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## Review

# Contextual learning and context effects during infancy: 30 years of controversial research revisited<sup>☆</sup>

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## HIGHLIGHTS

- This article reviews 30 years of research on contextual learning during infancy.
- The results show substantial evidence of contextual learning during infancy.
- In some cases context-effects were greater in infants than in adults.
- Procedural factors favoring contextual learning during infancy are examined.
- The results are discussed in terms of the neuromaturational and ecological models.

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## ABSTRACT

Over the last 30 years a considerable number of reports have explored learning about context during infancy in both humans and rats. This research was stimulated by two different theoretical frameworks. The first, known as the neuromaturational model, postulates that learning and behavior are context-independent during early ontogeny, a hypothesis based on the idea that contextual learning is dependent on the hippocampal function, and that this brain structure does not reach full maturity until late in infancy. The second theoretical framework views infants not as immature organisms, but rather as perfectly matured ones, given that their behavioral and cognitive capacities allow them to adapt appropriately to the demands of their specific environment in accordance with their maturational level. This model predicts significant ontogenetic variations in learning and memory due to developmental differences in what is perceived and attended to during learning episodes, which can result in ontogenetic differences in contextual learning depending on the specific demands of the task. The present manuscript reviews those studies that have examined potential developmental differences in contextual learning and context effects in rats. The reviewed results show that, during infancy, context can exert a similar influence over learning and memory as that described for the adult rat. Moreover, in some cases, contextual learning and context effects were greater in infants than in adults. In contrast, under other experimental conditions, no evidence of contextual learning or context effects was observed. We analyzed the procedural factors of these studies with the aim of detecting those that favor or impede contextual learning during infancy, and we discussed whether existing empirical evidence supports the claim that the functionality of the hippocampus is a limiting factor for this type of learning during infancy. Finally, conclusions from human research into contextual learning capacities during infancy were also examined. In view of the wealth of evidence showing contextual learning and context effects during infancy, we suggest that future research aimed at exploring the involvement of the hippocampus in this type of learning should be conducted using parameters which allow the expression of contextual learning during each ontogenetic period.

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<sup>☆</sup> This paper is dedicated to Professor Norman E. Spear and to the memory of Professor Carolyn Rovee-Collier for their invaluable contributions to the field of developmental psychobiology.

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## 1. Introduction

The ontogenetic study of learning and memory has been and continues to be a major issue for psychology. Several general theories have been proposed to guide research on this topic, all differing in a number of basic assumptions. One of the main current hypotheses, sometimes referred to as the neuromaturational account (see [99,136,155]), holds that there are important qualitative differences in memory skills between infancy and adulthood, which are explained by a sequential development of different memory systems throughout the course of early ontogeny [9,99]. One of the historical roots of this theoretical approach lies in the so-called Jacksonian hierarchical hypothesis, according to which those cognitive abilities that weaken firstly during aging are the last to emerge in ontogeny [35,66]. Following this argument, it was suggested, for example, that the implicit memory system, which allows the acquisition of certain basic forms of learning, would be functional from birth, while the explicit memory system would reach functional maturity later in ontogeny. The explicit memory system allows representations of contextually specific events and complex associations, and its function depends on the hippocampus and related structures of the medial temporal lobe [9,99,133,136,139]. In general, this hypothesis predicts that those behavioral and cognitive functions which depend on the hippocampus will emerge late in development.

Alternatively other authors have adopted a completely different approach to the development of cognitive functions. Their starting point was to consider the infant not as an immature organism, but rather as a different organism, perfectly matured and with specific behavioral and cognitive capacities which allow it to adapt appropriately to the demands of its environment in accordance with its maturational level [132–134,155,157]. Given that the environments to which organisms are naturally exposed throughout ontogenetic development undergo rapid, major changes, significant ontogenetic variations may be expected in what the organism perceives and selects during learning episodes [133,134,136,154,157]. Within this theoretical framework (which is known as the ecological model), infantile learning and retention capacities cannot be considered poorer or weaker than those of the adult organism; rather, these capacities allow the infant organisms to respond adaptively to their environment in each ontogenetic stage [131,133,134,136,157]. This theoretical alternative was decisively influenced by the work of two authors (and their co-authors): N.E. Spear, who carried out his research with rats, and C. Rovee-Collier, who worked with preverbal human infants. The results of these two seminal research projects consistently showed that when infant organisms are evaluated in memory tasks whose testing demands are adapted to their perceptual and motor capacities, they are capable of acquiring complex forms of learning and can also respond accurately in tasks considered to be hippocampus-dependent [133,134,136,157].

