Animal cognition and the rat olfactory system

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Is smell a 'primitive' sense used primarily to guide biologically basic behaviors or might it be the sensory modality that allows some species to express complex learning and other forms of cognitive behavior? Historically, the olfactory system has been considered primitive and it is not surprising that, until recently, cognitive neuroscientists have ignored odor-guided behavior. However, we now know that the olfactory system has projections to the prefrontal cortex, entorhinal cortex and hippocampus, and that these connections support the acquisition of simple and higher-order instrumental tasks, as well as a robust memory for odors. It appears that animals with a well-developed sense of smell have the neural machinery to think with their noses.

Smell is often thought of as a 'primitive' sense used to guide basic activities such as finding a mate, finding food, identifying young and avoiding danger. However, the term 'primitive' can be used historically, morphologically or functionally and these usages need not be congruent.

Morphologically, the organization of the olfactory system is relatively simple, even in mammals. There is no decussation in the olfactory system (each nasal epithelium projects to the homolateral forebrain) and olfactory bulb projections terminate, without an intervening thalamic relay, upon a simple three-layered cortex.

Although olfaction is 'primitive' in the historical sense – it is present in the earliest vertebrates – it is functionally highly developed in these animals. Indeed, the olfactory ability of sharks, catfish and bloodhounds to detect chemicals exceeds that of gas chromatographs and other physical detectors. But recent discoveries have revealed that the olfactory system is less simple and less primitive than is generally assumed: olfactory impulses have fairly direct inputs to brain areas implicated in complex functions, including limbic structures and the prefrontal cortex.

Functional studies have overcome many of the technical difficulties of controlling vapor stimuli and demonstrate that, with odor cues, rats display highly efficient learning rivaling that of primates. In short, the evidence indicates that rats can 'think with their noses' and have the neural machinery so to do. This evidence, combined with advances in the molecular biology of olfaction[1], has resulted in a renaissance in research on olfaction and to the surprising and occasionally controversial suggestion that the rodent olfactory system could serve as a model for neurobiological studies of cognition[2,3].

The first link between olfaction and cognition was the finding that cells in olfactory cortex project to the segment of the thalamic mediodorsal nucleus that connects to the orbital prefrontal cortex[4]. Subsequent reports confirmed the existence of an 'olfactory thalamocortical' circuit[5] and delineated olfactory connections to the amygdala, entorhinal cortex and hypothalamus (Box 1). Projections from the olfactory bulb and olfactory cortex have three primary targets: prefrontal cortex, subcortical limbic structures and hypothalamus. As a first approximation, it seemed reasonable to suggest that these pathways mediate complex learning, emotional or species-specific behaviors and more basic biological functions, respectively. The relations between anatomy and behavior may be more complex but the evidence clearly implicates smell in functions dear to the heart of cognitive scientists.

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Learning sets, olfaction and cognition

In his classic studies on 'learning set', Harlow[6] showed that, over time, monkeys presented with hundreds of simple, two-object visual discrimination tasks gradually made fewer errors, eventually achieving nearly errorless learning. They did this by learning something about the rules of the game. The first trial of each new task provided information about which choice would be rewarded; errorless learning was revealed by a monkey's correct responses on subsequent trials. Adopting the rule 'win–stay, lose–shift' would allow a monkey to solve each new problem based on first trial choices. Thus the monkeys acquired a strategy or, as Harlow suggested, they had learned to learn. The analogy with human learning was clear and these primate learning-set studies provided one of the earliest demonstrations of animal cognition in a laboratory setting.

Learning-set performance soon became the method of choice for studies of comparative intelligence. In initial studies, tree shrews, raccoons, pigeons and rats showed only limited improvement over successive discrimination tasks, even after extensive training. Cats and marmosets performed better but the best performance was achieved with the primate order, within which a rank ordering of performance correlated with the presumed relatedness of the species to humans[7,8]. But all these studies used visual discrimination tasks and it was unclear whether the outcomes reflected the evolution of intelligence or of the visual system.

