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EARLY LEARNING CAPABILITY IN RODENTS: A REVIEW (*Rattus norvegicus* and *Mus musculus*)

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ABSTRACT: Available data on learning capabilities in immature rodents are briefly summarized and some new findings on early learning in mice are presented. We omit the comparatively small number of works concerning precocial species of rodents, that is, guinea pigs and spiny mice. In a comparison we have already made (D'Udine and Alleva, 1983) we found that rodent species characterized as precocial types appeared to be affected in a dramatic way by environmental factors during postnatal development, as shown by profound modification of their adult behavioral patterns. Since the aim of our contribution is to review the methodological paradigms used to assess early learning capabilities in rodents, we shall focus here on the Norway rat and the house mouse, because they are the only species for which evidence has progressively been built up through the use of different tests.

SOMMARIO: I roditori di laboratorio hanno rappresentato storicamente il materiale di base sul quale sono stati sviluppati i paradigmi sperimentali dell' "apprendimento" animale. E' stata posta relativamente troppa attenzione su un numero estremamente ridotto di specie, per di più tra loro simili, il che ha causato parecchie restrizioni nel definire leggi più generali sull'apprendimento. Tale atteggiamento è stato criticato ma ci si è occupati molto meno di un altro tipo di distorsione causata dall'uso di animali adulti, e della conseguente costruzione di modelli molto poco validi per stadi immaturi.

Un esame critico della letteratura mostra che con l'uso di saggi appropriati possono essere evidenziate capacità di apprendimento anche nel periodo perinatale. Vengono anche discussi aspetti comparativi e altri riguardanti lo sviluppo ontogenetico nelle specie ratto e topo.

Sono riportati alcuni dati originali nel topo, specie sulle cui capacità neonatali di apprendimento e ritenzione esistevano solo risultati negativi.

ONTOGENY of LEARNING and RETENTION CAPABILITIES in the NORWAY RAT (*Rattus Norvegicus*)

We have restricted our field of interest to the preweaning period as far as the rat is concerned. Learning capabilities in the rat around

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the weaning period have been extensively studied in the past, and there is good evidence of full-fledged capabilities as early as ten days of age (Goldman and Tobach, 1967). The considerable developmental transitions occurring in the early stages of altricial rodents have been carefully described by Rosenblatt (1976, 1983) who defined three major stages, according to the sensory motor capabilities of the developing organism, in particular, the preeminent role played by thermotactile and olfactory stimulation. Therefore, we shall discuss here only data collected before the tenth day of age.

We shall also omit all papers where the authors used available methods to analyze the outcome of manipulations aimed at interfering with a normal path of development. In other words, all the papers where learning capabilities were used as developmental markers for pharmacological or toxicological treatments are not considered here.

The aim of our review is mainly to stress the evolution of the methodology that has been used to assess learning capabilities in pups, in order to show that the demonstration of more precocial capabilities parallels the use of more appropriate tests to check them. In order to cope with the considerable literature which has increased over the last few years, we have roughly classified works in this field into four main categories, albeit with some minor methodological heterogeneities.

1. Motor response following footshock
2. Aversion for a set of novel stimuli
3. Conditioning through suckling response
4. Conditioned aversion to olfactory or gustatory cues

The first category "Motor response following footshock," includes tests ranging from simple forelimb withdrawal of immobilized rats suspended in a harness, to complex locomotor requirements, such as escape responses in unidirectional and multidirectional tasks. We stress that we are dealing here with footshock as an unconditioned stimulus (US) because it has been demonstrated that an interoceptive electrical stimulation (as intraperitoneal shock) produces very different results from an exteroceptive one (Haroutunian and Campbell, 1979). It is necessary to recall also that in tests requiring a certain level of locomotor capability as when the animals must proceed through an alley or a Y-maze, the pups often receive an additional rewarding unconditioned stimulus by being held in the warm hands of the experimenter for 30 seconds after the end of the test. The authors never openly discuss the possible joint effect of footshock and handling on their results.

The second category "Aversion for a set of novel stimuli," includes either neophobic reactions to novelty or, quite obviously, preferences for previously familiar conditions. In rodents, the developmental changes in neophobia have been thoroughly investigated as that set of precocial experiences defined as "imprinting" in the past. Our second category

therefore, subsumes the effects of various kinds of stimulation during the so-called "sensitive periods." This category includes goal-directed behavior towards the nest (homing behavior) and the aversive reactions to atypical thermic conditions. In one case thermal stimulation has been used also as reinforcement for instrumental conditioning (Guenaire et al., 1982b).

The third category "Conditioning through suckling response," includes more recent work and focuses on a particular behavioral item typical of the early stages of development. The suckling response is an adequate sensory motor response for altricial pups, since it occurs naturally in nest conditions. Furthermore, suckling occupies a key position in the hierarchical order of reactions for the survival of the pups (Blass and Teicher, 1980). Suckling, either rewarded or not by milk intake, has been therefore successfully used to show appetitive conditioning and instrumental learning capabilities.