Both theoretical models (the neuromaturational and the ecological) coincide in highlighting the relevance of studying the ontogeny of contextual learning, and each give rise to some important predictions. Since it assumes that contextual learning is hippocampus-dependent, the

neuromaturational hypothesis predicts that, until the hippocampus reaches functional maturity, thus allowing adult-like memories, infants will have a limited capacity to acquire contextual learning, therefore, behavior and learning will be independent of the hippocampus [102]. From this perspective, the developmental analysis of contextual learning has been used as a marker to infer the possible sequential development of the explicit memory system and the brain structures underlying this type of memory. The hypothetical age limiting the emergence of hippocampal-dependent capacities was established at postnatal month nine in the human infant [105], and at the end of the preweaning period (postnatal day 21, PD21) in the rat [118,145]. In contrast, the ecological model does not necessarily predict a progressive development of contextual learning capacities [157]. Since infants and adults may differ in the way in which they attend to and encode information gleaned from learning episodes, this model predicts that there may be developmental differences in the way in which contextual information is incorporated into the memory, depending on the specific demands of the task [157]. Furthermore, this approach also expects that the detection of contextual learning and context effects during infancy may require the procedures to be adapted to the perceptual and motor capacities of the infant [157]. The early studies conducted by Spear and his co-authors on contextual learning during infancy were influenced by this ecological conception of development, as well as by his interest in memory development. Indeed, his first series of experiments exploring contextual fear conditioning in infants was designed with the aim of elucidating possible developmental differences in stimulus selection, which may be relevant for the understanding of infantile amnesia [81,90]. Spear also remarked on the importance of studying the ontogeny of contextual learning in relation to the relevance of incidental learning for the developing organism, with contextual learning being considered a specific example of this type of learning [81,159].

Although the debate about which of these approaches (neuromaturational and ecological) is more valuable for research within the developmental psychobiology framework may be considered overdrawn by some researches, the neuromaturational perspective still guides some developmental research. For example, in some cases it is still assumed that contextual learning during infancy should be exclusively dependent on the maturational level of the hippocampal memory system [114], or that the maturity of the hippocampus determines the context-dependence of interference learning [70]. In some cases the authors do not consider the procedural variables that may modulate this type of learning during this ontogenetic period. During the last decade important researchers in the field still considered this dichotomy relevant for discussing the interpretation of results from studies about the ontogeny of memory [133,134,136].

The present manuscript reviews those studies conducted over the past 30 years that have examined potential developmental differences in contextual memory. Research with both human and non-human animals on this topic has produced a wealth of knowledge, although it is striking to note also the diversity of results and discrepant conclusions regarding the infantile capacities underlying contextual learning and

memory. We will examine this conflicting literature, comparing the results with the predictions derived from the aforementioned theories (neuromaturational and ecological). We will also pay special attention to procedural differences between those studies that reached opposite conclusions, in order to determine which variables are important for modulating the expression or detection of infantile contextual learning, and under which conditions infantile learning is susceptible to a context-change effect. Furthermore, these behavioral studies will be compared with evidence of hippocampal function during infancy. Finally, conclusions from human research into contextual learning capacities during infancy will be examined.

We will start by defining context and its functions, and discussing some procedural issues that should be taken into consideration when studying context learning during infancy.

## 2. Context definition: structure and functions

There seems to be a consensus regarding the need to include context as an important variable in theories of learning and memory. Theorizing about the different roles played by context in learning and memory requires an operational definition of what context actually is. This definition should distinguish between the background (the context) and the discrete events or cues that may happen there [159]. It is assumed that context is long lasting and relatively static and constant. Cues, on the other hand, are usually of short duration and occur once or several times in the presence of the context. In the framework of associative learning, foreground context has been defined as the one in which the unconditioned stimulus (US, usually a foot-shock) is not preceded or signaled by any discrete or target cue (conditioned stimulus, CS), while the background context refers to the context in which target cues predict the occurrence of the US (for example, [17]).

