (calibrated) by the analogue delay line, it was possible to locate the moment of response initiation with an accuracy of about 10 ms (Fig. 7).

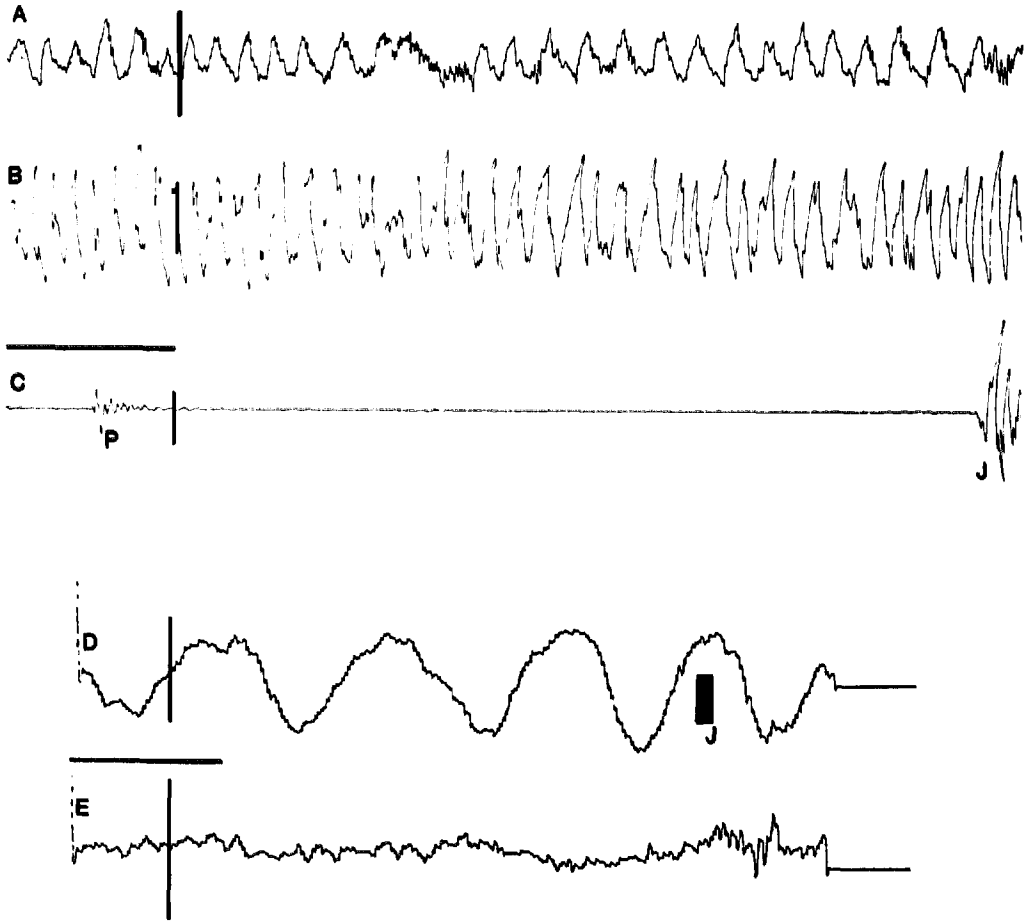

Fig. 7. Slow wave activity in the hippocampal formation and olfactory mucosa in a rat (#2924) during a conditioned jump response. A: monopolar record from the olfactory mucosa (inspiration upwards), B: monopolar record from the region of the hippocampal fissure. C: movement sensor output. D: hippocampal activity averaged over 32 trials. E: olfactory mucosal activity averaged over 32 trials. J: time of jump initiation (also indicated by black bar in D and E). Negativity upwards in A, B and C; positivity upwards in D and E. Voltage calibration: for A and B, 1.0 mV; for C, 33.0 mV; for D and E, 0.5 mV. Time calibration: 1.0 s for A, B and C; 100 ms for D and E.