To test whether the apparent inferiority of rodents would remain if an ecologically more

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Box 1. Central olfactory projections of the main olfactory bulb

The lateral olfactory tract (LOT) originates from axons of olfactory bulb mitral and tufted cells. These axons terminate throughout the outer (plexiform) layer of the olfactory cortex (the piriform cortex and olfactory tubercle) and the lateral entorhinal cortex (Fig. I) (Ref. a).
A substantial projection to the central component of the mediodorsal nucleus (MD) and the ventral part of the submedius nucleus (SM) originates from cells in deeper layers of olfactory cortex. Neurons in these components of MD and SM project to ventrolateral orbital and lateral orbital prefrontal cortex[b]. Disruption of these connections produces deficits in complex but not in simple odor discrimination tasks.

A smaller component of the LOT extends posteriorly to terminate in the lateral entorhinal cortex and this, in turn, projects via the perforant pathway to the dentate gyrus and area CA1 of the hippocampus. Lesions of lateral entorhinal cortex result in deficits of short-term odor memory.

The hypothalamus receives secondary olfactory input from olfactory cortex and the anterior cortical nucleus of the amygdala (not illustrated). These projections travel in the medial forebrain bundle to terminate in the rostral hypothalamus and posterior lateral hypothalamic area. Interestingly, double label experiments indicate that many cells in the olfactory cortex contribute axons to both the thalamus and hypothalamus[c]. The olfactory input to the hypothalamus probably regulates several of the autonomic and neuroendocrine changes that occur in response to odors.

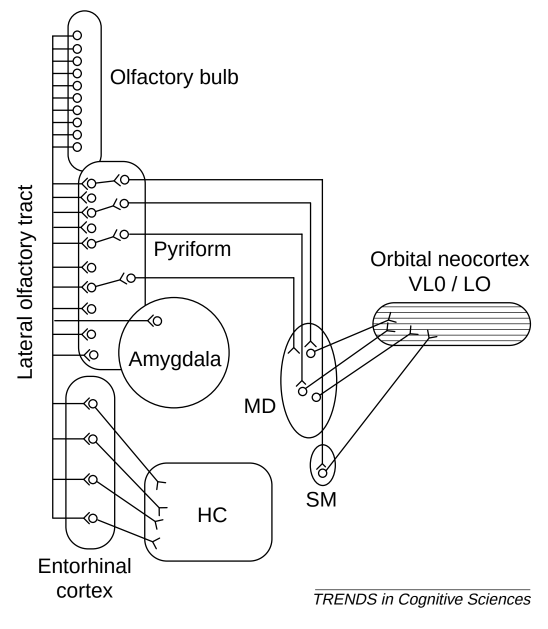

Fig. I. Schematic diagram of projections from the main olfactory bulb to the olfactory cortex and projections from this cortex to the thalamic mediodorsal (MD) and submedius (SM) nuclei and to the limbic system (hippocampus, HC). The connections of the accessory olfactory bulb are not shown here. The diagram summarizes results of axonal transport and electrophysiological studies of the forebrain olfactory system.

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relevant sensory system was engaged, Jennings and Keefer[9], using a relatively crude apparatus, found that some rats showed surprisingly good interproblem transfer over a series of 28 two-odor discrimination problems. Subsequent studies using operant conditioning and an automated odor generator confirmed that rats attended preferentially to odor cues (Box 2, Fig. I) and that, when trained on a series of novel two-odor discriminations, they showed a dramatic improvement in performance, solving most of the last five or six problems with few or no errors. Not only did they acquire a learning set but did so within a series of only 20–30 problems (Box 2, Fig. IIa).

These findings provided the impetus for further studies of odor-based cognitive behaviors, the outcomes of which demonstrated that, when provided with odor cues, the macrosmatic rat is not only able to master complex tasks but displays a remarkable memory for individual odors and odor associations.

Olfactory matching-to-sample

In a matching-to-sample test an animal is given a sample stimulus and then one or more comparison stimuli (see Fig. 1). It is a potentially powerful method for assessing non-spatial working memory, the relationship between inter-item interference and short-term memory and other aspects of cognitive behavior. The subject's task is to choose the comparison stimulus that is identical or most similar to the sample. A brief delay before presenting the comparison stimuli can be used to assess short-term memory for the sample stimulus. Both monkeys and pigeons easily learn to solve visual matching-to-sample problems but rats are notoriously deficient in acquiring even the simplest tasks with visual or auditory stimuli[10–13].