Manipulation of the suckling response allowed associative capabilities to be demonstrated in very young rats and these assessments immediately follow the development of the technique of intraoral cannulation, first developed by Hall and Rosenblatt (1977). Suckling has been successfully employed to elicit and mold age-typical behavior responses such as rooting, pivoting, mouthing and probing, which in turn have been used to demonstrate learning capabilities.

The last category "Conditioned aversion to olfactory and gustatory cues," is again a newly developed technique, and the one that has so far given the best results because it has either made possible the proof of learning capabilities at very early ages, or it has shown retention for extremely lengthened intervals. In fact, only through the use of this technique has it been possible to prove prenatal capabilities of learning in rodents, as well as retention of learned aversion over periods of days or even weeks.

With the organization of the tests according to the above mentioned four categories, we summarize in Table 1 all the recent work in this field with the sole exception of the work of Moral et al., (1981) who have been able to prove associative learning and spatial discrimination in three-day-old pups in a task where brain self-stimulation was used as a reward during a single 18 hour session.

Table 1 shows early learning capabilities in the Norway rat, the most extensively studied rodent species. In this table we list a survey of the existing literature going back to 1962. The developmental ages considered start from the prenatal period, specifically the last two days of pregnancy, here marked as -2, up to postnatal day 9, an age at which some locomotor capabilities are detectable in the nest, while the full locomotor capacities and weaning occur at ten days of age or later.

To summarize the results of different studies, we use a "black dot" in the case of full-fledged learning capabilities, i.e., for clear conditioned responses retained for at least 24 hours. A question mark indicates

Table 1
Postnatal Day

| | -2 | -1 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | | |
|------|----|----|---|---|---|---|---|---|---|---|---|---|--------------------------|---|
| 1962 | | | ? | | | | | | | | | | Caldwell et al. | 0 |
| | | | ? | | | | | | | | | | Caldwell & Werboff | 0 |
| 1967 | | | ? | | ? | | | ? | | | | | Gray et al. | 0 |
| 1968 | | | | | | ? | | | | | | | Thoman et al. | X |
| 1970 | | | | | | | | ? | | ? | | ? | Misanin et al. | 0 |
| 1971 | | | | - | - | - | - | - | - | ? | ? | ? | Gregory & Pfaff | X |
| | | | | | | | | ? | | ? | | | Misanin et al. | 0 |
| 1973 | | | | | | | | | ? | | | | Bulut & Altman | X |
| | | | | | | | | ? | | ? | | ? | Misanin et al. | 0 |
| 1974 | | | | | | | | ? | | ? | | | Misanin et al. | 0 |
| 1976 | | | | | ● | | | | | | | | Rudy & Cheatle | X |
| 1977 | | | | | | ? | ? | ? | ? | | | ? | Cornwell-Jones & Sobrian | X |
| | | | | | | | | | | ● | | | Kenny & Blass | 0 |
| | | | | | | | | | | ● | | | Cheatle & Rudy | X |
| | | | | | | | | | | ● | | | Hinderliter et al. | X |
| 1978 | | | | | ● | | | | | | | ● | Rudy & Cheatle | X |
| | | | | | | | | | | | | | Smith & Spear | X |
| | | | | | | | | | | - | | ? | Spear & Smith | 0 |
| | | | ● | | ● | ● | ● | | | | | | Bachevalier & Blozowski | 0 |
| | | | | | - | - | ? | ? | ? | ? | ? | | Guenaire et al. | X |
| 1979 | | | ? | | ● | | | | | ● | | | Haroutunian & Campbell | X |
| | | | | | | | | | | | | | Johanson & Hall | 0 |
| | | | | | | - | | | | ? | ? | ? | Martin & Alberts | 0 |
| | | | | | ● | | ● | | ● | | ● | | Rudy & Cheatle | X |
| | | | | | | | | ? | | | | | Gemberling et al. | X |
| 1980 | | | | | | | ● | | | | | | Johanson & Teicher | 0 |
| | | | | | | - | | ? | | ● | | ● | Misanin et al. | 0 |
| | | | | | ● | | | | | | | | Smith & Spear | X |
| 1981 | | | | | | | | | | ? | | ? | Smith & Spear | 0 |
| | | | | ● | | | | | | | | | Gemberling & Domjan | X |
| | | | | | | | ? | ? | ? | ? | ? | ? | Guenaire et al., a | X |
| | | | | ? | ? | ? | ? | ? | ? | ? | ? | ? | Guenaire et al., b | X |
| 1982 | | | | - | | ● | | | ● | | | ? | Johanson & Hall | 0 |
| | | | | | | ● | ● | | | | | | Martin & Alberts | X |
| | | | | | | ? | | | | | | | Pedersen et al. | 0 |
| | ● | | | | | | | | | | | | Smotherman, a | X |
| | ● | | | | | | | | | | | | Smotherman, b | X |
| | ● | | | | | | | | | | | | Stickrod et al. | X |
| 1983 | | | | | | | | | | ● | | | Rudy & Cheatle | 0 |
| | | | | | ● | | | | | | | | Smith et al. | X |
| 1984 | | | | ● | | ● | | | ● | | | ● | Johanson et al. | 0 |
| | | | | | | | | | | | | | Rudy et al. | X |

