Analysis of Behavior in Laboratory Rodents

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Introduction

To see the world in a grain of sand
And a heaven in a wildflower
Hold infinity in the palm of your hand
And eternity in an hour
John Donne (1)

The nervous system is designed to produce behavior, and so behavioral analysis is the ultimate assay of neural function. In this chapter we provide an overview of the behavior of rodents. We also provide references for testing details. Most of the behavioral methodology comes from research on rats, but the ethograms of rodents are similar enough to allow for generalization of the methods, if not many aspects of behavior, to other species. The testing method can be conceive of as having a number of stages, sequentially involving the description of: (I) general appearance, (II) sensorimotor behavior, (III) immobility and its reflexes, (IV) locomotion, (V) skilled movement, (VI) species-specific behaviors, and (VII) learning. For convenience, tables summarizing each class of behaviors are given in the relevant sections that follow.

The thoughts expressed in the opening line of John Donne's poem (above) provide advice for behavioral neuroscientists, in both the surface and deep meaning of the words. The surface meaning is that the observation of details can provide insights into the larger structure of behavior. The behaviorist in the neuroscience laboratory who is attempting to diagnose the effects of a drug, a neurotoxin, or a genetic manipulation can heed the advice that it is often subtle cues that provide the insights into the effects of the treatment (Hutt and Hutt 1970). The deeper meaning is quite simply that one should believe what one sees and not be biased by theory to the extent that observed behavior is ignored, even when the particular behaviors seem at odds with theory.

To make this point in another way, the beginning student and even the seasoned worker may have been taught that the proper way to do science is to state a theory consisting of a number of postulates, logically deduce predictions about behavioral outcomes from the theory, and then compare the predictions with the obtained results of carefully controlled experiments, which leads to a revision or a confirmation of the theory. This way of doing science is potent, but unfortunately, this has not been an especially productive way of conducting behavioral neuroscience. This is because our current understanding of how the brain produces behavior is not sufficiently advanced to per-

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mit the generation of non-trivial and readily testable theories. Put another way, there is no one-to-one congruence between behavioral effects and brain function (Vanderwolf and Cain 1994). Consider the following example.

Let us suppose that Professor Alpha believes that he has discovered a gene for learning. He predicts that if the gene is knocked out in an experimental animal, the animal, although otherwise normal, will no longer be able to learn. He develops a "knock-out" mouse that does not have the gene and then examines the learning ability of the mouse in an apparatus that is widely used for testing learning. Sure enough, the mouse is unable to solve the task and Professor Alpha publishes to much acclaim. Some time later Professor Alpha's knock-out mouse is examined in another laboratory where it is discovered that it has a defect in its retina rendering it functionally blind. Of course, the reader may argue that Professor Alpha is unlikely to be so naive, but in actuality errors of this sort are common (see Huerta et al. 1996 for an example of avoiding such an error). Even when the more obvious sensorimotor functions that could affect learning are examined, there are potentially dozens of other subtle problems that might keep the animal from learning.

A different way of proceeding in behavioral neuroscience is to use an empirical and inductive approach (Whishaw et al. 1983). Empirical means that an animal's behavior is carefully assessed, without regard to theories, in order to describe its condition. Inductive means that from the description, generalizations and conclusions are drawn about the effects of the treatment. Inductive science has been criticized, because, it has been argued, there is no way to tell which conclusions are correct and which are incorrect. We argue, however, that for behavioral research in general and behavioral neuroscience in particular, conclusions arrived at through induction can be subject to a rigorous evaluation using the theoretical method. The inductive technique is widely used as a first analytical step in clinical medicine (Denny-Brown et al. 1982) and in neuropsychology (Kolb and Whishaw 1996). For example, when a patient goes to see a physician with a specific complaint, the careful physician will administer a physical examination in which sensory processes, motor status, circulatory function etc. are examined. Only after such an examination does the physician venture a conclusion about the cause of the patient's symptoms. In neuropsychology, a wide-ranging battery of behavioral and cognitive tests are given to a patient and then the outcome of the tests is compared to the results obtained from patients who have received known brain damage. Similar clinical tests have been developed for rodents (Whishaw et al. 1983). Had Professor Alpha administered a physical and neuropsychology examination to his knock-out mouse, he may have noticed that the mouse was blind and therefore tested it in conditions in which vision would not be essential for performance. The testing protocol given here is designed to provide an "ethogram" that becomes the foundation for subsequent detailed testing. For studies of genetically-manipulated rodents in particular, this comprehensive behavioral evaluation is intended to cast as wide a net as possible, to capture multiple brain functions that may have been altered by even a single gene manipulation.

Methods

The three main ways of evaluating behavior are:

- End-point measures,
- Kinematics, and
- Movement description.

End-point measures are measures of the consequences of actions, e.g., a bar was pressed, an arm of the maze was entered, or a photobeam was broken (Ossenkopp et al. 1996). Kinematics provide Cartesian representations of action, including measures of distance, velocity and trajectories (Fentress and Bolivar 1996; Fish 1996; Whishaw and Miklyaeva 1996). Movements can be described using formal languages that have been adapted to the study of behavior, such as Eshkol Wachman Movement Notation (Eshkol and Wachmann 1958). This system has been used for describing behaviors as different as social behavior (Golani 1976), solitary play (Pellis 1983), skilled forelimb use in reaching (Whishaw and Pellis 1990), walking (Ganor and Golani 1980) and recovery from brain injury (Golani et al. 1979; Whishaw et al. 1993). For a comprehensive description of behavior, all three methods are recommended (see example below). Endpoint measures provide an excellent way of quantifying behavior, but animals are extremely versatile and can display compensatory behavior after almost any treatment. There are many ways that they can press a bar, enter an alley or intersect a photobeam. Kinematics provide excellent quantification of movement, but unless every body segment is described, ambiguity can exist about which body part produced a movement. Movement notation provides an excellent description of behavior but quantification is difficult.

Video Recording

As a prelude to behavioral analysis, we recommend that behavior be video-recorded. Regardless of the type of experiment, equipment for video recording is relatively inexpensive, as off-the-shelf camcorders and VCRs are suitable for most behavioral studies (Whishaw and Miklyaeva 1996). Equipment required is a hand-held video recorder that has an adjustable shutter speed. Most of the filming of human movements uses a shutter speed of about 1/100 of a second, but in order to capture blur-free pictures of the rapid movements made by rodents, who have a respiratory cycle, lick rate and whisker brushing rate of about seven times per second, shutter speeds of 1/1,000 and higher are required. Fast shutter speeds require fairly bright lights, but with a little habituation, rodents do not appear distressed by lights.

Video Analysis

To analyze the film, a videocassette recorder that has a frame-by-frame video advance option is necessary. A VHS model cassette recorder can be used and the record acquired on the recorder cassette can be copied over to the VHS tape. Optional, but not essential, equipment includes a computer with a frame grabber that allows individual frames of behavior to be captured for computer manipulation. Once a video tape of behavior is made, the behavior can be subject to frame-by-frame analysis. Each video frame provides a 1/30 s snapshot of behavior. If rat licking is being studied, a single lick cycle would be represented on three successive video frames, a resolution that is adequate for most purposes. One important feature of video frames, however, is that they are actually made up of two fields that are superimposed. Because computer-based frame grabbers can capture each field, a computer image of the video record increases resolution to 1/60 of a second. The analysis of some behaviors may require still greater resolution and higher speed cameras are available, but they are presently very expensive. For most studies, it is helpful to use a mirror to film the animal from below (Pinel et al. 1992) or so that the surface on the animal's body that faces away from the camera can also be seen (Golani et al. 1979). A typical recording set-up is illustrated in Fig. 1.

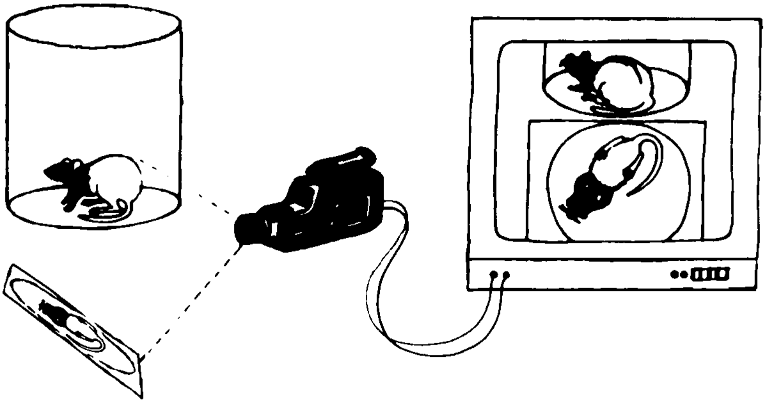


Fig. 1. Video-recording method. The video camcorder is placed so that it simultaneously records the rat from a lateral view and, through an inclined mirror, from a ventral view. Thus the rat can be seen from two perspectives on the monitor (After Pinel et al. 1992).

Example 1: Video-based Behavioral Analysis

The following example illustrates the complementary role of the different types of video-based behavioral analysis. The reaching for food by rats with unilateral motor cortex injury was studied using an end-point, videorecording, and movement notation analysis (Whishaw et al. 1991). The study began with an end-point measure. The animal was allowed to obtain a piece of food on a tray by reaching through a slot in its cage. To force the rat to use its non-preferred limb, a light bracelet was placed on the normal limb, thus preventing it from going between the bars. The end-point measure of behavior was the success in reaching for food with the limb contralateral to the lesion. The end-point measure revealed that motor cortex lesions impaired the grasping of food. Normal control animals have a success rate of about 70% and rats with motor cortex lesions had success rates that varied from near 20% to about 50%, the extent of impairment varying directly with the lesion size. Thus, this type of analysis shows that the forelimb representation of the motor cortex of the rat plays a role in skilled reaching movements. Note, however, that although this analysis identifies that the motor cortex lesion interferes with reaching for food, it does not identify the reason for the poor reaching. This question was addressed by the movement notation and kinematic analyses (Fig. 2). Analysis with the Eshkol-Wachman movement notation system, which is designed to express relations and changes of relations between parts of the body, revealed that the motor impairments were attributable to an inability to pronate the paw over the food in order to grasp it, as well as an inability to supinate the paw at the wrist to bring the food to the mouth. Finally, once a movement description was established with movement notation, a number of other aspects of the movement were measured and documented using a Cartesian coordinate system, with initial and terminating components of the movements serving as reference points. For this analysis, points on the body were digitized and the trajectory of the movements of the limb reconstructed. This analysis revealed that in addition to the inability to supinate and pronate properly, the animals with motor cortex injury also had an abnormal movement trajectory of the limb so that the aiming of the limb to the food was impaired.