However, when tested with odors, rats quickly learn to solve such problems (see Box 2). Thus, in one study[14], rats were required to sample one of three odors and, a few seconds later, a second odor. If the second odor was identical to the first then responding via a key was rewarded. Rats not only learned this task in just a

Box 2. Learning about and remembering odors

In an olfactory/visual learning experiment, rats were trained initially on a two-odor discrimination task and then provided with redundant visual cues for 140 trials (Ref. a, results shown in Fig. I). The odors were then turned off and training was continued. Note the rapid acquisition of the odor-discrimination task (Fig. Ia), that introduction of the redundant visual stimuli did not disturb performance (Fig. Ib) but that performance dropped to chance levels when odor cues were removed (Fig. Ic). By contrast, rats were slow to acquire a simple visual-discrimination task (Fig. Id), were then distracted when redundant odor cues were provided (Fig. Ie), but had attended to and learned the significance of the redundant odor cues (Fig. If).

In another experiment (Ref. b), performance in the first 20 trials of sequential novel tasks improved rapidly and, by the end of training, rivaled that of the essentially perfect performance of rats given extensive training on the same set of odors (Fig. IIa).

Rats are not only capable of learning a large number of odors but can also remember their reward (S+) and non-reward (S–) assignments. Performance on sequential novel-odor tasks gradually improved, even when each task required discriminating among eight different odors (Ref. c, Fig. IIb). The poor performance seen when the odors used in set 6 were again presented as a reversal task shows that rats remember each of the training odors.

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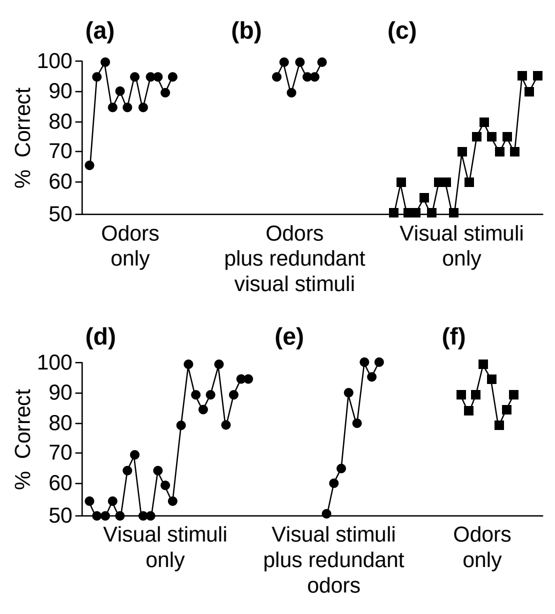

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Fig. I. Top: performance accuracy of one rat on its first exposure to a two-odor discrimination task (a), after introduction of redundant visual cues (b) and after turning off odor stimuli (c). Bottom: performance accuracy of one rat on its first exposure to a visual discrimination task (d), after introduction of redundant odor cues (e) and after turning off visual stimuli (f). The odors used were ethyl acetate and amyl acetate and the visual stimuli were a steady light and 5 Hz flashing light.

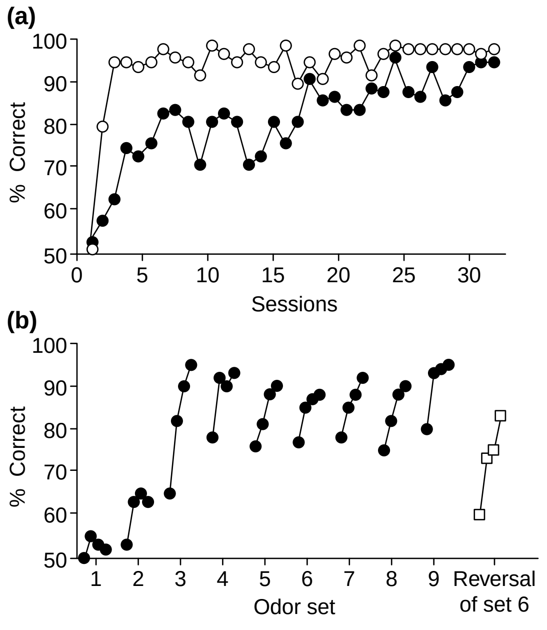

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Fig. II. (a) Performance accuracy on the first 20 trials of each session for rats given the same odor throughout training (open circles) and those given novel odors in each session (filled circles). (b) Performance accuracy in each of nine eight-odor sets and on reversal of set 6. In each of the first nine sessions, eight different and novel odors were presented in a mixed order. Four odors served as positive (S+) and four as negative (S–) stimuli. Each data point represents 40 trials (five exposures to each of the eight odors). In the last session the odors given in set 6 were presented but with the significance of the odors reversed (the previous S+ odors were now S–; the previous S– odors were now S+).