● + conditioning retained for more than 24 hrs

? + conditioning retained for less than 24 hrs or unclear response

- + no conditioning was evident

0 + motor response following footshock

X + aversion for a novel set of stimuli

0 + conditioning through suckling response

X + conditioned aversion to olfactory or gustatory cues

unclear evidence or evidence of short-term retention. The minus sign is used only where the authors have been unable to prove learning. Vertical columns show the ages at which the tests were performed, on the horizontal, each line shows (at the left) the results of a single study, the authors, and, on the extreme right, a symbol indicating the kind of test used. Note that the four symbols correspond to the four categories of tests we have already presented.

As far as the demonstration of learning capabilities in immature rats is concerned, it is pretty evident that:

1. Good learning and retention capabilities were not proved in the first postnatal week, until fairly recent years, as shown in the table by the absence of black dots until 1977.
2. Since 1976, when the first breakthrough happened, the age of demonstrated learning and retention capabilities goes down until it reaches the prenatal period (day -2).
3. The evidence of early learning and retention parallels the use of more appropriate tests for the assessment of the capabilities of rat pups. This trend is clearly illustrated if you look at the last column on the extreme right where the four kinds of tests are listed. The two white symbols on the black field correspond to tests that are unsuitable for the age of the pups when tested, while the normal X and O correspond to more appropriate testing conditions.

It is evident that over the years there is a transition between the predominance of white symbols on a black field and the normal Xs and Os. Therefore it is worth stressing the correspondence between the conditioned aversion test (indicated in the table by Xs) and the demonstration of full-fledged capabilities at early stages. In summary, our table shows how a methodological evolution permitted a new insight into the learning capabilities of the pups.

In this section we shall try to illustrate the major methodological changes that resulted in such an evolution by means of the observations that were done and the discussion of those findings.

a) Quantity, Quality and Age-dependent Effectiveness of the Unconditioned Stimulus (US)

As far as footshock as US is concerned some papers analyzed the age dependent reactivity to comparatively ineffective USs. In 1983 Misanin and Hinderliter found no substantial age differences in footshock reactivity evidenced in the locomotor activity of rats aged 5-13 days, whereas younger rats typically had lower levels of activity than older ones. In two-day pups Haroutinian and Campbell (1979) analyzed

differences in reactivity to both foot and intraperitoneal shock over a large range of intensities (0-0.2 mA). They found that only intraperitoneal shock was effective as US in producing conditioned odor aversion. From a qualitative point of view, Haroutinian and Campbell found a high degree of similarity between two different kinds of interoceptive stimulation, i.e., intraperitoneal shock and intraperitoneal injection of lithium chloride (LiCl), an illness-inducing drug. Very recently Kucharski and Spear (1984) demonstrated the efficacy of footshock as US in six- and ten-day-old pups.

In 1980 Gemberling et al., demonstrated that an isotonic solution of LiCl was effective in producing conditioned aversion in pups, while the hypertonic LiCl solution was not. In a recent paper, Rudy and Cheatle (1983) examined the effects of preexposure to LiCl on learning capabilities in rat pups of different ages. They found a long lasting effect of LiCl preexposure only in the younger animals and attributed this to ontogenetic differences in the excreting processes.

The role of temperature as US has been more often discussed as an interacting agent than as a determinant one. Hinderliter et al., (1978) exposed pups to a cold metal grid and the poor results they obtained could be attributed to the "freezing" produced in young rats placed in hypothermic conditions in an unfamiliar environment. Martin and Alberts (1982) got similar results using a LiCl injection or a low temperature (10 C) as US. Guenaire et al., (1979) obtained good results using a thermotactile stimulation consisting of a warm air stream. In a series of studies using temperature as US, Guenaire et al., (1979; 1982a; 1982b) found a clear-cut age-dependent effectiveness of the stimulus. Johanson and Hall (1979) used milk to elicit appetitive responses and the combined role of temperature and milk delivery was investigated by Johanson and Teicher (1980). They reported that low temperature interferes with both levels of milk intake and activity, suggesting that milk might not be as reinforcing if presented in a cold environment. The combined effect of milk intake delivered directly from the nipple and LiCl intraperitoneal injection interfered dramatically with conditioning, lowering or canceling the effect of LiCl. It has been correctly observed that suckling behavior per se, even without nutritive consequences is reinforcing to rat pups. Therefore, it is possible that suckling reinforcement can override or neutralize the flavor-toxicosis association in young pups.