The context is usually defined by either its structure or its function, or in other words, it is defined either by alluding to its components and the relationships between them, or in terms of the different roles it plays in learning and memory. For example, a broad definition of context considers it as the background or setting in which other events occur [159], with no particular limitations regarding the type of components comprising it, and with no explicit reference to the relationships which exist between its elements. This definition includes both the external and the internal contexts. The external context refers to the physical components of a particular environment, which in animal research include, for example, the experimental room, the apparatus used for the experiment (e.g. skinner box), which can in turn be characterized by a number of qualities, such as position in the room, lighting, sound, odor, texture, size and shape, among others, and in general all the cues that remain constant throughout the experimental sessions [24,154,159]. The internal context includes states of the organism, such as those induced by hormonal or neurochemical changes as a result of a particular drug administration or exposure to a particular circumstance, deprivation schedules or expectation of events [24,130,154,159]. The passage of time or temporal events has been also considered as part of the context [23,27]. In any case, the only feature required for external and internal cues to be considered part of the context is that they must be both constant and present for longer than discrete cues. In human research, context has been defined in the same way as in animal research, with the main exception being that, in some cases, it also includes linguistic attributes (i.e. linguistic context) [159].

Contextual learning supported by elemental associations, i.e. by direct associations between the individual features of the context and the US, has been distinguished from contextual learning mediated by a configural representation of the context. In the latter case, contextual learning involves the construction of a configural or unitary representation [52,100,144]. Rudy defined the context as a set of concurrent elements that are stable. When these elements are processed contiguously, the configural representation is built, and this

representation is not subsequently affected by variations in any particular component of the context or in the relationship of its elements [144]. Configural and elemental contextual learning may involve different brain systems, with the configural type being hippocampal-dependent [52,144]. However, evidence also exists of the involvement of the dorsal hippocampus in unimodal context learning, employing contexts differentiated exclusively by its odor content [108].

Context has also been defined functionally. Associative learning models developed to account for classical conditioning effects consider, either explicitly or implicitly, context to play an important role in modulating learning acquisition and its expression. Research into memory phenomena has also pointed out the importance of contextual information for memory retrieval [126,154,159]. Several roles of context in associative learning have been proposed [78,130,159,168]. First, context can act as a CS, predicting the occurrence of biologically relevant stimuli [121]. For example, in contextual fear conditioning, when a subject is given a foot-shock in a novel context, that context can induce defensive reactions in the organism later on [15,26,51]. As a CS, the context can enter into competition with other cues, or in other words, context can block or overshadow cue-conditioning (for example, [106,119]). Another example is when, in a contextual fear conditioning procedure, the foot-shock is signaled by a target cue. In this case, the conditioned response (CR) induced by the cue tends to be stronger than the one elicited by the context [30,87], although in some cases the context can also strengthen cue-conditioning [30]. The context can also assist memory retrieval. Thus, memory retrieval improves with the degree of similarity between the training and testing contexts [126,154,159]. Finally, context can help disambiguate current conflicting information [26,120]. In other words, context can set the occasion for expecting specific relationships between the CS and the US, even without a CR being elicited. Evidence compatible with this modulatory role has been reported in studies analyzing interference learning effects, such as extinction or latent inhibition [22,23]. All of these contextual roles have been described for adults. In Section 4 of the present review we will analyze whether these roles can also be observed in the infant rat, but before that, we shall describe some procedural issues which should be taken into account when exploring contextual learning during infancy.

## 3. Some considerations for the study of contextual learning in the infant rat

The question of whether learning and memory capacities differ in infant and adult subjects needs to be answered through experiments in which subjects from each age group are tested in comparable circumstances [36,157,159]. It is important to control for perceptual and motor capacities, as well as for many other sources of variance that may differentially affect performance in each age group, for example, prior experience or direct transfer from other learning situations, motivation, the effectiveness of the rewards or USs or the impact of the procedures used on the organisms' internal state [36,157,159]. These procedural variables are important, particularly in those cases in which conclusions about infantile capacities are extracted from direct comparisons of infants and older organisms.