few training sessions but, when tested with a series of new odors, began to show near errorless acquisition of novel matching to sample problems, that is, they could learn to learn to match to sample (Fig. 2).

Rats also readily learn a non-matching-to-sample rule; that is, they learned to respond only if the odor being sampled differed from the last odor presented[15]. Performance on this task was sensitive to between-item interference: rats performed better when many odors were used than when only two odors were used (Fig. 3).

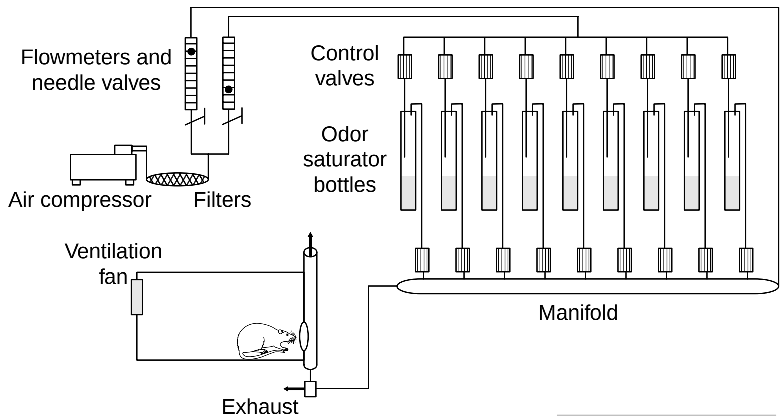

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Fig. 1. In most behavioral studies, operant conditioning Is used to train rats to insert their snout into an odor delivery port and respond via a key for a water reward when certain odors are presented (S+ odors) and not to respond to the presentation of other odors (S– odors). A variety of odor generator systems have been used; this figure shows a simple olfactometer capable of presenting any one of eight odors or combination of odors. Odorants are diluted in an odorless solvent and each odor saturator bottle is isolated by closed solenoid valves. Operation of the control valves introduces a 50 cc/min stream of odorized air into a continuous 1.95 liter/min flow of clean carrier air.

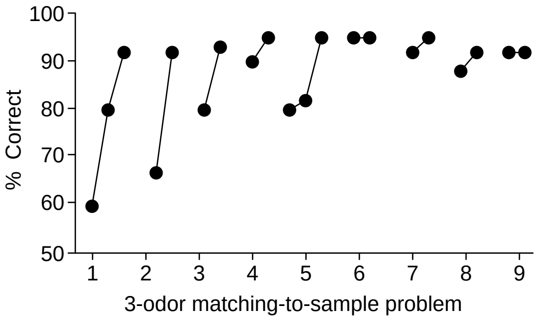

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Fig. 2. Performance accuracy on nine sequentially presented odor matching-to-sample problems. Each data point is the mean score for 180 trial sessions. The trial procedure was as follows: (1) present sample odor A, B or C for 1 s; (2) after a delay of 1 s, present comparison odor A, B or C; (3) rat is to respond if sample and comparison odors match; (4) after a 5 s inter-trial interval, the next sample is presented. A novel set of odors is used for each problem. Modified from Ref. 14.

Memory for odors

Otto and Eichenbaum[15] used the non-matching-to-sample procedure to examine short-term odor memory by imposing a delay between sequential presentations of odors. Under optimal conditions (use of many odors and a short delay between odor presentations) non-matching-to-sample accuracy was 90%; this declined to 75% with a 60 s delay (Fig. 3). Considerably better short-term memory was demonstrated using a procedure that essentially eliminated interitem interference[16]: after being trained on a learning-set task, rats were able to respond correctly when a 10 or 30 min delay was imposed between the first and second trials of novel odor discrimination. Although exposed to cage odors during the delay interval, they were apparently highly resistant to this source of potential interference (Fig. 4).