The activating effect of simple exposure to milk intake has been examined by Johanson and Hall (1982). These authors extensively studied ontogenetic changes in the effectiveness of the role of temperature and previous deprivation. Johanson et al., in 1984 carefully examined the age-specific response to milk ingestion with peculiar behavioral patterns of arousal that it elicits at different ages.

Stimulation of very young pups ends up with a high level of their arousal, age-specific responses, and ultrasound emission, the last being

used as a marker during learning and extinction (Amsel et al., 1977). Tactile or amphetamine-induced stimulation may act as powerful events in the odor conditioning paradigm, as Pedersen et al., demonstrated in 1982. An interesting result of this study was that tactile and amphetamine stimulation, if provided in combination, produced a complete disruption of the learning process but only at nest temperature and with a high level of CS intensity. On the other hand, caffeine, in spite of being effective at the age tested, did not produce the stimulating effect of amphetamine.

In some cases the results of arousal level induced by different kinds of stimulating US indicate that any external manipulation (for example, handling or simply moving the home cage) can have strong rewarding effects on the pups especially after previous isolation from the mother.

b) Quality and Age-Dependent Effectiveness of the Conditioning Stimulus (CS)

The sensory competence of rat pups is reduced in the olfactory and thero-tactile stages (Rosenblatt, 1976; 1983). Obviously, therefore, vibrotactile stimulation provided by an audio-oscillator has been used since 1962 by Caldwell et al., in a classical conditioning paradigm through leg-flexion.

Bulut and Altman (1974) demonstrated clear age-dependent variations in the efficiency of tactile stimuli, which improved with age. A recent comparison between vibrotactile and olfactory CS (Johanson and Hall, 1982) shows a better efficacy of olfactory cues at least in the case of an ingestional response.

Qualitative differences in attractiveness among odors have been noticed several times during the development of the pups. Nest odor has been demonstrated to exert an increasing attraction on pups from birth to 17 days (Gregory and Pfaff, 1971). Cornwell-Jones and Sobrain (1977) demonstrated an inverted U-shaped trend in the attractiveness of nest odor, peaking at seven to nine days. In the same study these authors monitored the ontogeny of the unconditioned response to a currently used CS cue, lemon essence, in two strains of rat. In Wistar, but not in Sprague-Dawley rat pups, the olfactory cues provided by lemon exerted an aversive effect per se during ontogeny and it is worth noting here that this strain-dependent aversion effect was only evident in the six to eight day period. It has been discussed several times that different types of olfactory stimulation (as well as gustatory cues) exert an attractive or repulsive effect per se, so that the conditioned aversion paradigm may vary from an enhancing aversive property of CS to the counterbalancing of an attractive effect.

At this point, it is worth recalling that, owing to the dramatic differences in olfactory competence between human experimenters and

test animals, some "new" stimuli used as CS in the conditioning paradigm might be similar in quality or differ only in intensity with respect to odors already experienced by the animals. Johanson and Teicher (1980) demonstrated a clear aversion effect of cedar essence in pups while an almond-like odor (benzaldehyde) proved more attractive if compared with cedar, at least at the age of three days (Pedersen et al., 1982). Using two different kinds of olfactory cues, Martin and Alberts (1982) showed CS-specific heart rate changes, an observation that is in agreement with other data on the profound qualitative effects of different responses to particular olfactory cues.

CS intensity has been partially explored by Pedersen et al., (1982) whereas the duration of CS exposure has been studied by Rudy and Cheatle (1978; 1979). They demonstrated that longer CS exposure resulted in facilitation and that some effects were age-dependent. Subsequently Smith et al., (1983) analyzed the critical role played by the duration of olfactory CS exposure in rat pups as young as two days. Preexposure to CS has been discussed in terms of degree of "familiarity" of CS during CS/US pairing (Rudy and Cheatle, 1979) and in terms of the maturation of sensory or motivational systems that altered the saliency of the stimulus.

To conclude, it is also interesting to note that the capability of rat foetuses to detect odors while still *in utero* (Pedersen et al., 1983) has been demonstrated only after a conditioned aversion paradigm indicates associative processes between an olfactory-gustatory CS and drug-induced illness in such an early age (Stickrod et al., 1982; Smotherman, 1982a, b).

c) Conditions under which CS/US Pairing Occurs

Intertrial length (Gray et al., 1967) and the duration of CS/US intervals were examined by several authors (Caldwell et al., 1962; Smith et al., 1983; Rudy and Cheatle, 1979; Gemberling et al., 1980). Rat pups younger than five to six days did not seem to show "long delayed learning," i.e., the capability to associate CS preexposure to US if they are separated by a long time interval. The developmental influences of CS/US interval has also been examined by Smith et al., (1983).