The first important issue to take into consideration in ontogenetic studies of contextual learning is that the context ultimately depends on the perceptual capacities of the organism. In rodents, perceptual systems mature dramatically in just a few days during infancy. Infant rats open their eyes and ears by the end of the second postnatal week of life, while the olfactory function is already functional even during the gestational stage [2], which may explain the ineffectiveness of distal contextual cues to guide infantile behavior [1,80]. In fact, olfactory cues are critical for guiding infant rats' behavior during the first weeks of postnatal life [2,161]. This is remarkably relevant because some studies have supported their conclusions regarding infantile capacities for contextual learning on explicit comparisons between preweaning

(around PD17) and weaning rats (around PD23), using contexts constituted mainly by visual cues, or without explicit odor cues. This may put older subjects at an advantage, since, for example, it has been shown that a substantial period of time passes between the functional emergence of a particular sensory system and the moment at which it can support simple conditioning [98,159]. Ontogenetic variations in perception may inherently involve a contextual change, because the same subject may perceive the same context differently when training and testing occur at two time-points in which its perceptual capacities are different. This contextual change may be considered a source of forgetting [127,128,155].

Ontogenetic studies should also pay particular attention to behaviors used as indexes of memory and strive to ensure that there are no ontogenetic differences between the different age groups included in the experimental design regarding their capacity to display such behaviors. The most commonly used paradigm for assessing contextual learning, at least in ontogenetic studies, is contextual fear conditioning, in which one or several aversive stimuli (usually electric shocks) are delivered in a novel context [52]. The dependent variable analyzed most frequently is the freezing response. It is assumed that the CR reflects the formation of a context–shock association (CS–US) [78], or alternatively, but not exclusively, freezing is considered a response produced by an intermediate intervening variable, namely “*fear*” [26,52]. Therefore, the magnitude of the CR is indicative of the strength of the CS–US association, or of the intensity of fear, and the absence of this response is taken as indicative of lack of memory. In general (including also ontogenetic studies), conclusions about contextual memory are drawn solely on the basis of this dependent variable, although there are procedural variables that seem to affect the induction of freezing. For example, if an escape route is available, flight may prevail over freezing (for example, [16]). The freezing response is also critically modulated by contiguity between the CS and the US [47]. In addition, the freezing response is not displayed identically throughout the entire infantile period [166]. Infant rats do not respond to a threat with freezing or immobilization until approximately the end of the second week of postnatal life [40, 163,164]. Furthermore, despite the fact that after weaning (PD23) the freezing response is qualitatively comparable to that displayed by adult rats, involving an arched-back and a clear crouching posture, this is not seen in preweaning rats (PD17), although at this age they do respond with immobilization. Some authors have recommended paying special attention to the selection of the criteria used to determine whether or not a given response is classed as freezing, since this can also affect the results [166]. Alternatively, other authors have measured latencies, i.e. time required to reach a certain level of activity (for example, [30,90]) or to display the first freezing response (for example, [32]), as indexes of fear memory during infancy.

Also, and maybe more importantly, there are a number of key differences between preweaning (PDs 15–17) and weaning subjects (PDs 23–25) in relation to the locomotor activity displayed in a novel environment. Younger rats have been described as hyperactive in comparison with weaning rats [37,154]. It has been suggested that hyperlocomotion may interfere with the subject's ability to stay still or to engage in freezing [14]. The same issue has been raised when comparing hippocampal-lesioned rats with sham-controls, because this lesion induces hyperactivity in a novel environment (see [52] for a discussion on this topic). Other factors such as the size of the experimental chamber (context) may also affect the expression of behavior. If a similar cage is used for preweaning and weaning rats, it is possible that differences in exploration across age may affect the expression of freezing. Furthermore, regardless of the ontogenetic period, the freezing response is not always sensitive enough to detect the effects of conditioning, especially in the case of low-intensity electric shocks or after extinction [113,171]. Even in the absence of the freezing response, differences may occur in the inhibition of other behaviors, such as vertical exploration or grooming. In other words, differences in the magnitude of freezing do not necessarily imply differences in memory. Thus, care

must be taken when drawing conclusions about memory solely on the basis of an analysis of freezing behavior [85,156].

There are many other potential sources of variance that are not always controlled. For example, the perceived intensity of the shock may vary across ages, since the nociceptive threshold changes considerably during infancy [6,40,73], although some control experiments have been added in some studies to rule out the possibility that ontogenetic differences in fear conditioning may be due to the sensitivity to the foot-shock (for example, [145]). Also, the impact of social isolation on the expression of behavior may differ, which in turn may interfere with the acquisition or expression of learning in specific tests [151]. Since isolation affects the response to a contextual fear conditioning preparation [143], in ontogenetic studies it is important to consider whether or not isolation affects learning in the same way in all the different age groups included in the design.