Evidence for long-term odor memory is equally impressive. Male guinea pigs vigorously sniff sample urine odors from novel female guinea pigs but show little interest in odors from familiar females. Those that had sampled an odor showed little interest when it was presented one week later but responded vigorously to the odor of novel females[17].

In a study that combined a test for learning set and long-term memory, rats were trained to discriminate between nine sequentially presented sets of eight novel odors[18] (Box 2, Fig. IIb). As expected, performance accuracy improved in each sequential set and rats made few errors in learning the last few sets. Next, those odors given in set 6 were presented again but the odors that had been positive were now negative and those that were negative were now positive. If rats had little or no memory for these odors then the set would be acquired with few errors. However, rats made many errors, especially in the initial trials, demonstrating that, despite the ample opportunity for anterograde and retrograde interference among the 72 odors they had learned, they remembered those of set 6 and their prior positive and negative assignments.

Subsequent studies have shown that both rats and mice retain an essentially perfect memory for a set of eight odors learned many (up to 30) days previously[19]. The excellent performance in these studies suggests that the animals find such tasks relatively trivial and that they have an impressive capacity to learn and remember many different odors.

Odor paired-associate learning

Other odor-cued tasks further extend our appreciation of what can only be viewed as 'higher order' learning by rats. To study paired-associate learning, rats were trained to sample two successively presented odors and were rewarded if they responded only to certain pairs (the paired-associate odors)[20]. Responses after presentations of other odor pairs were not reinforced. There were eight pairs of associate odors and 112 types of trial containing other (non-reinforced) odor combinations. Rats reached the criterion performance of at least 80% correct responses within 21 of 120 trial sessions. This represents remarkably rapid learning for this rather complex task. However, as Bunsey and Eichenbaum[20] note, paired-associate odor learning is probably an ethologically relevant task because rats appear to be predisposed to form durable associations between food odors even after a single pairing.

Odors, transitive patterning and transitive inference

In a conditional discrimination task in which subjects are rewarded if they respond to only one of two simultaneously presented stimuli using stimulus pairs A+/B–, B+/C– and C+/A– (where + and – indicate the reinforced and non-reinforced stimuli, respectively, in each odor pair), the correct choice is dependent upon

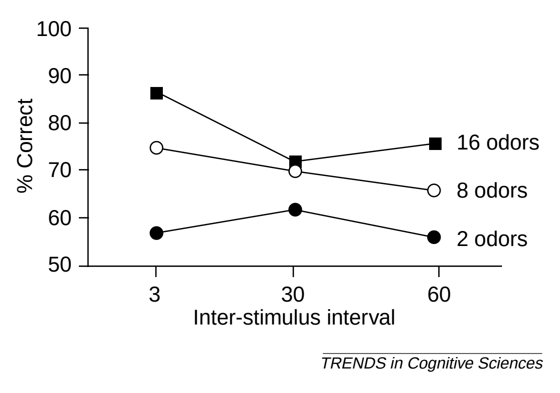

Fig. 3. Performance accuracy on an odor non-matching-to-sample task as a function of the number of odor stimuli used and the delay between the sample and comparison stimuli. Modified from Ref. 15.