Rudy and Cheatle (1983) discussed the ontogenetic differences observed after such different CS/US interval conditions as a joint function of time and developmental change in US efficiency. In the case of LiCl US, in fact, ontogenetic changes in the rate of excretion may confound the results obtained using different levels; so, it is quite difficult at this time to discern when CS and US exposure eventually overlap.

An important interaction between CS/US interval and the temperature at which conditioning occurs had already been noticed in 1962 by Caldwell et al., and concern about the critical role of temperature

during testing has increased over the years. According to several authors, a temperature lower than the one of the nest interferes with learning (Caldwell et al., 1962; Johanson and Teicher, 1980; Johanson and Hall, 1982; Hinderliter et al., 1978), a warm temperature improves the pups' capabilities. These observations led to the current use of incubators as the test environment or as enclosures where the animals were transferred when separated from the mother (in cases in which a deprived condition seemed necessary to enhance motivation). According to the above mentioned authors, some learning capabilities were detectable *only* in animals maintained at conditions of nest temperature and humidity.

Spear and Smith (1978) were the first to demonstrate the dramatically disruptive effects on learning performance of pups experiencing CS/US pairing *in isolation*. The simple presence of home cage shavings improves learning (Smith and Spear, 1981). Social isolation, more than the hypothermic effect due to separation from littermates, is the critical factor for such a disruption (Smith and Spear, 1980). The disruptive effect of social isolation has been explained in terms of high arousal state produced by separating the pups from their nest environment. Age-specific defense reactions (for example ultrasound emissions) seem to interfere with the "optimal" level of arousal required for learning. In other words, isolation stress may modify attentional processes and interfere with the channeling of arousal levels into more appropriate behavioral response (Smith and Spear, 1980; 1981).

Some results are strongly inconsistent with the idea of "emerging" learning capabilities during ontogeny, and it has often been suggested that specific factors acting on the CS/US association may play an important role. Age-dependent sensitivity to various environmental cues (including those provided by CS and US stimulation) has been invoked to explain apparently strange results. Pedersen et al., (1982) using two CS and three US had surprising results, obtaining facilitating or disrupting effects according to particular combinations of factors. Rudy et al., (1984) using a gustatory cue in a conditioned aversion paradigm, were unable to find learning capabilities at ages in which the same paradigm was successful using an olfactory cue as CS. Therefore the pairing of CS with LiCl injection seems to be different according to the quality of CS exposure. Haroutunian and Campbell (1979) showed differences in learning performances using various CS/US combinations, but Martin and Alberts (1979) and Guenaire et al., (1982b) obtained the most surprising results involving learning capabilities that seem to be very strongly age-specific. It is likely that these capabilities are more clearly revealed at particular ages by specific combinations of CS, US, and conditions of CS/US pairing.

In connection with the different conditions at which CS/US pairing can occur, the uterine environment of the mother must be taken into account also. Only the skillful surgical manipulation described by Blass and Pedersen (1980) can permit intrauterine CS and US exposure.

d) *Test Used to Assess Learning and/or Retention*

As we stated previously, the majority of tests used in the early studies of the ontogeny of learning in rodents involved suspending and immobilizing the animals and subjecting them to footshocks of different intensities (Caldwell et al., 1962; Caldwell and Werboff, 1962). Also, in subsequent tests centered on an escape response, factors such as fatigue, habituation or locomotor requirements deviating from the natural repertoire of pups' responses made the assessment of learning capabilities dubious or impossible in the early stages of development. In particular, the so-called competing responses (a strongly age-dependent stereotyped locomotor response), make the evaluation of full-fledged learning and retention capabilities difficult since it competes with behavioral responses better suited to the requirements of the avoidance task (Misanin et al., 1971; 1974; 1980).

Recent tests have begun to use elements of the natural repertoire of the pups, such as head raising following thermotactile stimulation (Guenaire et al., 1982a); crowding, mouthing or probing behavior (Johanson et al., 1984). The authors use relative changes of elicitation of these typical neonatal patterns of response as a measure of conditioning, while Johanson and Hall (1979) have demonstrated instrumental learning at very early stages through the crawling behavior of the pups in an appetitively motivated task. Martin and Alberts (1982) used heart rate changes as a useful parameter of learning assessment.

Other tests used the dyadic mother/infant interaction to demonstrate modifications in the pups' approach to the mother. In particular, only recently has the role of pups' saliva (Teicher and Blass, 1976) and the joint use of olfactory and tactile cues (Larson and Stein, 1974) been studied in the process of nipple localization and orientation. This response has been fruitfully used by Kenny and Blass (1977); Stickrod et al., (1982) and Smotherman (1982b) to demonstrate conditioning. More recent data (Johanson et al., 1984) implicate a critical involvement of olfactory stimulation in the control of rat pups' suckling behavior.

The growing use over the past few years of the conditioned aversion paradigm indicates that olfactory stimulation is a highly suitable stimulus event to use in the case of newborn pups subjected to associative learning tasks requiring the retention of an olfactory preference over a relatively long period of time.