In sum, in order to capture ontogenetic differences in learning and memory it is vital to control all these variables as much as possible when designing learning tasks and experimental settings, using environmental stimuli that are representative of the organism's ecological environment and selecting behaviors that belong to the repertoire of the organism at each age of testing [154,156,157,159].

#### 4. Context learning and context effects in infant rats

This section describes the different results obtained in studies exploring contextual learning in infant rats, taking into consideration for the discussion, when pertinent, the methodological issues mentioned above. We will discuss the main conclusions drawn from the different studies in relation to the predictions of the two main hypotheses (neuromaturational and ecological) described in Section 1.

##### 4.1. Context as a source of forgetting/remembering in the infant rat

We mentioned earlier that contextual stimuli are those that are both constant and present for a long period during a learning episode. Hence, in most cases, context is a worse predictor of the occurrence of relevant events, such as USs, than discrete neutral stimuli (CSs) [121]. However, this characteristic of contextual stimuli does not preclude context from being encoded as part of the conditioning episode, and it can therefore act as a powerful source of retrieval or forgetting, regardless of whether or not it is present at testing, respectively. The degree of similarity between learning and testing contexts is considered a broad determinant for retention [154]. This statement is widely accepted for adult organisms, but the consensus is less widespread for infants. The first series of studies aimed at exploring contextual learning during infancy in rats was designed to answer the question of whether a context change may affect retention of excitatory conditioning during this ontogenetic period [41,153]. Specific experiments were designed to test whether retention of learning could be improved by providing the infant organism with a salient context, in such a way that this distinctive context would help compensate for some other potential sources of forgetting inherent to ontogenetic development. In this regard, it was suggested that rapid maturational changes in stimulus selection or perceptual capacities during the retention interval may result in the organism processing the training and testing contexts differently, which in turn would result in retrieval deficits [155]. The authors expected that, if this hypothesis was true, by providing the infant organism with the same salient context at both training and testing, retention would be better than in the absence of this salient context. This effect is known as the distinctive context effect [159]. According to the same logic, a context change between training and testing would result in greater forgetting, while recreating the training conditions at the moment of testing would alleviate rapid forgetting (contextual change effect) [159]. Detection of these effects during infancy would imply that infants encode contextual information along with other stimuli (i.e. CSs and USs) present during the conditioning episode. Alternatively, if infants are not capable of



encoding contextual information due to a functional immaturity of the hippocampus and related structures, these effects (contextual change and distinctive context effects) would not be observed, i.e. retention of learning would not be affected by a context change.

In general, most of the studies that explored these effects followed two different strategies. Firstly, they compared retention of associative learning within the infantile period in two experimental conditions, one in which the context was more salient than in the other, and usually evaluated at the same time whether or not retention of learning was affected by a context change. The exact nature of this “distinctive context” that was required in order to observe an effect was not explored in any real depth, although it was suggested that it may be limited to explicit odors, due to the importance of odor cues in guiding infantile behavior, or to internal states (induced by the administration of glucose or drugs such as sodium pentobarbital, LiCl or ethanol) [41,54,64,127,128,153]. Secondly, in some cases the distinctive context and the contextual change effects were compared between infant and adult organisms, to test whether or not these effects were homogeneous throughout ontogenetic development.

Remarkably, the results indicate that the context in which learning occurs is important for infants. Firstly, several studies using classical and operant conditioning tasks consistently demonstrated that retention of learning was facilitated when the same (rather than different) internal or external context was present at both training and testing [54,64,127–129,153]. It is also worth noting that in some cases, this contextual change effect was found to be even greater for preweanling than for adult rats [153], although in a more recent study the context-shift was observed to be less effective in affecting retention (48 h after training) in infants than in adults [3]. This finding was explained in terms of memory loss of specific attributes of the context, a result that is compatible with prior findings indicating that infants are more susceptible than adults to forgetting elements that are not good predictors of the US [97]. The second main finding frequently reported in these studies is that retention of learning in infant rats is facilitated when subjects are trained and tested in a more salient context, rather than in a more neutral one (the distinctive context effect) [41,127,128]. However, the opposite result, i.e. poorer retention in the more salient context, has been also observed (see [81] for potential explanations of the divergent results).