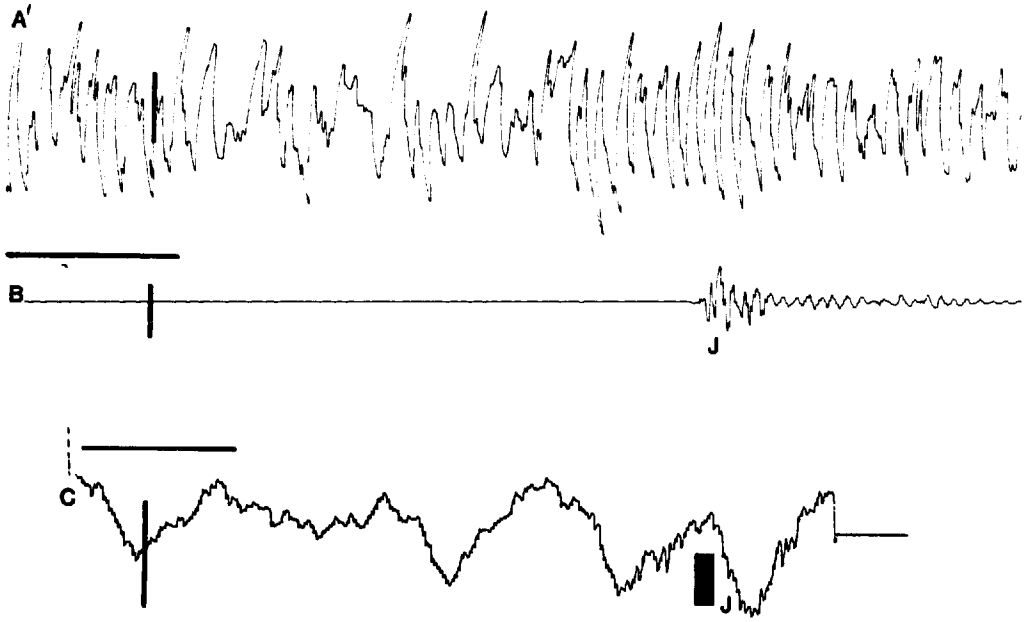

Fig. 8. Slow wave activity in the hippocampus during jumping following treatment with scopolamine (rat #2924). A: monopolar record from region of hippocampal fissure. B: movement sensor output. C: average hippocampal activity (16 sweeps) triggered by output of movement sensor. Black bar indicates jump (J) initiation. Calibration: hippocampus, 1.0 mV; movement sensor, 33.0 mV; average hippocampal trace, 0.5 mV; horizontal bars indicate 1.0 s in A and 100 ms in C. Scopolamine (5.0 mg/kg, s.c.) was given about 30 min prior to this record. Prior to the jump shown in A and B, the rat stood immobile, then crouched down slightly and jumped.

The degree to which the initiation of the jump response was phase locked to the RSA waveform appeared to vary from one rat to another. In rat #2924, 13 averages (each based on 16–64 trials) all gave the same result: jumping was initiated near the positive peak of RSA waves recorded monopolarly from the region of the hippocampal fissure. This occurred both in the normal state and after treatment with scopolamine (Figs. 7 and 8). Averages taken by triggering the averager manually during locomotion induced by pushing the rat did not yield any consistent result. The evidence for a phase relation between RSA and jump initiation in rat #2924 was confirmed by a visual trial-by-trial analysis that showed that jump onset occurred in the positive-going phase of the RSA wave, usually close to the positive peak, in 79.4% of 218 trials. Measurement of a sample of 10 individual RSA waves showed that, on average, the positive-going phase of the RSA wave occupied about 57.9% of the total wave duration. Therefore, it seems clear that, in rat #2924, jump initiation occurred in the positive-going phase of the RSA wave cycle more often than would be expected by chance.

In contrast, in rat #2918 no consistent phase relation was observed between the RSA cycle and the onset of jumping in 19 averages each based on 16 or 32 trials. Further, a visual trial-by-trial analysis showed that 69.9% of 166 jumps occurred during the positive-going phase of RSA recorded monopolarly near the hippocampal fissure. Since the positive-going phase of the RSA wave cycle averaged 68.9% of total wave duration in this rat, it appears that there was no more than a chance relation between the phase of the RSA cycle and the occurrence of jumping.

Of the remaining 5 rats, one yielded a consistent relation between jumping and the phase of the RSA cycle, but the results were less reliable in the remaining 4.