ONTOGENY of LEARNING and RETENTION
CAPABILITIES in the HOUSE MOUSE
(*Mus musculus*)

The total number of studies of the other extensively studied species of rodents, i.e., the house mouse, is much more restricted and focuses

Table 2

**Evaluation of Learning and Retention in Mice Aged 3-13 Days
Postnatal Day**

| | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | | |
|------|---|---|---|---|---|---|---|---|----|----|----|----|---|--|
| 1970 | | | | 0 | 0 | | | 0 | 0 | | | | 0 | Nagy Misanin & Newman* |
| 1971 | | ? | | 0 | 0 | | | 0 | 0 | | | | | Nagy Misanin * Olsen* |
| 1972 | | 0 | | 0 | 0 | | | ■ | ■ | | | | | Nagy Misanin Newman Olsen & Hinderliter* |
| | | | | 0 | 0 | 0 | | ● | ● | | | | | Nagy Misanin & Olsen* |
| | | | | 0 | 0 | | | 0 | 0 | | | | 0 | Nagy & Misanin* |
| 1973 | | | | | | | 0 | | ● | | | | | Nagy Misanin & Wetzel* |
| | | | | | | 0 | 0 | ● | ● | | | | | Nagy & Mueller* |
| | | | | | | | | ? | | ● | | ● | | Nagy & Sandmann |
| 1974 | | | | | | ? | | 0 | | ● | | ● | | Nagy & Murphy |
| 1975 | | | | | | | | 0 | | ● | | | | Nagy |
| | | | | | | | | ● | | | | | | Nagy* |
| 1976 | | | | | | | | ● | | | | | | Nagy Anderson & Mazzaferri* |
| | | | | | | | | 0 | | ● | | | | Nagy Pagano & Gable |
| 1977 | | | | | | ? | | ● | | ● | | ● | | Herman & Nagy |
| | | | | | | 0 | | | | | | | | Nagy Burley & Kikstadt* |
| 1978 | | | | | | 0 | | | | 0 | | | | Ray & Nagy |
| 1979 | | | | | | | | | | | | | | |
| 1980 | | | | | | | | | | | | | | |
| 1981 | | | | | | | | | | 0 | 0 | | | Lavooy Lavooy Hahn & Simmel |

■ + conditioning and retention for more than 24 hrs
 ● + conditioning and retention for 24 hrs
 0 + conditioning and retention for less than 24 hrs
 ? + no conditioning or unclear response

* + STRAIGHT ALLEY USED

on the range of age between postnatal days 3 and 13. All these studies use footshock as US and escape behavior or passive avoidance as test performance.

Table 2 shows the studies aimed to characterize the ontogeny of learning in mouse pups. The solid symbols refer to demonstration of retention capabilities for 24 hours or more. As indicated in Table 2, Nagy and co-workers described the increase in 24 hour retention performance in mice aged 9-11 days. Postnatal day nine was critical for the appearance of early retention capability in those cases in which a simple straight alley task was used (studies using a straight alley are marked in the Table with an asterisk after the name of the last author). A slight retardation in the appearance of 24 hour retention was evident when a more complex test (for example the T-maze test) was used. In the T-maze test in fact, pups nine days old were often unable to retain the correct turning choice while eleven-day-old pups were able.

Nagy et al., (1978) examined the relative aversion threshold for electric shocks administered from constant current or fixed impedance sources, and other studies examined the age-dependent effects of varying intensities of footshock (Nagy and Misanin, 1973; Nagy, 1975, 1976; Nagy et al., 1978) on both escape performance and intrasession improvement. Age-related differences in motivational level were also noticed.