In sum, the main conclusions drawn from these studies were that during the preweanling period, subjects are highly susceptible to the influence of context on forgetting and retention of learning, and furthermore, that learning about the context during infancy is strongly influenced by the salience of said context. These conclusions can only be applied to infant rats over 16 days of age, since no studies systematically explored these context effects in younger subjects.

#### 4.2. Contextual fear conditioning in the infant rat

Contextual conditioning in infant rats has been analyzed mainly by using the contextual fear conditioning paradigm. In weaning, adolescent or adult rats, contextual fear conditioning has been widely and consistently observed using contextual foreground and background conditioning procedures. In background procedures with adult rats, the context can enter into competition with the cue [30,106] and when contiguity between the cue and the US is reduced, response to the context can increase [30].

Despite all the research exploring contextual fear conditioning during infancy, the conditions under which infants can acquire and/or retain this type of learning remain poorly understood, and in some cases, infantile capacity to learn about the context is still questioned (for instance, [114]). Table 1 contains a long list of studies assessing contextual fear learning in infant rats, including a brief description of some critical procedural parameters such as the age of the infants participating in the study, the US used and whether or not it was signaled by a CS, the type of context, the behavioral index and the retention interval after which subjects were tested. The results

vary from an absolute absence of any evidence of conditioning, to observations of strong CRs to the context, which in some cases were equal to or even higher than those displayed by adult rats. In this section we aim to help to elucidate which experimental conditions favor or hamper the expression or detection of contextual conditioning during infancy.

In an important series of studies [29,30,48,81,88–90], Spear and his co-authors used background contextual fear conditioning procedures to study possible developmental particularities in stimulus selection, with the aim of gaining a better understanding of infantile amnesia (see [5,36] for a discussion about the possible relationship between infantile amnesia and stimulus selection; [155]). In these studies, subjects were trained in basic episodes of Pavlovian conditioning, in which they were exposed to contingent or non-contingent tone-foot-shock pairings in a specific context. In light of the distinctive context effect observed in infant rats (see Section 4.1), these studies compared contextual learning in both a standard context (usually a transparent conditioning chamber) and a sensory enriched one (usually containing an explicit odor). Two main results were derived from these studies: a) infants were able to acquire and retain contextual fear conditioning [29,30,48,81,88–90], and in some cases, this effect was even stronger in the infant than in the adult rat [29,30,81,88–90], and b) the findings also revealed some differences in the conditions that favored the expression of this effect during infancy, in comparison with adulthood. The first main difference was that, while in adult rats a cue predicting the US overshadows the context, when the foot-shock was signaled by a discrete cue, the CR induced by the context was significantly increased in infant rats [30,90]. Furthermore, the better the CS predicted the occurrence of the US, the stronger the CR to the context. For example, response to the context was greater with a cue-delay than with a cue-trace conditioning [90]. In addition, context fear conditioning was more clearly observed in infants when the context was more salient (containing explicit odors) than in more standard contexts [29,30,90]. Therefore, in the infant rat it seems that the cue potentiates contextual conditioning. In fact, during infancy cue conditioning is also strengthened by the presence of salient contextual cues [90]. These observations are compatible with prior findings demonstrating that infants, in comparison with adult rats, have a greater predisposition towards potentiation rather than overshadowing [75,76].

Ontogenetic differences in contextual conditioning observed by Spear and his co-authors were also discussed in terms of ontogenetic differences in modal vs. amodal processing [30,81,90]. In infant rats an amodal type of processing stimuli would hypothetically prevail over a modal one. In other words, infants would tend to encode a given stimulus attending to attributes such as intensity or familiarity, while adults would tend to respond on the basis of the sensory modality of the stimulus [96]. The reason why infants show stronger contextual conditioning when the US is better predicted by a cue may be that infants perceive the net intensity of both (i.e. the context and the CS) and form a salient configuration. Since the salience of the CS influences positively its associability [169], this configuration would be associated more easily with the US than when its elements are presented separately [90]. Consistent with this interpretation, follow-up studies showed that, in the infant rat, a sensory enriched context increases orienting responses to the CS [74] and the unconditioned response produced by the US [29].

