Lower animal conditioning studies help in the understanding of human memory and its disorders: the merits of conditioned taste, odor, and flavor aversion research

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Research on learning and memory in lower animals points us down a path to the modeling of human memory deficits. Every form of memory—from the Aplysia to the human—seems to be based on a limited number of identical biochemical principles, which justifies the study of these principles in lower animal species (7). But the abovementioned path is an eroded and rutted one. Conditioning, which is required to teach something to an animal, is seldom the basis of learning in humans and is difficult to test (21). The literature on animal conditioning on the one hand and on human memory on the other has developed separately (11). Similarities between animals and humans remain in the background, hidden behind a heterogeneous set of concepts, each one sustained by specific experimental methods (3). Another difficulty in extending findings on molecular aspects of memory to conditioning and higher order learning processes is our poor conceptualization of what occurs in large neuronal networks. The high number of interactions between neurons—and between neurons and glial cells with nonlinear mathematical properties—makes it extremely difficult to bridge the gap between the cellular and more integrated levels (1, 9, 24).

Certain improvements in conditioning protocols in lower animals may have filled some of the rats in the path. Examples will be given, illustrated by the paper by Rowland et al. (20) published in this issue of the American Journal of Physiology—Regulatory, Integrative and Comparative Physiology. These authors used a conditioned flavor paradigm. This paradigm consists of provoking a digestive malaise in an animal after it has ingested a tasty or aromatic food or beverage. The memory of this bad experience elicits disgust and avoidance of the food or beverage. Rowland et al. used a gelatin dessert to provide rats and mice with a flavor. They provoked a malaise by intoxicating them with an injection of LiCl, which is the standard approach in such studies. Using a gelatin dessert is an improvement, because it can be easily customized in a laboratory. Its content can be designed so that it does not feed the animal, which would alter its internal state. It is worth noting that, before eating this dessert, rats and mice were not hungry or thirsty, i.e., the experiments do not need to deprive the animals. Therefore, the paradigm precludes criticism on ethical grounds and side-effects due to interfering motivational effects. Rowland et al.’s work is also an example of the need to give priority to careful parametric approaches in conditioning. Provided with an appropriate parameter setting, Rowland et al. could compare rats and mice directly, the main difference being the shorter retention time of the flavor before experiencing the digestive malaise in mice. The fact that the gelatin dessert is mainly made of water makes it possible to compare this eating access to the flavor with the more standard conditioned taste-aversion drinking method.

Research on learning and memory in lower animals started at the beginning of the last century, when academic curiosity about the determinism of behavior arose. The corresponding research work began with observations on cats and dogs (14, 23). It then focused on rats for fundamental aspects and monkeys when applications to cognitive sciences were considered. Such research led to significant improvements in the understanding of learning and memory. The study of the contribution of emotions and motivation revealed that drug addiction may result from a long-lasting anatomic and biochemical change in the brain (18, 19, 25), the consequence of which is a change in motivated forms of behavior (17). Complemented by neurophysiological and biochemical observations, a contribution of the dopaminergic mesocorticolimbic system to motivation was highlighted (10, 12). Such information reoriented individual as well as social treatment of drug addiction. In line with such research, Rowland et al.’s paradigm raises an interesting question about what motivates the rat or mouse to ingest the gelatin when it is neither hungry nor thirsty.

The methods developed for experimental psychology have been applied intensively to pharmacology. As the general organization of the brain and its main neurochemical systems are the same in the rat and the human, it was conceivable that a modification of the rat’s behavior by a drug could serve to predict its effect in humans (4). This idea justifies the profuse research on learning and memory in lower animals, especially on the effect of cholinergic drugs, stimulated by the increasing market for drugs to treat Alzheimer’s disease (16). However, using drugs in learning experiments can lead to more or less obvious technical and conceptual difficulties. Drug-producing companies are beset by the variability of behavioral measurements, their ethical constraints, their complexity, and the cost of obtaining conclusions that remain uncertain. An animal may remember the effect of a drug, which superimposes, alters, or combines with the memory of the target stimulus. Being hungry or thirsty because of deprivation interacts in a similar way with the memory of the target stimulus. Rare is the experimental strategy that does not require deprivation, as in Rowland et al.’s study. Another source of difficulty is the sensitivity of measurements to the experimental parameters. They vary from one species to another, or even from one strain of rats to another, or even from one individual to another (15). The example of Rowland et al. illustrates how fruitful it can be to consider this point carefully and it reminds us that paramet-
ric controls are an essential condition of every behavioral experiment. They explored the interspecific parametric differences between rats and mice, which has become essential for the development of genomic research.

Most diseases comprise genetic factors. Research on Alzheimer’s, schizophrenia, etc., is already under way using mice carrying induced modifications of their genome, although the genetic aspect of such diseases is still unclear. This is a useful means of distinguishing genomic causes of the diseases from environmental ones. Other studies are not motivated by pathophysiological demands but by some surrealist aims, for example keeping a mouse’s infant neuronal receptors active in adulthood so that it retains its childhood learning capacity (22). Applied to humans, this seems like a revival of the myth of the fountain of youth. Genetic manipulations are common in mice, but not in rats. Rowland et al.’s study represents a significant improvement, as they propose the same protocol for rats and mice.

The studies presented by Rowland et al. were based on conditioned flavor avoidance or aversion in rats and mice. Taste, odor, or flavor avoidance is not the most common approach to learning and memory (2). Conditioning methods based on light, tones, and electrical foot shocks are preferred, probably because we humans have a better idea of the effects of such stimuli. Anthropomorphism may be a poor counselor. Rats and mice have an olfactory and tactile representation of their environment. Combined with a proper understanding of the neuronal circuitries involved, taste or odor learning should prove the same protocol for rats and mice.

The paradigm proposed by Rowland et al. enables us to avoid a number of difficulties and opens the door to new research. This malleable and easily assessed paradigm could be used more for the evaluation of learning and memory.

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REFERENCES