All 7 rats received scopolamine on 1–2 of their test sessions. In all cases the long trains of 6–7 Hz RSA that normally precede jumping by several seconds were abolished, but 1–2 RSA wave cycles always preceded the onset of the jump response. This could be demonstrated by visual inspection, by the use of the averager (Fig. 8), and by the use of the RSA detector (not shown).

In 6 rats, averages were taken of the activity of the olfactory mucosa during avoidance performance by triggering the averager by the movement of the avoidance box in the same way as was done in the case of the hippocampus. Low-amplitude rhythmical averages were obtained in all cases. In 4 rats, jumping occurred at or just after the peak of inspiration, but in the other 2 rats it occurred during expiration (Fig. 7).

DISCUSSION

In freely moving rats, olfactory stimuli elicited a burst of rhythmical waves of 15–30 Hz (fast waves) in or near the hilus of the dentate gyrus. This response is not detectable at the hippocampal fissure or in the stratum oriens of CA1. The dentate fast wave response may be specific to olfactory stimuli since it was not elicited by a variety of auditory, visual, or somatosensory stimuli. In addition, R. Heale (personal communication) has recently observed that taste stimuli (solutions of quinine, table salt, acetic acid and sucrose) do not elicit a fast wave response in the dentate gyrus. Noxious vapors such as ammonia are also ineffective. Ammonia may stimulate primarily the trigeminal system while the substances that elicited fast waves, particularly toluene and xylene, have long been recognised as having aromatic properties.

Hippocampal RSA, recorded in or near stratum oriens and at the depth of the hippocampal fissure, could also be elicited by olfactory stimuli, but this effect was completely non-specific and dependent on the capacity of such stimuli to elicit a motor response of locomotion, head movement or manipulation. Olfactory stimuli that do not elicit such motor activity elicited little or no RSA, while head movements or locomotion occurring in the absence of any deliberately applied stimulus were reliably accompanied by RSA. The correlation between RSA and motor activity is well established[47].

In contrast to RSA, the dentate fast wave response could be elicited in fully developed form in the absence of significant motor activity and was not necessarily present when gaseous stimuli elicited motor activity. For example, ammonia elicited a vigorous escape response but generally did not elicit a dentate fast wave response. Therefore, the dentate fast wave response appears to be related primarily to olfactory input, while the RSA response is related primarily to motor output. These facts tend to support early views[22] of the hippocampal formation as an olfacto-motor mechanism.

Electrical stimulation of the olfactory bulb elicited a complex evoked potential with an initially positive deflection, at a latency of 16 ms or more, in the hilus of the dentate gyrus. This finding in freely moving rats is consistent with previous work in anesthetized animals which indicates that olfactory inputs through the perforant path produce an active sink in the dendrites of granule cells[12,17,53]. Further research is necessary to determine whether the hilar fast wave response is also dependent on this pathway. It may be significant that all sites in the dentate gyrus that yielded prominent spontaneous fast wave activity also yielded clear fast wave bursts in response to odors. Bland and Whishaw[6] found that the hilus of the dentate gyrus in the rat is a prominent source of spontaneous fast waves, but the cells generating this activity have not yet been identified.

Electrodes at the hippocampal fissure or in the stratum oriens of CA1 did not detect an evoked response to stimulation of the olfactory bulb unless the stimulus current was very large, raising the possibility of a volume-conducted effect from the dentate gyrus. However, all electrodes (those in the hilus and stratum oriens as well as those at the hippocampal fissure) registered an initially positive potential ('a' potential) that merged with the stimulus artifact. A similar-appearing response was present at the surface of the olfactory bulb. A potential generated by the CA1 pyramidal cells would be expected to display phase-reversed responses at the stratum oriens and the hippocampal fissure. Such phase reversal was commonly seen in the case of spontaneous RSA confirming previous reports[5,6,16,54,55], but was not observed in case of the 'a' potential. Consequently, the 'a' potential in the hippocampus is probably a volume-conducted local response of the olfactory bulb. A low-resistance pathway between the olfactory bulb and the hippocampus is provided by the lateral ventricle, which has a spur extending into the interior of the bulb[56].