Taken together, these three analyses provide a description of the various motor components that are affected by the motor cortex injury, as well as the subsequent effect that the impairments have on the behavior. Such an analysis is necessary not only to under-

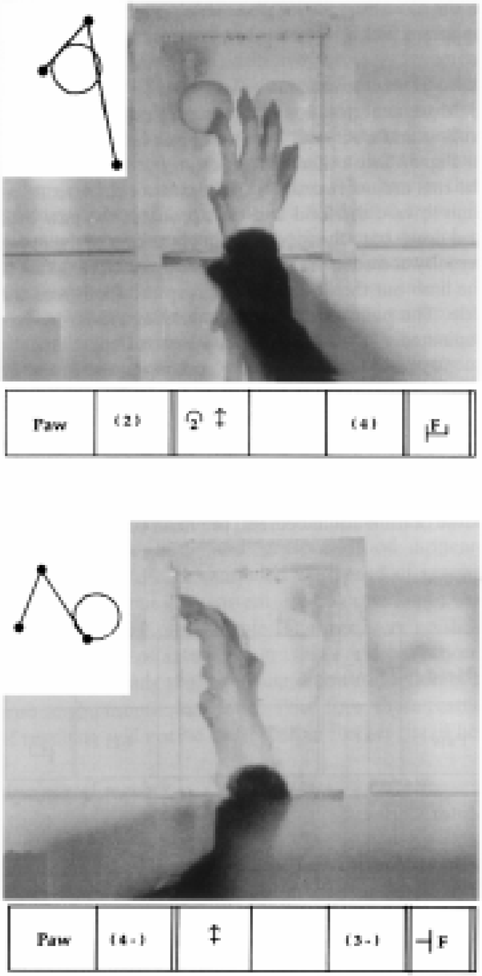


Fig. 2. Three methods of describing behavior. (1) End-point measure. The photographs are of a rat reaching through a slot in order to obtain a food pellet located on the shelf. In the top figure a control rat is about to grasp the food while in the bottom photo a rat with a motor cortex lesion has knocked the food pellet off the shelf and lost it. (2) Movement notation. On the bottom of each figure a movement notation score describes the movement. The first box indicates that it is the paw that is being described, the second box indicates the starting position of the paw and the last box indicates the end position of the paw. The notation in the three middle boxes indicates movement in three video frames (1/30 sec). Top: The paw advances and pronates and grasps the food pellet (F). Bottom: The paw advances and turns sideways without pronation to swipe the food away. (3). Cartesian reconstruction. The insert shows the trajectory of the tip of the third digit of the paw relative to the food pellet on the same three video frames. The three forms of analysis are necessary for a complete description of the movement and its result (After Whishaw et al. 1991).

stand the role of a neural structure in the control of movement but also to investigate the effects of different treatments on the observed impairments. Thus, it might be shown that a particular drug influenced “recovery of function”, which could be documented by an improvement in an end-point measure. The subsequent movement notation and kinematic analyses would be required, however, to determine which aspects of the movement had been affected. For example, it has been shown that rats with motor cortex lesions show some recovery of skilled limb reaching but this is largely due to changes in a variety of whole body movements that compensate for the deficits in aiming (Whishaw et al. 1991). The impairments in pronation and supination remain.

The Neurobehavioral Examination

Many tests can be administered quite quickly, while an animal is in its home cage, whereas others are given when the animal is removed from its cage. Most tests require no special equipment and are intended to be simple, rapid, and inexpensive ways of evaluating an animal's condition. In administering the clinical examination, the stand-

Table 1. Examination of Appearance and Responsiveness

Appearance	Inspect body shape, eyes, vibrissae, limbs, fur and tail, and coloring.
Cage examination	Examine the animal's cage, including bedding material, nest, food storage, and droppings.
Handling	Remove the animal from its cage and evaluate its response to handling, including movements and body tone, and vocalization. Lift the lips to examine teeth, especially the incisors, and inspect digits and toenails. Inspect the genitals and rectum.
Body Measurements	Weigh the animal and measure its body proportions, e.g., head, trunk, limbs, and tail. Measure core temperature with a rectal or aural thermometer.

ard is that a healthy laboratory animal is clean, lively, inquisitive, but not aggressive. The tests that we describe may require innovative and liberal use paraphernalia found around the laboratory. For all of the tests described, it is assumed that control animals are also examined to provide the standard against which an experimental group is compared. Often in studies of genetically altered animals, several classes of control animals are needed in order to be able to attribute behaviors to particular genetic alterations (Crawley et al. 1997; Upchurch and Wehner 1989).

I. Appearance

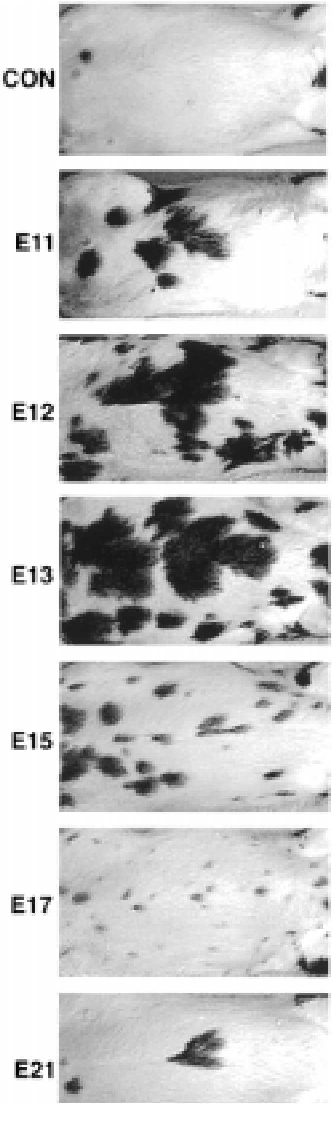
The main features of the physical examination are given in Table1. Animals should be examined in the home cage and also removed for individual inspection.

1. The appearance of the fur and its color should be noted.
2. The proportions of body parts should be examined, including the length of the snout, head and body, limb, and tail.
3. An examination of the eyes includes using a small flashlight to test pupillary responses. The pupils should constrict to light and dilate when the light is removed, which indicates intact midbrain function. Rodents secrete a reddish fluid, called Hardarian fluid, from the eye glands. This fluid is collected on their paws as the paws are rubbed across the eyes during grooming. It is then mixed with saliva when the animal licks its paws, and the mixture is spread onto the fur during subsequent grooming. This material maintains the condition of the fur and aids thermoregulation. Reddening of the fur around the eyes due to the accumulation of Hardarian material, usually more obvious in albino rats, indicates that the animal is not grooming. Rodents are fastidious groomers and a rich rough appearance to the fur also indicates normal grooming.
4. An animal's teeth should be inspected by gently retracting the lips. The incisor teeth of rodents grow continuously and they are kept at an appropriate length by chewing. Excessively long or crooked teeth indicate an absence of chewing or a jaw malformation. Long teeth can be safely cut short with a pair of cutters. If the teeth are inadequate for chewing, an animal can be fed a liquid diet.
5. During grooming, rats cut their toenails, especially the toenails of the hind feet, and so these should be short with rough tips, indicative of daily care. Long unkept toenails may indicate poor grooming habits, or problems with teeth and mouth, which are used for making the fine nail cutting movements. (We must note, however, that many inbred strains of animals display less than propitious toenail care).
6. During the examination, the genitals and rectum should be examined to ensure that they are clean, indicating an absence of internal infection or illness.

Example 2: Analysis of Appearance

The power of a simple analysis of appearance is illustrated in Fig. 3. In the course of studying the embryological development of neurons in the rat cortex we noticed a dramatic effect of our treatments on coat coloration pattern. Pregnant rats were injected with a standard dose of bromodeoxyuridine (BrdU, 60 mg/kg) on different embryonic days ranging from E11 to E21. In the rat, neocortical neurons are generated during this period and we were interested in the effects of different postnatal treatments on the numbers of neurons generated at different ages. The BrdU labels cells that are mitotic during the two or so hours following the injection. Labeled cells can later can be identified using immunohistological techniques. It turned out, however, that Long-Evans hooded rats with BrdU injections on days E11 to about E15 had a dramatically altered pattern of black and white coloration in their fur coats and this pattern varied with the precise age of BrdU treatment. The injections produced spots, much like those on a Dalmatian dog, the size of the spots varying with injection age (see Fig. 3). Because we knew

Fig. 3. Coat color on the ventrum of Long-Evans rats whose mother had received bromodeoxyuridine at different times of gestation. The changes in coat color are paralleled by changes in brain and behavior (After Kolb et al. 1997).



that the skin cells (specifically the melanocytes in this case) and the brain cells were derived from the same embryonic source, we immediately became suspicious that the BrdU was not only altering skin cells but also the pattern of migration of neurons (Kolb et al. 1997). This led us to analyze the behavior of the animals in more detail and it turned out that the BrdU treatment was producing marked changes in many behaviors. This discovery was only possible because we had observed the general appearance of the animals.

Body Weight Animal suppliers provide weight curves for the strains of animals that they sell, so it is a simple matter to weigh an animal and compare its weight to a standard weight curve. Growth in rodents is extremely sensitive to nutrition, being accelerated or retarded by changes in nutritional status at any age. It is also influenced by the behavior of conspecifics, as subordinate animals are typically smaller than dominant conspecifics. Rats, especially males, continue to increase in size and weight throughout life, but size and rate of growth vary appreciably across strains. Differences in actual weight from expected weight may signal malnutrition, overfeeding, developmental disorders, or any of a variety of peripheral and central problems.

Body Temperature At the time of weighing the animal's temperature can be recorded with a rectal or aural thermometer. Rodent core temperature is quite variable and can fall to about 35 °C when an animal is resting in its home cage and can increase to 41 °C when the animal is aroused upon removal from its home cage. Temperatures lower or higher than these ranges indicate hypothermia or fever. Animals display a variety of postures, reflexes, and complex behaviors in order to maintain temperature and these are described in detail by Satinoff (1983).

Response to Handling During handling, an animal may typically make soft vocalizations. Excessive squeaking may indicate distress or sickness. Rodents maintained in group housing are usually unaggressive when handled by an experimenter. Animals raised in isolation, e.g., housed individually, may be very sensitive to handling and squeak and struggle or even display rage responses. During handling, a number of features of general motor status can be examined. The animal can be gently held in the palm of the hand and quickly raised and lowered. Limb muscles should tense and relax as the rat adjusts itself to the movements of the hand. Absence of muscle tone or excessive rigidity are both indicative of problems with motor status, e.g., drugs that stimulate dopamine function produce flaccid muscle tone whereas drugs that block dopamine function produce rigidity.

II. Sensorimotor Behavior

The objective of sensorimotor tests is to evaluate the sensory and motor abilities of animals (see Table2). The tests evaluate the ability of animals to orient to objects in the environment in each sensory modality. The term *sensorimotor* derives from the recognition that it is ordinarily very difficult to determine whether the absence of a response is related to an inability to detect a stimulus or to an inability to respond to a detected stimulus. For the purposes of the present overview, such distinctions are not necessary, but it is worthwhile pointing out that some theoretical positions suggest that such distinctions are not possible (Teitelbaum et al. 1983).