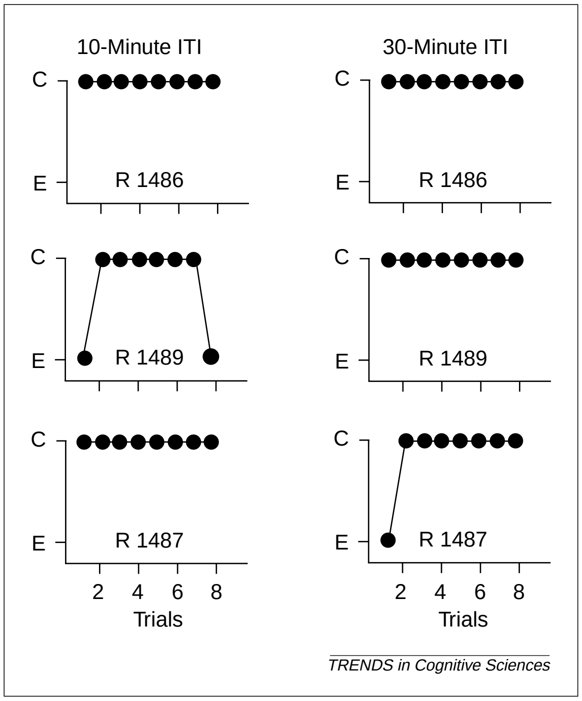

Fig. 4. To avoid the potential confound of retrograde interference, which would result in the underestimation of memory for trial-unique stimuli, extended inter-trial intervals can be used. Such methods reveal that memory for brief odor samples is retained for many minutes[16]. Correct (C) and incorrect (E) responses on each trial of a two-odor discrimination task for each of three rats (R 1486, R 1489, and R 1487) tested with novel odors using a 10 min or 30 min intertrial interval (ITI). These rats were initially trained on a learning set task using a 10 s intertrial interval. Modified from Ref. 16.

the configuration of the stimuli and not on associations between individual stimuli and reinforcement. Dusek and Eichenbaum[21] found that, with odor cues, rats readily learned this transitive patterning task and performed at high levels of accuracy in sessions where all stimulus pairs were presented in random order.

A modification of this task provided a test for transitive inference[20]. After training to discriminate odor pairs A+/B–, B+/C–, C+/D– and D+/E– rats were tested on odor pair B/D. As stimulus B was positive when paired with C and stimulus D was negative when paired with C, choosing B over D in the B/D pairings would provide evidence of transitive inference. Rats readily learned the four initial discriminations and demonstrated transitive inference by choosing B in the B/D pairings. Clearly, they have a robust capacity to learn the relational organization among a series of odor items.

The behavioral studies reviewed here are representative of an emerging program of research exploring what appears to be an extraordinary and rapid ability of rats to acquire complex, odor-based tasks. Other studies have used odor learning to examine cross-modality matching[21], reversal learning[22], social transmission of food preferences and assessing declarative and other forms of memory[23]. Many of the initial technical difficulties in generating and controlling odors have been resolved[24] and most studies have used operant conditioning and olfactometers to gain reasonably precise control of behavior and stimulus presentations, although much simpler methods (e.g. digging through scented sand to obtain a food reward) also work (see the conditional discrimination studies of Dusek and Eichenbaum[21,22]). As described below, these learning capacities provide tools for examining the neural basis of cognitive behavior.

Neurobiology of olfactory cognitive behavior

Two classes of neurobiological investigation have emerged from the rodent studies described above: (1) those that have addressed the question of which olfactory pathways mediate different types of olfactory learning; and (2) those using odor learning to examine more general issues in cognitive neuroscience. An example of the first approach is a study on the role of olfactory pathways in the acquisition of an olfactory learning set[25]. Rats with lesions of the mediodorsal thalamic nucleus (MD) or lesions that deafferented the amygdala and entorhinal cortex from olfactory input were trained on a learning-set task. Intact controls and rats with amygdala/lateral olfactory tract damage performed equally well but rats with MD lesions failed to acquire a learning set.

In a complementary study, Lu and Slotnick[26] also found that rats with MD lesions had few deficits in learning novel, two-odor discriminations but were significantly impaired on the acquisition of an odor-based learning set. These results support the hypothesis that the olfactory thalamocortical circuitry may mediate acquisition of a strategy needed for efficient odor learning.

The MD is a complex thalamic nucleus, only one component of which receives an olfactory input. It is therefore questionable whether deficits in olfactory tasks in rats with MD lesions are specific to odor learning or represent a more general disruption of cognitive ability. This was addressed by comparing the performance of rats with bilateral lesions of MD with the performance of rats with a unilateral lesion of MD plus removal of the olfactory bulb in the contralateral hemisphere[27]. Rats in the latter group had olfactory input into the hemisphere with the MD lesion but no olfactory input in the hemisphere with an otherwise intact MD nucleus. When tested on an odor-reversal task, both groups made many (and an equivalent number of) errors but normal rats and those with various control lesions performed well. The results indicate that the deficit in olfactory learning in rats with bilateral MD lesions is probably due entirely to the disruption of the olfactory thalamocortical component of the MD complex. This study also illustrates a practical advantage of the olfactory system for neurobiological studies of cognition: because olfactory projection pathways are well defined, in many cases cross-hemisphere lesions can be used to study the role of target structures without having to produce bilateral lesions in those structures.