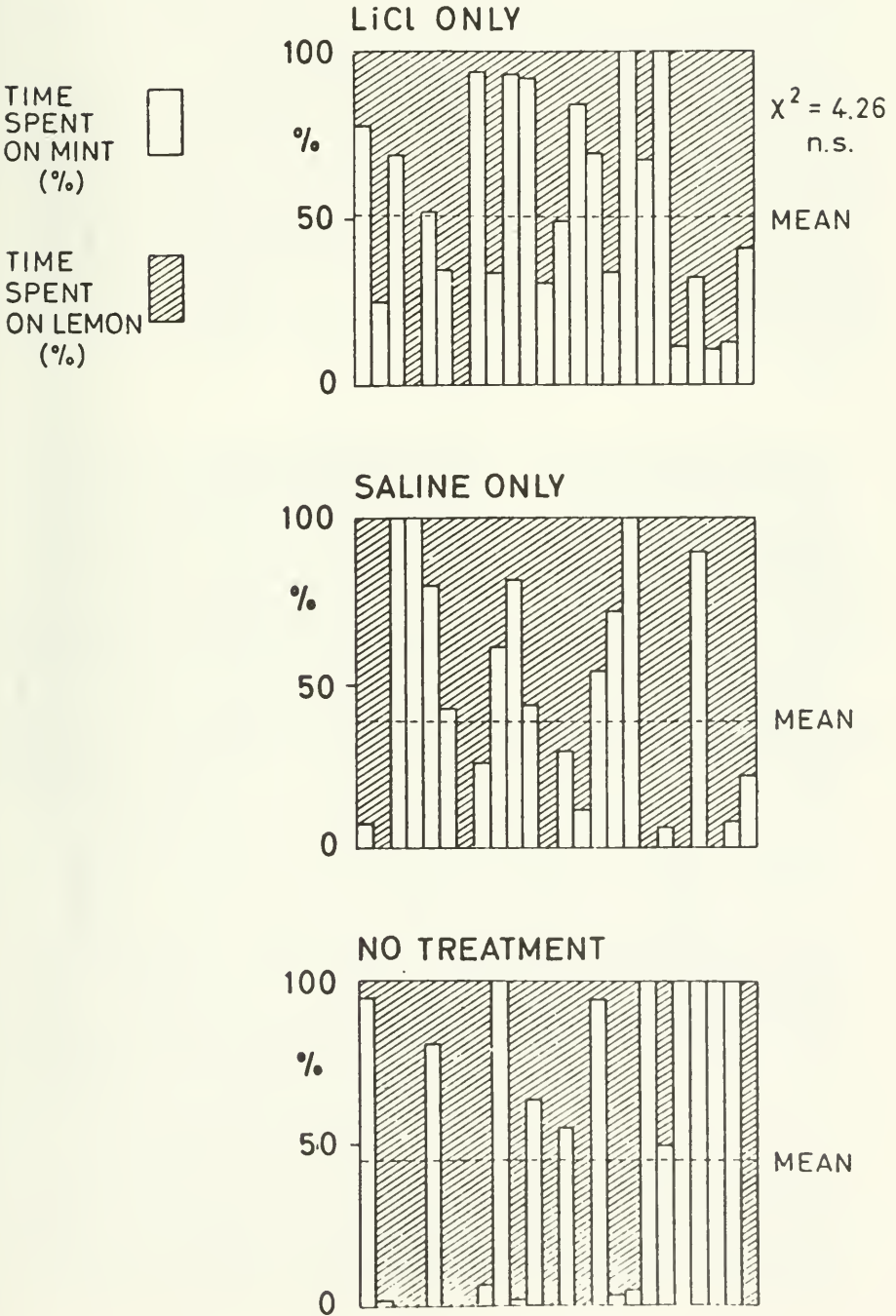
The amount of footshock-elicited competing response varies largely with age, with a clearly evident peak at day nine in several studies (Nagy et al., 1972a, 1971b; Nagy, 1976). Particular combinations of factors gave apparently strange results. For example, Nagy et al., (1973) obtained better learning in younger mice in tasks where the mice received a great number of trials. Herman and Nagy (1977) found performances that decreased with age in a particular strain. Furthermore, Ray and Nagy (1978) showed decreased learning performances in mice between seven and fourteen days in a passive avoidance task. The deviations have been readily explained as a joint function of age-typical behavioral responses and of nonmonotonic trends in various test factors.

On the whole, the data on mice did not show full-fledged learning capabilities in pups younger than nine days and give the impression of a limited range of testing conditions.

Recently, Alleva and Calamandrei (1983) applied the conditioned aversion technique to mice in an attempt to demonstrate earlier learning capabilities. In their experiment, the pups were exposed at the age of seven days to a conditioned aversion paradigm. Two olfactory CS (mint or lemon essence) and LiCl 0.2 M, 0.2% body weight (an illness-producing US) were used. All the mice were tested three days later in a two-choice olfactory test, where performance for a novel or LiCl-paired olfactory stimulus was measured over a 180-second session.

Figure 1 presents the data for three control groups having experienced only LiCl injection (top), only saline injection (middle), or which had been left undisturbed (bottom). None of the pups of these

Figure 1. Olfactory preferences of ten day pups pre-exposed three days before to: LiCl only; saline only; no treatment.