Electrodes placed in the labyrinth of the ethmoid recorded, at each inspiration, a negative slow wave potential with some superimposed faster activity. A similar slow wave potential, but with reversed polarity, plus superimposed fast wave activity, was recorded from the olfactory bulb. Previous work indicates that the slow wave potential is generated by the olfactory receptors in the mucosa, while the faster waves are generated in the olfactory bulb[1,35,36]. The slow wave potential was reduced in amplitude by toluene or xylene, an effect that is probably due to a direct narcotic action on the olfactory mucosa.

Fast wave responses similar to those seen in the olfactory bulb have also been observed in the pyriform cortex by Freeman[15], who described sinusoidal oscillations of 20–100 Hz in cat. Fast waves are generated in the CA1 region of the hippocampus as well[28], but do not appear to be related to olfaction.

With respect to the question of phase relations between sniffing and RSA, the present results confirm the previous findings of Macrides[30,31]. Such relations are not restricted to exploratory sniffing since they were also observed during struggling elicited by handling. As noted by Komisaruk[27] Macrides[30,31] and other authors, the phase relation between RSA and sniffing is labile and inconstant. Hippocampal RSA can occur

in the absence of sniffing, or even in the absence of breathing (apnea), and sniffing can occur in the absence of RSA[32,46,49,51,52]. All these findings were confirmed in the present investigation.

The present experiments also revealed a phase relation between RSA and the initiation of jumping. This relation was very consistent in 2 rats, present but weaker in 4 rats, and apparently non-existent in 1 rat. When present, the phase relation between RSA and jumping persisted after scopolamine treatment. Thus, it was found that scopolamine-resistant RSA precedes the act of jumping by 1–2 wave cycles and that motor activity may show a degree of phase-locking to this type of RSA. These findings extend previous work by Buno and Velluti[9] and Semba and Komisaruk[42], who reported a relation between lever pressing and the phase of RSA. Arnolds et al.[3] have also reported correlations between hippocampal activity and respiration and stepping.

The observation of phase relations between RSA and jumping and lever pressing on the one hand, and RSA and sniffing on the other hand, can be interpreted in terms of (a) a relation between RSA and motor activity, and (b) a relation between motor activity and respiration. Hippocampal RSA, especially the atropine-resistant type, is closely correlated with type-1 motor activity, and in many cases there is a relation between the phase of the RSA cycle and the occurrence of movement, as we have seen. There are also a number of reports that the phase of the breathing cycle may be coupled to motor activity[4,20,21,23] as a result of mechanical factors, reflexive control of breathing and central neural coupling[7,24]. However, movement–respiratory coupling is generally not found in all subjects, and in some studies[25,26] it was not present at all. In the present study, evidence that the initiation of jumping was related to the phase of respiration was obtained in each of 6 rats, but the phase relation was not the same in all cases. Four rats did what humans might do under similar circumstances; they took a breath and jumped. If the phase of the respiratory cycle is coupled to motor activity, and motor activity is at least moderately coupled to the RSA cycle, then one would also expect a weak coupling of the respiratory cycle to the RSA cycle. This is what is observed. A direct coupling of sniffing or other respiratory patterns to RSA is unlikely since, as already noted, sniffing can occur in the absence of RSA and RSA can occur in the absence of sniffing.

The present results are relevant to the larger question of the overall function of the hippocampal formation. Early studies indicated that large hippocampal lesions did not abolish olfactory conditioned responses[2,45]. More recent studies have suggested a role for the hippocampus in more complex olfaction-guided behavior[13,14,44]. However, these results are controversial[39]. It might be helpful if future work making use of brain lesion techniques placed more emphasis on naturally occurring olfactory control of behavior (foraging, predator avoidance, reproduction) and less on contrived complex conditioning tasks.

The hypothesis that the hippocampus plays an essential role in learning and memory has inspired an enormous amount of research but, despite this, it does not have strong empirical support. There is much evidence that surgical lesions restricted to the hippocampus do not result in a generalized amnesic syndrome in either man or beast[10,18,19,32]. It may be that the amnesic syndrome observed in some human patients is always a result of rather diffuse damage[32].

If the hypothesis that the hippocampus is critically involved in memory is open to doubt, then alternative hypotheses should also be considered. The data reported here encourage a re-examination of the old view that Ammon's horn is an effectory structure activated not only by olfactory inputs but also by inputs related to other sense modalities[8,22]. However, much additional work is needed to assess the role of the dentate gyrus and hippocampus in olfaction.

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