Home Cage Tests of sensory and motor behavior are best administered to an animal in its home cage, preferably a hanging wire mesh cage because the holes in the mesh allow easy access to the animal. (Sensorimotor behavior of animals is radically different if they are assessed in an open area where even neurologically intact animals will act as though

Table 2. Sensory and Sensorimotor Behavior

Home Cage	Response to auditory, olfactory, somatosensory, taste, vestibular, and visual stimuli. The home cage should provide easy viewing of an animal. Holes in the sides and bottom of the cage provide entries for probes to touch the animal or to present objects to the animal or to present food items. Animals are extremely responsive to inserted objects and treat capturing the objects as a "game". Slightly opening an animal's cage can attenuate its responses to introduced stimuli, showing that it notices the change.
Open Field	Response to auditory, olfactory, somatosensory, taste, vestibular, and visual stimuli. The same tests are administered. Generally animals taken out of their home cage are more interested in exploring and so ignore objects that they responded to when in the home cage.

they are neglecting sensory information, see below.) For the cage examination, put food pellets into the cage and place some paper towels beneath the home cage to catch residue. If the tray is slid out from beneath the animal's cage a day to two later, residue can be examined. Rodents are fastidious in their eating and toilet habits and so feces and urine will be found in one location on the tray and food droppings will be found in another location, an indication that the animal has compartmentalized its home spatially. Residue from food should be quite fine, indicating that the animal is chewing its food. Many rodents are central place foragers; they carry food to their home territory and store it for subsequent use. An examination of the inside of the cage should indicate that the food is piled in one corner of the cage.

Orienting

While the rat is in its home cage, its sensory responsiveness can be examined. In an analysis of animals recovering from lateral hypothalamic damage, Marshall et al. (1971) observed a rostrocaudal recovery of sensory responsiveness. Generally, normal animals are much more responsive to rostrally than to caudally applied stimulation. Schallert and Whishaw (1978) reported that a syndrome of hyperresponsiveness and hyporesponsiveness can occur after hypothalamic damage.

1. Take a cotton-tipped applicator, of the type used in surgery, and insert into the animal's cage, gently touching different parts of the animal's body, including its vibrissae, body, paws, and tail. The animal should perceive this as a "game" and vigorously pursue and bite the applicator, thus allowing assessment of the sensitivity of different body parts. Rubbing the applicator gently against the cage can be used to test the rat's auditory acuity, as it will orient to the sound. Placing objects on the rat provides an additional assessment of its sensory responsiveness, as a rat will quickly remove the object (Fig. 4). Pieces of sticky tape of various sizes placed on the ulnar surface of the forearm or bracelets tied with single or double knots provide tests of detection, obscuration, or neglect (Schallert and Whishaw 1984).
2. An animal's responsiveness to odors can be tested by placing a small drop of an odorous substance on the tip of the applicator. Animals will investigate food smells, recoil from noxious odors such as ammonia, and recoil from the odors of predators such as stoats and foxes (Heale et al. 1996).
3. Simple ingestive responses can be investigated by placing a drop of food substances on the blade of a spatula. In their home cage, rodents, unless water deprived, are usually indifferent to water, but they enthusiastically ingest sweet foods such as sugar water, milk, or a mash of sweet chocolate flavored cookie. Lip licking indicates that the animal's sensitivity to sweet food is normal. If the spatula is held adjacent to the cage, the animal will stick its tongue out to lick up the food, providing an indication of the motor status of the tongue. Bitter tasting food, such as quinine, elicits a series of rejection responses, including wiping its snout with its paws, wiping its chin on the floor of the cage, and tongue protrusion to remove the food. Grill and Norgren (1978)

Fig. 4. Left: A sticky dot placed on the ulnar pad of the forearm provides a simple test for orienting. Remove the tape, and sensitivity can be tested by reducing the size of the dot. Right: Competition between stimuli can be tested with bracelets tied with one or two knots. If a stimulus on the good side obscures the stimulus on the bad side, a rat will persist in attempting to untie the difficult right knot while ignoring the easy left knot (After Schallert and Whishaw, 1984).

have described taste-responsive reflexes in rats that have subsequently been widely used to assess gustatory responses.

An animal's ability to eat and chew may be further examined by giving the animal a food pellet, a piece of cheese, or some other food substance of a standard size. Rodents sniff the food, grasp it in their incisors, sit back on their haunches while transferring the food to the paws, and eat the food from the paws while in a sitting position. Observing the processes of food identification, food handling, and eating speed all provide insights into the function of the front end of the animal's body. More detailed analysis of rat eating speed shows that the animals eat more quickly when exposed than when in a secure environment and eat more quickly at normal meal times than at other times (Whishaw et al. 1992a).

Open Field Behavior

Sensory tests may also be given to an animal that is removed from its home cage, but here the meaning of the responses changes. Normally an animal in a novel environment ignores food in favor of making exploratory movements. Ingestion of food outside the home means it has habituated to that location or is insensitive to novelty. Generally, it may take a number of days or weeks to habituate an animal to an environment that provides no hiding place, as is the case with most mazes. Animals also display a number of defensive responses when they find food, and will turn or dodge away from other animals with the food, or run or "hoard" the food to a secure location for eating. These behaviors can be used as "natural" tests of orienting and defensive behavior (Whishaw 1988).

III. Immobility and Its Reflexes

Posture and locomotion are supported by independent neural subsystems (see Table 3). A condition of immobility in which posture is supported against gravity is the objective of a large number of local and whole body reflexes. Thus, immobility should be viewed as a behavior with complex allied reflexes. Even animals that are catatonic and appear

Table 3. Posture and Immobility

Immobility and Movement with Posture	Animals usually have postural support when they move about and they maintain posture when they stand still and remain still while rearing. Posture and movement can be dissociated: in states of catalepsy postural support is retained while movement is lost.
Immobility and Movement without Posture	An animal has posture only with limb movement. When a limb is still, the animal collapses, unable to maintain posture when still. When still, the animal remains alert but has no posture, a condition termed cataplexy.
Movement and Immobility of Body Parts	Mobility and immobility of body parts can be examined by placing a limb in an awkward posture or placing it on an object such as a bottle stopper and timing how long it takes an animal to move it.
Restraint-Induced Immobility	Restraint-induced immobility, also called tonic immobility or hypnosis, is induced by placing an animal in an awkward position, e.g., on its back. The time it remains in such a position is typically measured. Animals will maintain awkward positions while maintaining body tone or when body tone is absent. During tonic immobility animals are usually awake.
Righting Responses	Supporting, righting, placing, hopping reactions are used to maintain a quadrupetal posture. When placed on side or back or dropped in a supine or prone position, adjustments are made to regain a quadrupetal position. Righting responses are mediated by tactile, proprioceptive, vestibular, and visual reflexes.
Environmental Influences on Immobility	Feeding fatigue potentiates immobility. Warming induces heat loss postures, e.g., sprawling, and thus potentiates immobility without tone. Cooling induces heat gain posture with shivering and thus potentiates immobility with muscle tone.

completely unresponsive may move quickly to regain postural support if they are placed in a condition of unstable equilibrium (Fig. 5). Postural and righting reflexes are mediated by the visual system, the vestibular system, surface body senses, and proprioceptive senses. Although responses mediated by each system are allied they are frequently independent (Pellis 1996).

Postural Reflexes

If the animal is placed on a flat surface and gently lifted by the tail, it should display a number of postural reflexes. The head should be raised and the forelimbs and hindlimbs extended outward, while the forequarters are twisted from side to side. When mice are raised and then quickly lowered, their digits should extend, a response not seen in rats. The posture and movements are typical of an animal searching for a surface on which to obtain support.

Asymmetries in movement are used as tests of brain asymmetries that might be produced by unilateral injury (Kolb and Whishaw 1985). For example, when suspended by the tail, adult animals with unilateral cortical lesions usually turn contralateral to the lesion whereas animals with unilateral dopamine depletions turn ipsilateral to the lesion. The posture of the limbs provides a sensitive measure of central motor status. Flexion of the forelimbs toward the body, including grasping of the fur of the ventrum, and flexure of the hindlimbs toward each other, including grasping of each other, can indicate abnormalities in descending pyramidal or extrapyramidal systems (Whishaw et al. 1981b). On a flat surface, animals typically rotate toward the side of injury, and when placed on irregular surfaces, they may favor a limb contralateral to an injury.

Postural Support

Placing an animal on a flat surface allows inspection of its postural support. An animal may maintain a condition of immobility in which it has posture or it may adopt a position of immobility in which it lacks posture. The two types of immobility are independent. An animal without posture while immobile may achieve posture as a part of locomotion. DeRyck et al. (1980) have demonstrated that morphine, an opioid agonist, pro-

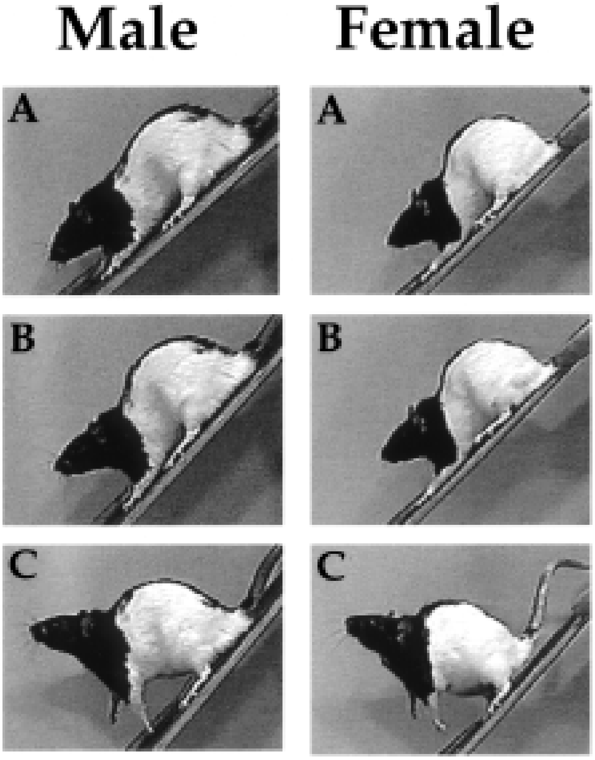


Fig. 5. Animals defend immobility when placed in a condition of instability. Rats treated with haloperidol (5 mg/kg) display immobility with postural support. When made unstable by tilting the substrate, they first brace (A) but eventually jump to regain a new supporting position when postural instability becomes too great (B, C). The tactics for maintaining postural stability prior to jumping are sexually dimorphic (After Field, Pellis and Whishaw, unpublished).

duces a condition of immobility without postural support whereas haloperidol, a dopamine antagonist, produces immobility with postural support.