Odor memory

A further study assessed whether odor memory was mediated by the thalamocortical system or by projections to the more posterior limbic structures (amygdala and entorhinal cortex)[28]. This study found that rats with bilateral MD lesions, and also those with transection of lateral olfactory tract projections to the amygdala and entorhinal cortex, demonstrated excellent memory for a series of eight preoperatively learned odors. However, rats that sustained both types of lesion had severe retention deficits but acquired new odor discrimination tasks quickly. These results indicate that both olfactory neocortex and limbic structures participate in odor memory storage (or recall).

Short-term or intermediate-term memory for odors appear to be mediated by olfactory projections to the entorhinal cortex. Thus, rats with lesions of the lateral entorhinal cortex or transection of olfactory projections to entorhinal cortex performed well on an odor discrimination task with short (< 2 min) intertrial intervals but appeared unable to remember the significance of odors when trials were spaced 5–10 min apart. Reversal learning provides a particularly striking example of this failure in short-term memory. Normal rats trained on a two-odor discrimination task and then tested 1 h later with the significance of the stimuli reversed make many errors, reflecting their memory for the training odors. Rats with entorhinal lesions learn the initial two-odor discrimination as well as controls but, on the reversal test, learn the task with fewer errors[29,30]. The simplest explanation for this enhanced learning of a reversal task is a faulty memory for original learning.

Associative learning

A second set of studies, using olfactory learning to examine more general issues of associative learning, provides support for promoting rodent olfaction as a model system for cognitive neurobiological studies. In several experiments, Eichenbaum and his associates have examined the role of entorhinal cortex and hippocampus in non-spatial learning, memory and related functions[31]. A focal issue in these studies is whether the rat hippocampus plays a role in non-spatial learning. Despite a large body of research on hippocampal function, this issue (first raised by O'Keefe and Nadel[32]) remains unresolved. Our interest here lies not in the specifics of the controversy[33,34], but in the contribution of olfactory learning to the problem.

To assess the potential role of the hippocampus in non-spatial declarative memory in the rat, Eichenbaum and colleagues have taken advantage of the rat's ability to solve odor-cued conditional associative tasks[20,21]. The outcomes allowed for separate evaluation of hippocampal lesion effects on procedural and declarative memories. One reasonably consistent result was that experimental animals had few or no deficits in executing the instrumental task (i.e. procedural memory was preserved) but that they failed or performed poorly on what was assumed to be the non-spatial declarative memory demands of the task as, for example, in delayed non-matching to sample, serial learning and transitive inference. Although the precise interpretation of these outcomes remains controversial[33,34], they suggest that in the rat, as in the human, the hippocampus may be involved in non-spatial associative learning.

Conclusions

Comparative psychology is replete with demonstrations of small-brained animals, including insects, exhibiting complex associate learning and of larger-brained animals failing to learn similar tasks. As Dyer has observed, a major challenge in understanding animal cognition is to account for limitations in solving cognitive problems[35].

One such limitation may be unwittingly imposed when the experimenter uses stimulus cues that are inappropriate for efficient task performance. Most, and perhaps all, species are sensory specialists and are particularly attentive to stimuli from one modality, even to the exclusion of others. Associations between signals and behavioral consequences will be formed slowly, weakly or not at all if those signals are from the 'wrong' or less relevant sensory modality for that species. An example familiar to most investigators is the almost total dependence on taste and intra-oral odor cues for single trial, long delay aversion learning[36]. Another example, more relevant to the present discussion, is the acquisition of visual and olfactory tasks in pigeons and rats: rats trained on odor cues perform extremely well, pigeons learn the same tasks poorly but excel when provided with visual stimuli[37]. Although the existence of stimulus-specific 'predispositions' or 'preparedness' to learn is often acknowledged, it too often receives more lip service than lab service. For rodents and, undoubtedly, other macrosmatic species, smell plays a dominant role in the control of behavior. The studies reviewed here demonstrate that this dependence on odors extends to many forms of complex learning.

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