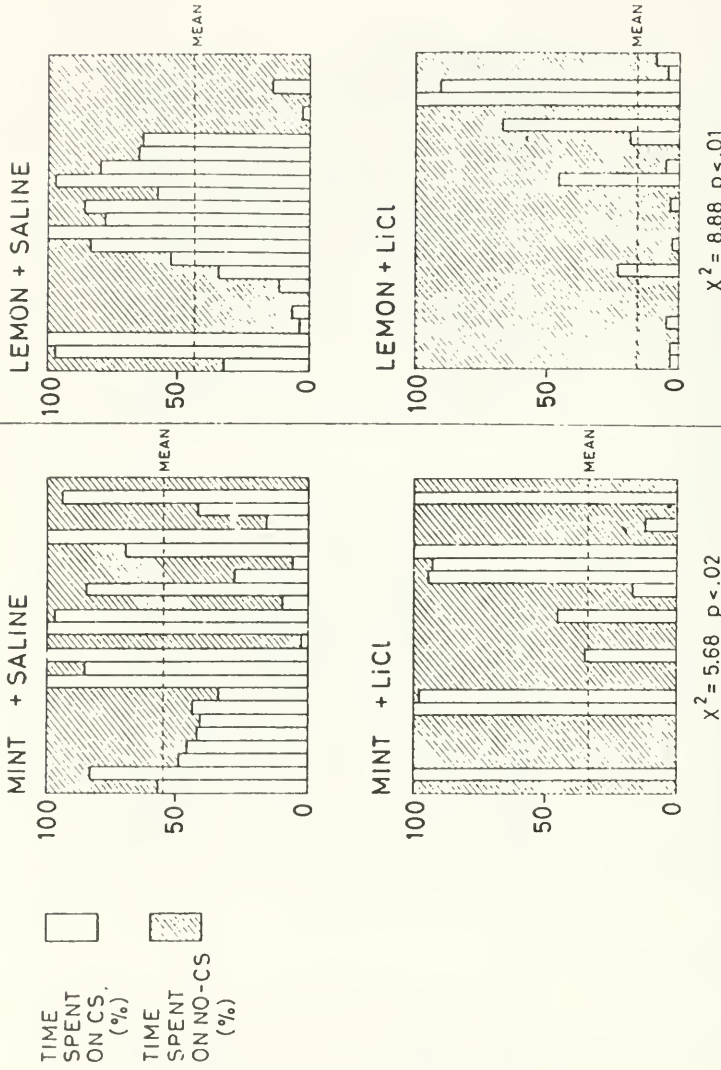


Figure 2. Olfactory preferences of ten day pups pre-exposed three days before to: mint and saline; mint and LiCl; lemon and saline; lemon and LiCl.

groups had been exposed to an olfactory CS. Individual scores for 24 pups in each group are shown and the mean of the group is reported as a dotted line. No differences were evident among the three groups and only a slight aversion for the lemon essence was present in the groups shown in the middle and bottom of the figure.

Figure 2 presents groups in which olfactory pre-exposure to mint or lemon were paired either with saline or LiCl injection. In both groups in which the CS was paired with US (lower part of the figure) a conditioned odor aversion is clearly evident, as is shown by the lowering of the mean line in both groups. The group that experienced lemon essence as CS showed a stronger effect. This is the first demonstration of a long-term retention in mice stimulated as young as seven days and confirms the validity of the conditioned aversion paradigm for revealing early learning capability in altricial rodents.

CONCLUSION

Early learning capabilities of pups may be better assessed using tests suited to age-dependent skills, and results may be explained in terms of nonmonotonic changes in the effectiveness of factors interacting with the developing organism. Profound differences in the processes underlying learning and retention performances must obviously exist, as discussed in the recent chapter by Norman Spear and David Kucharski (1984) and Zolman (1983) on the ontogenetic differences in stimulus selection during conditioning.

In recent years, there has been a growing acceptance of the idea that the maturation of the sensory and perceptual capacities of developing animals should be analyzed in greater detail and that those should be related to the ontogeny of learning and memory in each sensory channel. The characterization of the sequential development of response repertoires will expand the spectrum of behaviors that can be acquired.

Also, recognition that ecological considerations are relevant is generally more manifest, i.e., there is awareness of the fact that the developing animal faces changing ecological challenges at different points in its ontogeny (Spear, 1984). In the words of Byron Campbell in his 1984 essay *Reflections on the Ontogeny of Learning and Memory*, "the delineation of sequential sensory, central, and motor capacities and their interrelation to learning and memory should lead to an exciting decade of research in developmental psychobiology."

In the study of the "emerging" capabilities in altricial rodents, the considerations expressed by Bateson (1981) with regard to taking into account the different "larval" stages through which mammalian species pass during ontogeny seem particularly relevant. In invertebrates each developmental stage is clearly defined as in the case of caterpillar/butterfly transition. Similarly, a tadpole is not generally considered an

incomplete and incompetent version of a toad. In the case of the assessment of early learning capabilities in rodents, it sometimes seems that an attempt has been made to specify the "emerging flying capabilities" of an immature butterfly while forgetting the locomotor problems of being a caterpillar.

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Since the time the present paper was prepared and given as a lecture at the 1985 ISCP Conference, a number of rat papers appeared (see Kucharski D., & Hall, W.G. New routes to early memories. *Science* (1987, in press for a more recent overview), as well as a paper on early retention capabilities in mice (Alleva E., & Calamandrei, G. (1986). Odor-aversion learning and retention span in neonatal mouse pups. *Behavioral and Neural Biology*, 46, 348-357).

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