The two types of immobility are part of normal behavior, as an animal that is cold and shivering has postural support while otherwise remaining immobile while an animal that is hot will sprawl without postural support as part of a heat loss strategy. Immobility with postural support is characteristic of an animal that pauses during a bout of exploratory behavior or an animal that rears and stands against a wall. Immobility without postural support is typical of an animal that is resting or sleeping. Although difficult to achieve in normal rodents, if an animal is gently restrained in almost any position, it may remain in that position when released. This form of immobility, sometimes called animal hypnosis or tonic immobility, is usually accompanied by a good deal of body tone as the latter term implies (Gallup and Maser 1977). If an animal is frightened, it may "freeze" in place in a condition of immobility with postural support. When hiding or attempting to escape it frequently crouches into immobility without postural support. (The suggestion that animal hypnosis can be used as a condition of anesthesia is not supported by research, which indicates on the contrary that hypnosis is but one of many forms of adaptive immobility.)

Placing Responses

Placing responses are movements of the head, body or limbs that are directed toward regaining a quadrupedal posture. If an animal is lifted by the tail, then as the animal is lowered toward a surface, contact of its long whiskers with the surface will trigger a placing reaction of extending the forelimbs to contact the surface. Placing reactions of each of the limbs can be tested by holding the rat in both hands while touching the dorsal surface of each paw against the edge of a table. Upon contact, the paw should be lifted and placed on the substrate (Wolgin and Bonner 1985). Placing responses are sensitive to damage to corticospinal systems.

Bracing Responses

If an immobile animal is gently pushed, it will often push back against displacement to maintain static equilibrium, a behavior termed a bracing response. If the push begins to make the animal unstable, it will step or turn away to relieve pressure. Animals that have been rendered cataleptic by a treatment, that is they are immobile with postural support, may be unable to step and thus are reduced to bracing to maintain stability (Schallert et al. 1979). Bracing can be examined in a single limb. Animals that are made hemi-Parkinsonian with a unilateral injection of 6-hydroxydopamine, a dopamine-depleting neurotoxin, can be held so that they are standing on a single forelimb. When gently pushed forward, they will step to gain postural support with their good forelimb while being reduced to bracing with their bad forelimb (Olsson et al. 1995; Schallert et al. 1992).

Righting Response

When placed in a condition of unstable equilibrium, animals will attempt to regain an upright posture in relation to gravity, a behavior termed righting. Tests of righting examine visual, vestibular, tactile, and proprioceptive reflexes. If an animal is dropped from the height of less than a meter, onto a cushion, it will adjust its posture so that it lands "on its feet". If released with feet facing down, it arches its back, and extends its limbs to parachute to the surface. If it is released in a prone position, it will right itself by first turning the forequarters of the body and then the hindquarters, a response mediated by vestibular receptors. Video recordings of righting responses show that righting is also visually modulated. Sighted animals right proximal to the landing surface, whereas in the absence of visual cues, animals initiate righting immediately upon release. If a rat is placed on its side or back, on the surface of a table, it will right itself so that it returns to its feet. The righting responses of parts of the body can be tested by holding the head, forequarters, or hindquarters. Details of righting reflexes and their sensory control are provided by Pellis (1996).

IV. Locomotion

Locomotor behavior includes all of the acts in which an animal moves from one place to another (see Table4). It includes the acts of initiating movement, which is often referred to as warm-up, turning behavior, exploratory behavior, and a variety of movement patterns on dry land, water, or vertical substrates.

Table 4. Locomotion

General Activity	Video-recording, movement sensors, activity wheels, open field tests.
Movement Initiation	The warm-up effect: Movements are initiated in a rostral-caudal sequence, small movements precede large movements, and lateral movements precede forward movements, which precede vertical movements.
Turning and Climbing	Components of movements can be captured by placing animals in cages, alleys, tunnels, etc.
Walking and Swimming	Rodents have distinctive walking and swimming patterns. Rats and mice walk by moving limbs in diagonal couplets with a forelimb leading a contralateral hindlimb. They swim using the hindlimbs with the forelimbs held beneath the chin to assist in steering.
Exploratory Activity	Rodents select a home base as their center of exploration, where they turn and groom, and make excursions of increasing distance from the home base. Outward trips are slow and involve numerous pauses and rears while return trips are more rapid.
Circadian Activity	Most rodents are nocturnal and are more active in the night portion of their cycle. Peak activity typically occurs at the beginning and end of the night portion of the cycle. Embedded within the circadian cycle are more rapid cycles of eating and drinking, especially during the night portion of the circadian cycle.

Warm-up Movement is conceived of as being organized along three dimensions as is illustrated by warm-up. The initiation of locomotion, or warm-up, may be observed in an animal gently placed in the center of an open field (Golani et al. 1979). There are four principles of warm-up.

1. Lateral, forward, and vertical movements are independent dimensions of movement. During warm-up, an animal can be observed to alternate between lateral, forward, and vertical movements.
2. Small movements recruit larger movements. For example, a small lateral head turn will be shortly followed by a larger head turn and so forth until the animal turns in a complete circle.
3. Rostral movements precede caudal movements. That is, a head turn will precede movements of the front limbs, which will precede movements of the hind limbs.
4. The relationship between the movements is such that lateral movements precede forward movements which precede vertical movements. In a novel environment, warm-up may be lengthy while in a familiar environment it may precede quickly, e.g., an animal may simply turn and walk away. Almost any nervous system treatment or pharmacological treatment may affect warm-up. Conceptually, warm-up is thought to be a reflection of evolutionary and ontogenetic processes, and brain structural organization (Golani 1992). Functionally, warm-up allows an animal to systematically examine an environment into which it is moving.

Turning Rodents have a variety of strategies for turning. Turning may be incorporated into patterns of forward locomotion, in which case an animal turns its head and then "follows" using a normal walking pattern. Incorporated into this pattern, or used independently, it may make most of the turn with the hindquarters, thus pivoting in part or in whole around its hindquarters, or most of the turn with its forequarters, thus pivoting around its forequarters. These two patterns of turning are incorporated into a variety of other behaviors including locomotion, aggression, play, and sexual behavior. In rats, there is sexual dimorphism in the extent to which the patterns are used (Field et al. 1997). Females make greater use of forequarter turning whereas males make greater use of hindquarter turning. Dimorphism, in turn, may be related to the way the animals turn during sex and aggression, respectively. Animals may also turn by first rearing and then using the potential energy of the rear to pivot and fall in one direction or the other.

The incidence of turning as well as the form of turning is widely used as an index of asymmetrical brain function (Miklyaeva et al. 1995). For example, animals with unilateral dopamine depletions turn ipsilateral to their lesion when given amphetamine and contralateral to their lesion when given apomorphine. Some papers have suggested that direction of rotation can be used as an index of recovery after therapeutic treatments (Freed 1983). Miklyaeva and colleagues' analysis shows, however, that the depleted rats tend not to exert force with the limbs contralateral to their lesion and the impairment persists irrespective of turning direction or drug treatment (Fig. 6). Thus it is more appropriate to use analyses of limb use rather than turning direction in assessing functional recovery (Olsson et al. 1995; Schallert et al. 1992). The causes of turning direction induced by drugs remain enigmatic.

Walking and Running Although this may be a little difficult for the novice to observe, a rodent's major source of propulsion comes from its hindlimbs. During slow locomotion, the forelimbs are used for contacting and exploring the substrate and walls (Clarke 1992). Limb contact with irregular surfaces or the wall of a cage can be used as a test of normal forelimb function. At its simplest, the number of times a limb contacts a wall when an animal rears can be a sensitive measure of forelimb function (Kozlowski et al. 1996).

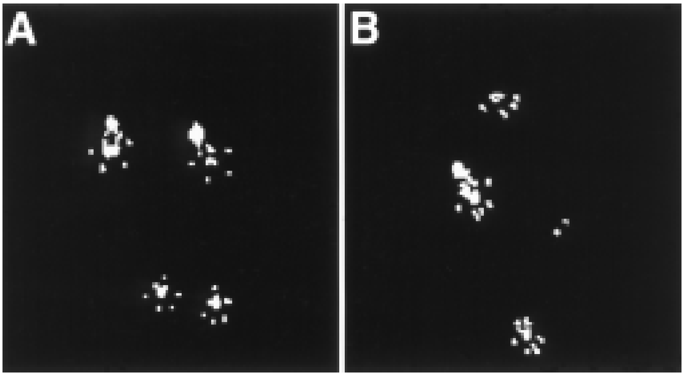


Fig. 6. Limb use can be examined using the reflectance technique, in which a light shone through the edge of a glass table top reflects from the paws of an animal standing on the table surface. The technique illustrates that a control animal distributes its weight evenly when standing while a rat with unilateral dopamine depletion rests its weight on its good (ipsilateral to lesion) limbs (After Miklyaeva et al, 1995).

When a rodent does walk, it moves with diagonal limb couplets. One forelimb and the contralateral hindlimb move together followed by the other forelimb and hindlimb. Rodents also have species typical movement patterns. For example, rats seldom walk. They move either hesitantly with turns and pauses or they trot. Patterns of locomotion are difficult to analyze by eye unless they are grossly abnormal, but a number of simple video-recording techniques have been used for detailed locomotor analysis (Clarke 1992; Miklyaeva et al. 1995). The structure of walking movements has been described by Ganor and Golani (1980).

Exploration

The movements of an animal can be observed by removing it from its cage and placing it in a small open environment or field. Golani and coworkers have described some of the geometric aspects of rodent exploratory behavior (Eliam and Golani 1989; Golani et al. 1993; Tchernichovski and Golani 1995). An animal will usually treat the place at which it is first placed as a "home base". It will pause, rear, turn, and groom at this location, often before exploring the rest of the open field. When it does rear, it will support itself by touching the wall of the field with its forepaws. As it begins to explore, it extends its forequarters and head and examines the area surrounding its home base. It will eventually begin to make trips away from its home base, usually along the edge of the walls of the enclosure. Exploration will proceed with brief and slow outward excursions followed by more rapid returns to the home base. The outward excursions become gradually longer until the surrounding area is explored. During the course of its exploration, the animal may choose another location as its home base and this can be identified because it circles and grooms at this location and uses the location as the home base for its outbound trips. Typically, return trips are more rapid than outbound trips. A ten-minute exploratory test can provide a wealth of behavior to analyze, including number of home bases, number of trips, kinematics of excursions and returns, number of stops, number of rears, incidence of grooming, duration of trips, etc. (Golani et al. 1993; Whishaw et al. 1994).

Another feature of open field behavior is habituation. Over time, animals normally will show a reduction in open field activity. Furthermore, they will show a shift in behavior and may spend more time grooming or sitting immobile once they are familiar with the environment. Animals with various forebrain injuries, such as frontal cortex or hippocampal lesions, may display slower habituation, even with extended exposure to the open field (e.g. Kolb 1974).

Swimming If a swimming pool is available, movements of swimming can be observed. Rats are semiaquatic, as their natural environments are usually along the margins of streams and rivers. Rats are proficient swimmers and propulsion comes entirely from the hindlimbs. Other rodents may be less proficient in water than rats, and some may use quite idiosyncratic swimming strategies. Hamsters, for example, inflate their cheek pouches and use them as "water-wings". In typical rodent swimming, the forelimbs are tucked up under the chin and the open palms of the paws are used for steering (Fish 1996; Salis 1972). Changes in the way that animals swim may occur with development and aging, under the effects of drugs and brain damage, but swimming itself is quite resistant to central nervous system damage (Whishaw et al. 1981b).

Circadian Activity Tests of circadian activity involve recording the general activity of animals across a day-night cycle. Usually the activity cycle is entrained by having lights come on at 0800 hrs and go off at 2000 hrs. Rodents are typically active during the dark portion of the cycle. The test requires a dedicated room in which lighting can be regulated with a timer. A test apparatus consists of a cage that has a photocell at each end. The photocells are connected to a microcomputer which records instances of beam breaks. The computer is programmed so that it records beam breaks at each photocell as well as instances in which beam breaks occur at successive photocells. Beam breaks at a single photocell provide a measure of stereotyped movements, such as head bobbing, grooming, circling etc. Successive beam breaks provide a measure of locomotion, i.e., walking from one end of the cage to the other. If an animal is placed in the activity cages at 1200, it is initially very active in exploring the apparatus but habituation occurs across the first hour or two. At 2000 hrs, when the light turns off, there is a burst of activity followed by bouts of increased activity across the dark cycle. Just prior to light on at 0800 hrs animals show another burst of activity. During subsequent lights-on periods, animals are typically inactive. These features of circadian activity can be recorded in a single twenty-four recording period and one recording session can frequently reveal distinctive differences between control and experimental groups. More detailed analysis of circadian activity can be examined in which the effects of light, sound, feeding and so forth are assessed (Mistleburger and Mumby 1992). Figure 7 illustrates circadian activity in eating speed in rats on different levels of food deprivation. Rats eat more quickly at their usual feeding times at the onset and offset of the lights-off period.

V. Skilled Movement

The term "skilled movements" is somewhat arbitrary in that it refers to movements in which the mouth or paws are used to manipulate objects. The term may also be used to include movements used to traverse difficult terrain, such as walking on a narrow beam or climbing a rope, and swimming (see Table 5). The cohesive feature of the movements is that they seem much more disrupted by cortical lesions than are species-typical movements or movements of locomotion on a flat surface. The distinguishing feature of the movements is that they require rotatory movements, irregular patterns movement, selective movements of a limb, and movements that break up the patterns of normal antigravity support (Fig. 8). Skilled movements in rodents and primates are quite comparable, which makes rodent models quite generalizable to humans (Whishaw et al. 1992b). Two commonly used tests of skilled movement are beam walking and skilled reaching.

Beam Walking When a normal rat walks a narrow beam, it has the surprising ability to move along rapidly with its feet placed on the dorsal surface of the beam. A sign of motor incoordination is that it grasps the edge of the beam with its digits as it walks. Following unilateral motor system damage, only the contralateral paws are likely to be used for grasping.

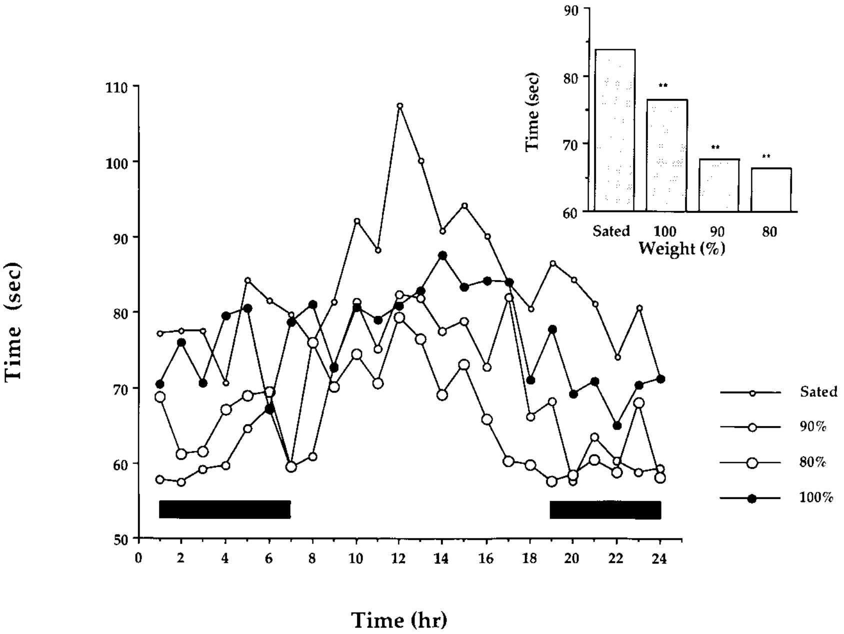
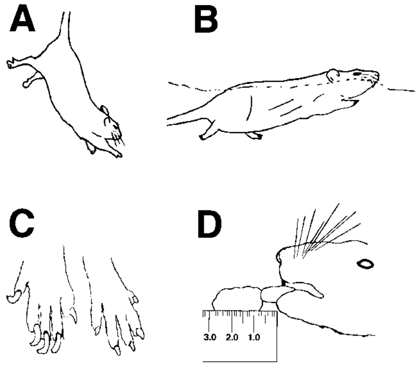


Fig. 7. Time taken to eat a one-gram food pellet as a function of time of day and food deprivation. Sated rats were never food-deprived, 100% represents rats previously food-deprived to 90 and 80% and returned to free feeding. Note that rats eat more quickly after having been subject to food deprivation, when hungry, and at usual feeding times (After Whishaw et al, 1992).

Table 5. Skilled Movements

Limb Movements	Bar-pressing, reaching and retrieving food through a slot, spontaneous food handling of objects or nesting material and limb movements used in fur grooming and social behavior. Rodents use limb movements that are order-typical and species-typical.
Climbing and Jumping	Movements of climbing up a screen, rope, ladder, etc. and jumping from one base of support to another.
Oral Movements	Mouth and tongue movements in acceptance or rejection of food such as spitting food out or grasping and ingesting food. Movements used in grooming, cleaning pups, nest building, teeth cutting.

Fig. 8. Examples of skilled movements. A: When lifted in the air, a rat reaches with its forelimbs to regain postural support. B: When swimming, a rat tucks the forelimbs under the chin and tilts the paws to steer. C: Toenails are regularly clipped (right) and if skilled movements of chewing are impaired, they grow long (left). D: Skilled movements of the tongue are used to reach for food as illustrated by a rat licking through the bars of a cage to obtain food from a ruler. Maximum tongue extension is about 11 mm.



Grasping can be measured by video-recording the placement of the paws on the beam or by painting the feet of the animals so that paw placement can be visualized (Becker et al. 1987). The overall body posture of the animal also may be abnormal on a narrow beam. This can be quantified by measuring the angle of the back and head relative to the beam (e.g. Gentile et al. 1978). Another formal test related to beam walking is balancing on a rotating rod, the "rotorod" test. The test consists of a rotating rod upon which the animal balances. As the animals learn to balance, the rod is turned increasingly faster. The measure of motor skill is the time the animal spends on the rotorod as a function of speed with which the rod rotates (Le Marec et al. 1997).

Skilled Forelimb Movements

Rodents use their paws and digits to reach for, hold, and manipulate food. Tests of skilled forelimb use have an animal reach through a slot to obtain a food pellet. One form of the test has animals reach into a tray to retrieve food (Whishaw and Miklyaeva 1996). Limb preference and success (number of pellets per reach) are used as performance measures. Limb use by an animal can also be controlled by restricting the use of one limb, thus forcing the animal to use the other limb. If the animal is reaching through a slot, a bracelet placed on a limb will prevent the animal from inserting its limb through the slot while otherwise leaving use of the limb unimpaired. A second form of the test has an animal reach for a single food pellet while its movements are filmed (Whishaw and Pellis 1990). Video analysis of skilled reaching shows that rodents use a variety of whole body preparatory movements and the reach itself consists of a number of subcomponents such as limb lifting, aiming, pronating, grasping, and supination upon withdrawal. Animals with central nervous system damage may learn to compensate for their impairments and regain presurgical performance as judged by success measures, but movement analysis will indicate that the movements used in reaching are permanently changed (see Fig. 2). Use of the forelimbs can also be evaluated by watching spontaneous food retrieval and manipulation. With the exception of guinea pigs, most rodent species have five "order-typical" movements in spontaneous eating (Whishaw et al. 1998). They (1) identify food by sniffing, (2) grasp food in the incisors, (3) sit back on their haunches to eat, (4) take the food from the mouth with an inward movement of the forelimbs, and (5) grasp and handle the food with the digits. Each of these movements has its characteristic features that can be subject to further analysis and there are species-typical features of the movements in different rodents (Fig. 9).

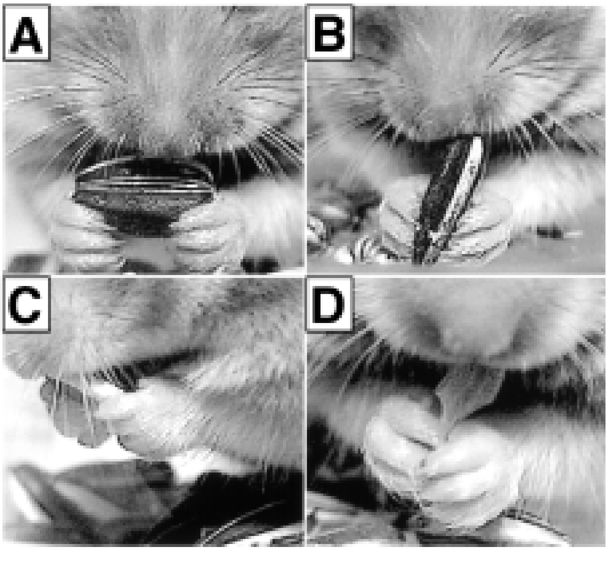


Fig. 9. Skilled paw and digit movements in a hamster. A,C: Food is held between digit 1 (thumb) and digit 2. B: Food is held with all digits. D: Food is held bilaterally with digit 1.

VI. Species-Typical Behaviors

Most movements performed by rodents are sufficiently stereotyped that they are recognizable from occurrence to occurrence and from animal to animal within a species. A variety of complex actions, however, are referred to as species-typical movements (see Table 6). Examples of species-typical behaviors include grooming, nest building, play, sexual behavior, social behavior, and care of young. With the resolution provided by a video record, it is possible to document successive behavioral acts in species-typical behavior in order to produce a description of their order or syntax.

Table 6. Species-Specific Behaviors

Grooming	Grooming movements are species-distinctive and are used for cleaning and temperature regulation. Begin with movements of paw cleaning and proceed through face washing, body cleaning, and limb and tail cleaning.
Food Foraging/ Hoarding	Food carrying movements are species-distinctive and used for transporting food to shelter for eating, scattering food throughout a territory, or storing food in depots. Size of food, time required to eat, difficulty of terrain, and presence of predators influence carrying behavior. Both mouth-carrying or cheek-pouching are used by different species. Rodents also engage in food wrenching, in which food is stolen from a conspecific, and dodging, in which the victim protects food by evading the robber.
Eating	Incisors are used for grasping and biting, rear teeth are used for chewing, tongue is used for food manipulation and drinking.
Exploration/ Neophobia	Species vary in responses to novel territories and objects. Objects are explored visually or with olfaction, avoided, or buried. Spaces are explored by slow excursions into space and quick returns to a starting point. Spaces are subdivided into home bases, familiar territories, and boundaries.
Foraging and Diet Selection	Food preferences are based on size and eating time of food, nutritive value, taste, and familiarity. For colony species the colony is an information source with acceptable foods identified by smelling and licking snout of conspecifics.
Sleep	Rodents display all typical aspects of sleep including resting, napping, quiet sleep and rapid eye movement sleep. Most rodents are nocturnal, thus sleeping during the day with major activity periods occurring at sun up and sun down. Cycles in natural habitats vary widely with seasons.
Nest-building	Different species are nest builders, tunnel builders, and build nests for small family groups or large colonies. All kinds of objects are carried, manipulated, and shredded for nesting material.
Maternal Behavior	Laboratory rodents typically have large litters that are immature when born. Pups are fed for the first two to three weeks of life and thereafter become independent.
Social Behavior	Colony or family rodents have rich social relations including territorial defense, social hierarchies, family groupings, and greeting behaviors. Solitary rodents may have simplified social patterns. Defensive and attack behavior in males and females is distinctive.
Sexual Behavior	Characteristic sexual behavior displayed by males and females. Males display territorial control or territory invasion, and engage in courtship and often group sexual behavior. Sexual behavior is often long-lasting with many bouts of chasing, mounting and intromission, and incidents of ejaculation. Mounting is followed by genital grooming and intromission is followed by immobility and high frequency vocalizations. Females engage in soliciting including approaches and darting, pauses and ear wiggling, and dodging and lordosis to facilitate male mounting.
Play Behavior	Many rodents have rich play behavior with the highest incidence in the juvenile period. Play typically consists of attack in which snout-to-neck contact is the objective and defense in which the neck is protected.

Grooming Berridge (1990) provides a comparative description of the grooming behavior of a number of species of rodents, including most rodents commonly used in laboratories. His method involved filming the animal through a mirror placed beneath the animal's holding cage. Grooming was elicited by spraying a little water onto an animal's fur. A typical grooming sequence consists of an animal walking forward and making a few body shakes to remove the water from its fur. Then it sits back onto its haunches, in which posture it performs a number of grooming acts in a relatively fixed sequence. The animal first licks its paws and then wipes its nose with rotatory movements of the paws. This is followed by face washing, which consists of wiping the paws down across the face, with the successive wiping movements becoming larger until the paws reach behind the ears and then wash downward across the face. Once an animal has finished a sequence of head grooming, it turns to one side, grasps its fur with a paw and then proceeds to groom its body (Fig. 10). A single grooming bout thus begins at the snout and moves caudally down the body and may consist of more than one hundred individual grooming acts.

Berridge has examined the internal consistency of grooming, that is the extent to which one grooming act predicts another, to derive a grooming syntax. The syntax, in turn, provides the baseline against which central nervous system manipulations are contrasted. The grooming syntax of rats and mice, which are each other's closest relatives, is slightly different in that mice make fewer asymmetrical limb movements when face washing. The grooming of other less closely related rodents is different still. For instance, an animal may use only a single limb to wipe the face. Grooming syntax in turn becomes a powerful tool for the analysis of neural control of action patterns. For example, to answer the question of whether grooming is produced by a grooming center or has its control distributed across a number of neural systems, Berridge and coworkers have sectioned the brain at various rostrocaudal levels to find that different features of grooming control are represented at many different nervous system levels (Berridge 1989).

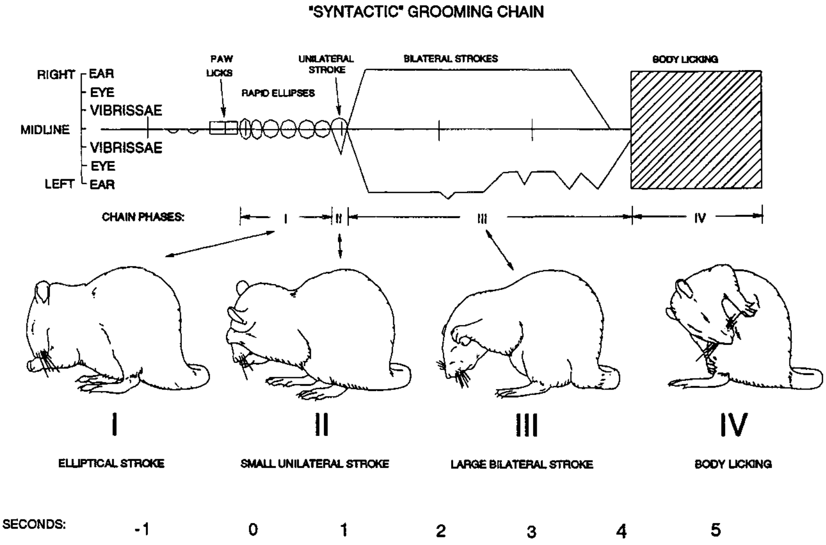


Fig. 10. Choreographic transcription of an idealized syntactic grooming chain. Time proceeds from left to right. The horizontal axis represents the center of the nose. The line above the horizontal axis denotes movement of the left forepaw. Small rectangles denote paw licks. Large rectangle denotes body licks. Chain phases are: (I) 5 to 8 rapid elliptical strokes around the nose (6.5 Hz); (II) unilateral strokes of small amplitude; (III) symmetrically bilateral strokes of large amplitude; (IV) licking the ventrolateral torso (After Berridge and Whishaw, 1992).

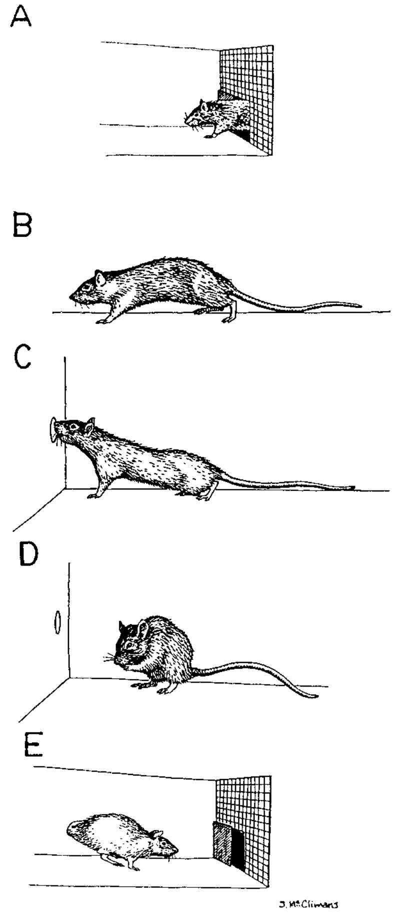


Fig. 11. Foraging in the rat for food items that are passed to it through a hole in the test apparatus. A: The animal "stops, looks and listens" before leaving its home base. B: The food location is approached cautiously. C: Food items that can be eaten quickly are swallowed. D: Larger items are eaten from a sitting position. E: Very large items are carried "home", usually at a gallop. (After Whishaw et al, 1990).

Food Hoarding

Rodents have a number of food handling patterns depending upon the time required to eat food (Fig. 11). Rodents are usually cautious in leaving the home base and cautious in approaching a food source. Small pieces of food that take little time to eat are consumed in situ, items that take a little longer to eat are consumed from a sitting posture, while items that take a long time to eat are carried to a secure location or to the home base. Rodents that cheek-pouch carry items of all sizes whereas animals that do not cheek-pouch eat smaller items at the location at which they are found and carry larger objects. The decision on whether to carry an object is based on an estimate of eating time. Food carrying animals may store food in a single central location, such as a nesting area, hide it at a number of locations, or hide individual items throughout a territory. Colony living rodents may carry food to a home area but here it is likely to be stolen and eaten quickly by other colony members (Whishaw and Whishaw 1996). Tests of food carrying are used to evaluate exploration, spatial abilities, time estimates, and social competition for food (Whishaw et al. 1990).

Foraging and Diet Selection

A rodent colony is frequently an information center, especially regarding novel foods (Galef 1993). Rodents, especially those that have been subjected to attempts at eradication, are extremely wary of novel objects and foods, a trait called neophobia. Thus, rodents in a colony may share information about types of foods, food safety, and food locations. An animal will sniff and lick the snout of a conspecific and so gain information about food types and sources. Sulfur dioxide on the breath of the conspecific indicates to the inquirer that the food is palpable. Tests of neophobia and information sharing can be used to study both learning and social behavior in animals (Galef et al. 1997). Pairing food items with a sickness-inducing agent is commonly used to study food aversion responses (Perks and Clifton 1997). Conditioned aversion is considered a special form of learning because the ingestion of food and subsequent illness may be separated by hours or days but will still be strongly acquired.

Nest Building

If rodents are provided with appropriate material, they will build nests (Kinder 1927). The nests contribute to thermoregulation and provide a place to gather young. The quality of a nest built by female rats will also wax and wane over the four-day esterous cycle. If an animal is given strips of paper about 2 cm wide and 20 cm long, each behavior involved in nest building can be recorded as it occurs, e.g., pick up material, carry, push, chew, etc. The quality of the nest constructed can be rated on a four-point scale over three to four days, the time required to fashion an optimal nest. Limbic system and medial frontal cortex lesions have been reported to disrupt nest building (Shipley and Kolb 1977).

Social Behavior

Social behavior can be defined as all behavior that influences, or is influenced by, other members of the same species. The term thus covers all sexual and reproductive activities and all behavior that tends to bring individuals together as well as all forms of aggressive behavior (e.g. Grant 1963). It is traditional to describe sexual behavior separately (see below), and in recent years aggressive behavior has also come to be seen as a separate form of social behavior as well (see below).

It is generally recognized that social behavior is not a unitary behavior with a unitary neurological basis. Rather, different aspects of social behavior have different neural and endocrine bases (e.g. Moyer 1968). It is therefore necessary to examine social behavior in a number of different situations before concluding that a particular treatment has produced a general change in social behavior; behavioral changes may be situation-specific. Most studies of social behavior in rodents usually utilize some type of test of free interaction in which a group of subjects are housed in a large group cage, often with several interconnected chambers (e.g. Lubar et al. 1973). A less natural version has animals paired in a novel situation, often repeatedly over days (e.g. Latane 1970). In both situations the behavior is videotaped and can either be analyzed by calculating specific behaviors, such as time in contact, or by writing a detailed description of the behaviors such as described by Grant and Mackintosh (1963). Other behaviors such as vocalizations (e.g. Francis 1977) or urine marking (e.g. Brown 1975) can also be recorded.

Aggression

Aggressive behavior is used to establish social hierarchies and to defend territories. As rodents vary widely in their tendency to live in colonies or in relative isolation, their tendency to engage in aggressive behavior also varies. Patterns of aggressive behavior are also usually distinctive in male and female animals. The targets of aggressive contact, e.g. the location on the body on which an animal attempts to inflicts bites, are usually quite distinctive from the targets of play contact (Pellis 1997). In rats, bites are typically directed to the back and rear. Fellow residents and strangers are usually identified by their odor. Aggressive behavior is widely used as an animal model of human aggression (Blanchard et al. 1989).

Sexual Behavior

Sexual behavior requires the integrity of hormonal systems and neural systems, requires developmental experiences, learning, context and an appropriate partner. Sexual behavior consists of at least two phases, courtship and consummation, and both are extremely complex requiring complex independent and interdependent actions by both the male and female. Dewsbury (1973) has described the social behaviors associated with sexual activity, including exploration, sniffing, grooming, soliciting, ear wiggling, hopping and darting in females, genital and nongenital grooming, as well as mounting, pelvic thrusting, ejaculation, lordosis, immobility, ultrasonic songs, etc. The patterning of movements of sexual behavior has been described by Sachs and Barfield (1976) for male rats and Carter et al. (1982) for female rats. Paradigms in which the female is given the opportunity to pace sexual activity are described by Mermelstein and Becker 1995. Paradigms in which interest in access to sexual partners and interest in sexual intercourse are described are presented by Everitt (1990). Michal (1973) provided a detailed discussion of the behavioral patterns of rats with limbic lesions.

Care of Young

Rodents are immature when born and are hairless with immature sensory and motor systems and receive extensive parental care (Grota and Ader 1969). Pups are cared for mainly by the mother with elaborate patterns of pup cleaning and feeding under hormonal and thermoregulatory control (Leon et al. 1978). Thermoregulation influences much of the pups' social behavior as they have elaborate huddling strategies (Alberts 1978).

Play

Rodents may display play behavior at any stage of development, but play is particularly prominent during the juvenile stage of life. Play is highly ritualized but incorporates many of the movements used by animals in other aspects of life, including sex, aggression, and skilled manipulation. In rodent play, the rich array of movements used by the participants appears to be orchestrated around the attempt of an initiator to thrust the tip of its snout into the neck of the recipient while the recipient attempts to avoid the contact (Fig. 12). The patterns of thrust and parry are distinctive in different rodent species (Pellis et al. 1996).

VII. Learning

Research on the neural basis of learning suggests that there are a number of at least partially independent learning and memory systems. These include short-term memory (thought to be a frontal lobe function), object memory (thought to be a function of rhi-

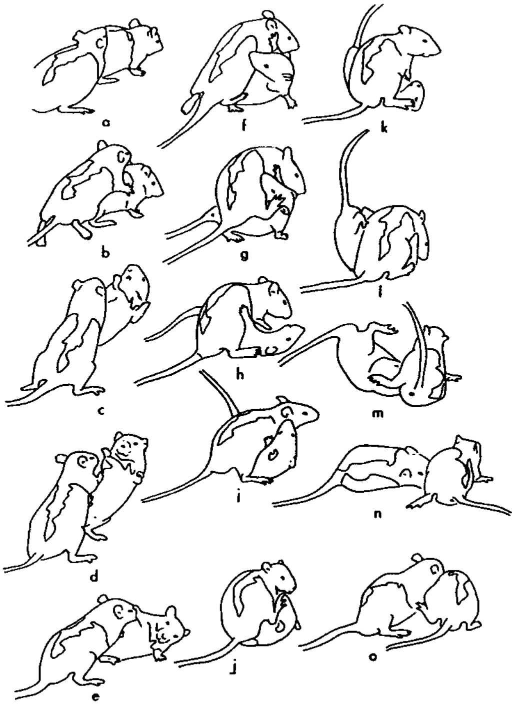


Fig. 12. A sequence of play fighting between two 30-day-old male rats. Note the repeated attack and defense of the **neck** (After Pellis et al. 1996).

Table 7. Learning

Classical Conditioning or Conditional Learning	Unconditioned stimuli are paired with conditioned stimuli and the strength of an unconditioned response to the conditioned stimuli is measured. Almost any arrangement of stimuli, environments, treatments, or behavior can be used.
Instrumental Conditioning	Animals are reinforced for performing motor acts such as running, jumping, sitting still, lever pressing, or opening puzzle latches.
Avoidance learning	Passive responses including avoiding preferred places or objects which have been associated with noxious stimuli such as electric shock. Active responses including moving away from noxious items or burying noxious items.
Object Recognition	Including simple recognition of one or more objects, matching to sample, and nonmatching to sample in any sensory modality. Tasks are formal in which an animal makes an instrumental response or inferential in which recognition is inferred from exploratory behavior.
Spatial Learning	Dry land- and water-based tasks are used. Spatial tasks can be solved using *allothetic cues,* which are external and relatively independent to movements, or *idiothetic cues,* which include cues from vestibular or proprioceptive systems, reafferance from movement commands, or sensory flow produced by movements themselves. Animals are required to move to/away from locations. *Cue tasks* require responding to a detectable cue. *Place tasks* require moving using the relationships between a number of cues, no one of which is essential. *Matching tasks* require learning a response based on a single information trial.
Memory	Memory includes *procedural memory* in which response and cues remain constant from trial to trial and *working memory* in which response or cues change from trial to trial. Tasks are constructed to measure one or both types of learning. Memory is typically divided into object, emotional, and spatial and each category can be further subdivided into sensory and motor memory.

nal cortex), emotional memory (thought to be functions of the amygdala and related circuits), and implicit and explicit spatial memory (thought to be a function of the neocortex and hippocampal formation, respectively). A quick overview of an animal's learning ability therefore requires a number of tests, in order to tap into all of these systems (see Table 7). Widely used tests for rodents include

- Passive avoidance,
- Defensive burying,
- Conditioned place preference,
- Conditioned emotional response,
- Object recognition task,
- Swimming pool place and matching-to-place tasks.

Although these tests provide a rapid way of screening for learning and memory deficits, all of the tests are sensitive to quite a number of different functions and brain regions. At this point, we emphasize that the enormous number of tests in all their variations and the diversity of opinion concerning what they actually measure requires consultation with more comprehensive sources than provided here (see Olton et al. 1985; Vanderwolf and Cain 1994).

Memory

Memory is also often described as being either procedural or working memory. *Procedural memory* is memory for the rules of task solution. For example, the rule may be that food is found at the end of an alley or that an escape platform is located somewhere in the swimming pool. *Working memory* is trial unique memory; that is, "on the last trial I found food here". It is thought that each sensory or motor system may be involved in system-specific procedural or working memory. For example, the visual pathway underlying the perception of objects is likely to be involved in the storage of object information. Memory is also described as being either *short-term*, to be used only for the moment, or *long-term*, to be used for long durations. That is, for each of the kinds of memory described above, there are procedural and working memory, short-term, and long-term memory. Detailed discussion concerning terminology, tests, and their significance can be found in comprehensive sources (Dudai 1989; Martinez and Kesner 1991).

Passive Avoidance

The passive avoidance apparatus consists of a box with two compartments and a connecting door. One of the boxes is white and the other is black, and the floor of both boxes is constructed of grids which can pass a small electric shock. An animal is placed in the white compartment each day for three days and is removed after it has crossed over into the dark compartment. As most rodents display a strong preference for the dark, by the third day the animal's passage between the boxes is quite quick. Now, however, the animal is given a brief electric shock when it enters the dark compartment. After one hour to twenty-four hours, the animal is once again placed in the white compartment of the box and the measure of learning is the time taken to again enter the now noxious dark compartment. Usually, a five-minute cutoff for entry is used. Passive avoidance has been found to be a very sensitive measure of the effects of drugs that affect memory, such as the muscarinic blocker atropine (or scopolamine). Certain kinds of brain damage, including damage to the limbic system and globus pallidus and their transmitters, are similarly sensitive to the passive avoidance task (Bammer 1982; Slagen et al. 1990).

Defensive Burying

The strength of the defensive burying test is that it provides a natural test of an animal's response to a threatening or noxious object. A large number of modifications of the test and their uses have been described by Pinel and Treit (1983). Traditionally, animals have been thought to have two primary defensive strategies, flight or fight. The defensive burying paradigm reveals that the responses of rats and mice (but not gerbils and hamsters) to threat are much more complex than has been thought and include investigating the object, removing it, or burying it so that it is no longer threatening. At its simplest, an animal is placed in and briefly habituated to a box that contains sawdust on the floor. After habituation, a probe that can deliver a shock is inserted into the box through a hole in the wall. When the animal investigates the object, it receives a brief electric shock from the probe. The response of the animal is to first withdraw from the object, then investigate it cautiously, and finally to use the forelimbs to cover the object with sawdust. Measures of the strength of learning about the probe include the number of times the animal investigates the object, the length of time that it spends burying the object, and the depth of the sawdust that eventually covers the object. A variety of variations of the task have been used, including burying objects that deliver noxious sounds or odors. Animals will also bury other objects that are proximal to the offending object, indicating that the burying response can be secondarily conditioned to other objects. Defensive burying has been used to examine the effects of aging on behavior and also to examine the effects of potential anti-anxiety agents (Pinel and Treit 1983).

Object Recognition

Object recognition can be tested in a three-compartment box, also called the Mumby box (Mumby and Pinel 1994; Mumby et al. 1989), or other similar test situations (Ennaceur and Aggleton 1997). The central compartment of the box is a waiting area and is connected to two side boxes, choice box one and choice box two, by sliding doors. A door is opened and the animal is allowed to enter choice box one, where it finds two food wells, one of which is covered by a "sample" object. When it displaces the sample, it receives a food reward. The rat then shuttles into the waiting area until it is allowed access to choice box two. Here it again finds two food wells, one covered by an object identical to the previously encountered sample in choice box one, and a novel object. To obtain food reward, it must displace the novel object. New sample and novel trials are given with new sample and novel objects. The measure of success is the animal's memory that sample objects will not provide reinforcement on two successive trials. The rodent object recognition test is similar to nonmatching-to-sample tests previously developed for primates. Both short-term and long-term memory for objects can be measured by introducing a delay of variable duration after the sample trial. Object recognition in more natural environments uses very similar methodology to that described above, but the time spent sniffing and examining objects or animals placed in the animal's home environment is used as the measure of recognition.

Conditioned Place Preferences

The conditioned place preference task takes advantage of the fact that objects, events, or substances that an animal finds pleasant or noxious become conditioned to the location in which the object, event, or substance is encountered (e.g., Cabib et al. 1996; Schechter and Calcagnetti 1993). Typically, a two-compartment box is used and the measure of behavior is the time spent in the compartments. For example, if the experiment wishes to determine whether a drug treatment is perceived as being pleasant, the animal is exposed to one of the compartments of the box while under the effects of the drug. At some later date, while undrugged, the animal is given access to the original box or to a different box. If the animal spends more time in the original "conditioned" box, that can be taken as evidence that the animal perceived the treatment as positively rewarding, while if it shows a preference for the other box, it perceived the treatment as negatively rewarding. Conditioned place preferences can be modified to measure the strength of memories and their duration by varying intervals between sample and test trials.

Spatial Navigation

A large number of maze tests has been used to measure spatial navigation (Fig. 13). The central idea for all of the tests consists of having an animal: (1) learn to find food at one or more locations, or (2) escape to a refuge from different locations. Most of the tests are administered on dry land, but because of the excellent swimming ability of the rat, tests have been developed in a swimming pool. The two most widely used tests are the radial arm maze and the swimming pool place task.

The radial arm maze consists of a central box or platform from which protrude a number of arms (Jarrard 1983; Olton et al. 1979). The location of the arms is either fixed or marked by a cue on the arm (e.g., roughness of the surface of the arm, the color of the arm, a light at its end, etc.). Food is located at the end of one or more arms. The task of the animal is to learn the location of the food over a number of test days. This evaluates its ability to form a procedural memory for the task. The animal's performance can be interrupted to see if it can "pick up where it left off" in order to evaluate its working memory.

The swimming pool task has become extremely popular, mainly because the animals do not have to be food- or water-deprived to motivate them to perform (McNamara and Skelton 1993; Morris 1984; Sutherland and Dyck 1984; Whishaw 1985). Although the task is excellent for the rat, which is semiaquatic, it may be less useful for other species (Whishaw 1995). The apparatus consists of a circular round pool about 1.5 m in diameter, filled with tepid water made opaque with powdered milk, paint, sawdust, or floating beads. A platform about 10 cm sq is placed in the pool with its surface either visible or hidden about 1 cm beneath the surface of the water. The animal is placed into the water facing the wall of the pool, and in order to escape from the water, must reach the platform. On successive trials, the animal is placed into the water at new locations, and its response time decreases until it escapes by swimming directly to the hidden platform. Its ability to learn to escape to a platform hidden at a fixed location is thought to be a measure of spatial procedural memory. If the platform is moved repeatedly to new locations, the task becomes mainly a test of spatial working memory (Whishaw 1985). That

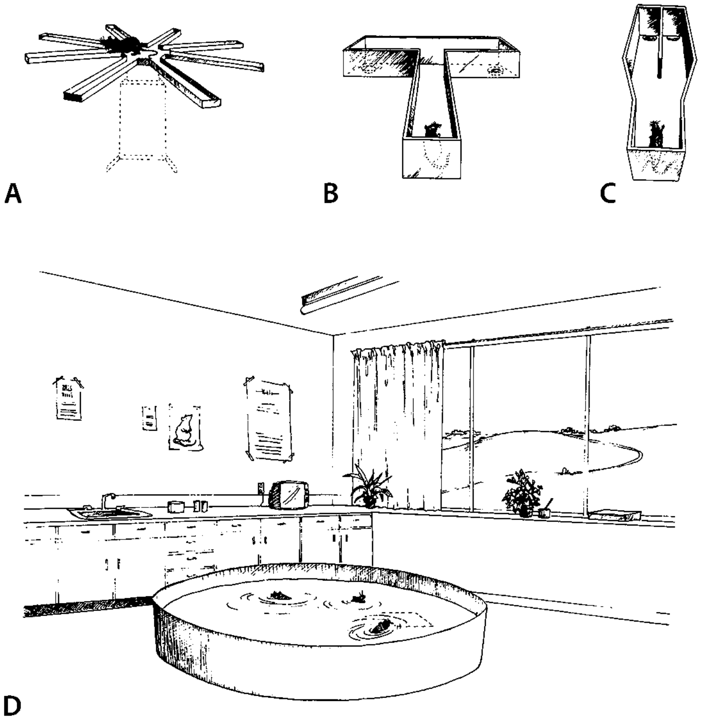


Fig. 13. Spatial tasks: A: radial arm maze in which food is located only at the end of some arms, B: T-maze in which food is located in one arm, C: Grice box in which food is located on one side, D: swimming pool task, in which an animal searches for a platform hidden just beneath the surface of the water. The tests are usually conducted in a open room that provides many spatial cues.

is, the animal has to match on its second trial the location at which the platform was found on the first trial.

At their simplest, spatial tasks attempt to measure three aspects of spatial behavior.

- Place tasks measure whether an animal can find a food item or an escape platform using the relational properties of ambient cues, usually visual cues.
- Cue tasks measure whether an animal can find a food item or an escape platform using a visible cue marking the location of the target.
- Response tasks measure whether an animal can use body cues, e.g., turn left or right, to locate an object.

It is widely assumed that these different types of spatial learning are mediated by different neural systems. Thus administration of more than one task can be used to dissociate spatial functions.

Comments: Generalizing from Behavioral Analysis

Because the ultimate goal of studies on rodents is to understand the brain-behavior relationships in humans, it is reasonable to ask to what extent the behavior of rodents is useful in understanding human brain-behavior relationships. Indeed, one difficulty with choosing any mammal or mammalian order to use as a model of brain function is that each species has a unique behavioral repertoire that permits the animal to survive in its particular environmental niche. There is, therefore, the danger that neural organization is uniquely patterned in different species in a way that reflects the unique behavioral adaptations of the different species. Stated differently, it is possible that the brain-behavior relationships of rodents are not representative of other mammalian species, especially primates.

We have emphasized elsewhere that although the details of behavior may differ somewhat, mammals share many similar behavioral traits and capacities (Kolb and Whishaw 1983). For example, all mammals must detect and interpret sensory stimuli, relate this information to past experience, and act appropriately. Similarly, all mammals appear to be capable of learning complex tasks under various conditions of reinforcement (Warren 1977), and all mammals are mobile and have developed mechanisms for navigating in space. The details and complexity of these behaviors clearly vary, but the general capacities are common to all mammals. Warren and Kolb (1978) proposed that behaviors and behavioral capacities demonstrable in all mammals could be designated as *class-common* behaviors. In contrast, behaviors that are unique to a species and that have been selected to promote survival in a particular niche are designated as *species-typical* behaviors. The distinction between these two types of behavior can be illustrated by the manner in which different mammals use their forelimbs to manipulate food objects. Monkeys will grasp objects with a single forepaw and often sit upright, holding the food item to consume the food. Rats too will grasp objects with one forepaw and then typically transfer the food to their mouth, assume a sitting posture, transfer the food back to both forepaws, and then eat. So many mammals use the forepaws to manipulate food (or other items) that it can be considered a class-common behavior. Nonetheless, the details vary from species to species. Some species-typical differences are large indeed, such as the use of the forelimbs in bats or carnivores versus rodents or primates. It would seem foolish indeed to use dogs as a model for studying the details of the neural control of object manipulation by humans, as their limb use is relatively rudimentary. But what about rodents? There are clearly species-typical differences among rodent species and between rodents and primates. The question is whether these species-typical differences necessarily reflect fundamental differences in the neural control of skilled forelimb use. One way to address this question is to examine the order-specific characteristics of forelimb use. That is, one can study the similarity in forelimb use in different species within an order. This type of analysis would allow us to determine the commonalities in behavior across species of an order, which would give us a better basis for comparing across orders (Whishaw et al. 1992b).

L'Envoie

The following example from our laboratory illustrates how behavioral analysis can provide insights into behavior. Aged Fischer 344 rats are widely used to examine the effects of aging on memory (Lindner 1997). We were interested in using these animals for studies that examine the ameliorative effects of exogenously supplied compounds thought to have neurotrophic properties. Since previous studies had used swimming pool spatial tasks, we first sought to confirm that 24-month-old Fischer rats were impaired relative to 6-month-old rats. We found that when the rats were given 8 trials a day on a task that required them to find a hidden platform at a fixed location in a swimming pool, the 24-month-old rats were indeed severely impaired relative to the 6-month-old rats. When given just one trial a day, however, they learned the task much more quickly, reaching the hidden platform as rapidly as the young rats after only 14 to 16 trials, indicating that learning per se was not impaired. Finally, when given a matching-to-place task in which they were given two trials a day with the platform in a new location each day, the aged rats were severely impaired and showed no improvement from the first (test) trial to the second (matching) trial, whereas the young rats showed a marked reduction in latency. Results from these three tests seemed to support the idea that the animals had a selective spatial deficit, since a very similar pattern of results is obtained from rats that have selective hippocampal lesions.

This conclusion was severely compromised by the results of further tests. In open field tests, the old rats were less active than the young rats as they walked, and they reared less. When given locomotion tests, they were slower swimmers and walked more slowly for food in a straight alley. When required to climb out of a 9-inch-deep cage to obtain food, they were extremely impaired. Further tests showed that the motor impairments of old rats were quite selective. The aged animals could protrude their tongue normally, eat one gram food pellets as quickly as the young rats, and they reached for food in a skilled reaching task as well as did the young rats. When given tests of righting, they were impaired relative to the young rats but when their forequarters and hindquarters were tested separately, forequarter righting was unimpaired whereas hindquarter righting was impaired. The results of these neurologic tests suggested that the old rats were selectively impaired in using their hindlimbs and this result was confirmed by kinematic analysis of hindlimb movements used in swimming and walking. Thus, it is unclear whether their “spatial” deficit was due to a learning impairment or related to impaired use of the hindlimbs.

These results are relevant to the discussion of methodology given in the opening of this paper. There is a general expectation that aged rats will be impaired in spatial memory tasks. Our tests confirmed this expectation. The comprehensive follow-up analysis showed, however, that the animals had a selective motor impairment in use of the hindlimbs to move themselves. The selectivity of the deficit was completely unexpected. Since commonly used spatial tasks require the animals to use their hindlimbs to move themselves, the results of the spatial tests are confounded by the rats' motor impairment.

The particular result from this study suggests two new hypotheses. Aged Fischer 344 rats may have only a motor deficit that impairs their swimming performance, or the animals may have both a learning deficit and a motor deficit. Subsequent testing, e.g., spatial tests that do not require movement, could be used to assess these hypotheses. Fortuitously, however, the finding of a selective motor deficit provides a very good model for studying motor impairments associated with aging.

The lesson from this example is, therefore, that a careful examination of behavior can provide insights into the specific impairments of an animal, can provide new models for behavioral analysis, and finally can assist in evaluating the specificity of animal models of functional disorders.

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