In sum, the studies described in the two previous paragraphs demonstrated that infants can acquire and consolidate contextual fear conditioning, and that procedural variables influence this type of learning differently in infants than in adults. Specifically, during the preweanling period, contextual fear conditioning is fostered by the presence of discrete cues predicting the US, as well as by the enhanced salience of the context. It is also important to mention that in all these studies the authors used latency for reaching a certain level of activity as an index of contextual fear conditioning, a measure that allowed clear detection of contextual learning in young rats.

**Table 1**  
 Studies analyzing contextual fear conditioning in infant rats. Age: age of training during the preweaning period. Only subjects younger than 21-day-old were included in this table. Procedure: Fear conditioning (context-foot-shock pairings) or context preexposure facilitation effect (CPFE). Context: relevant features of the context, particularly if explicit odors were included in the context. US: unconditioned stimulus used, including number of foot-shocks, duration and intensity. US signaled: whether the US was signaled by a discrete CS or not. Behavioral index: dependent variable analyzed as index of contextual conditioning. Retention interval: between conditioning and testing. Outcome: whether evidence of contextual conditioning were detected in infant rats, and if available, whether the magnitude of the effect was different than in older subjects.

Authors and year	Age	Procedure	Context	US	US signaled	Behavioral index	Retention interval	Outcome
Lariviere et al., 1990	PD16	Fear conditioning	Olfactory (lemon or banana)	2 foot-shock, 3 s, 0.5 mA	Yes (brightness)	Odor preference	30 min	Context conditioning in infants greater than in adults
Rudy, 1993	PD18	Fear conditioning	Clear Plexiglas chamber	1 foot-shock, 2 s, 1 mA	Yes, tone, but not in all the experiments	Freezing (%)	24 h	No evidence of conditioning on PD18. Evidence of contextual conditioning on PDs 21, 23 and 27
McKinzie et al., 1994	PD17	Fear conditioning	Black Plexiglas chamber, with home shavings	8 foot-shocks, 1 s, 1 mA	Yes, tone	Latency to reach activity level	24 h	Contextual conditioning and retention in infants potentiated by the CS, impaired by ethanol
Rudy and Morledge, 1994	PD18	Fear conditioning	Clear Plexiglas chamber	1 foot-shock, 2 s, 1 mA	Yes, tone, but not in all the experiments	Freezing (%)	1, 10, 60 min, 3 or 24 h	Contextual conditioning but not retention in infants
McKinzie and Spear, 1995	PD17	Fear conditioning	Black Plexiglas chamber, Plain or enhanced (odor)	8 or 16 foot-shock, 0.5 s, 1 mA	Yes, tone	Latency to reach activity level	24 h	Contextual conditioning and retention in infants potentiated by the CS
McKinzie et al., 1996	PD17	Fear conditioning	Black Plexiglas chamber, Plain or enhanced (odor)	16 foot-shock, 1 s, 1 mA	Yes, tone	Latency to reach activity level	24 h	Contextual conditioning and retention in infants potentiated by the CS, impaired by ethanol
Pugh and Rudy, 1996	PD18	Fear conditioning	Black or Clear Plexiglas chamber	1 foot-shock, 2 s, 0.4 mA	No	Freezing (%)	1, 10 min or 24 h	Contextual conditioning and retention in infants in the black context
Rudy and Pugh, 1996	PD18	Fear conditioning	Clear Plexiglas chamber	4 foot-shock, 1 s, 0.4 mA	Yes, tone	Freezing (%)	24 h	Adolescent rats showed more contextual freezing than infant rats
Brasser and Spear, 1998	PD17	Fear conditioning	Plain (black walls) or enhanced (with odors)	16 foot-shock, 0.5 s, 1 mA	Yes, tone with different trace intervals	Latency to reach activity level	24 h	Contextual conditioning and retention in infants, greater in the sensory enhanced context
Beane et al., 2002	PD18	Fear conditioning	Clear Plexiglas chamber	2 foot-shock, 2 s × 0.4 mA	Yes, tone	Freezing (%)	24 h, and 17 days later	Contextual conditioning and retention in infants, statistically equivalent in infants and in adolescent rats
Brasser and Spear, 2002	PDs 15, 17, 19	Fear conditioning	Clear Plexiglas chamber	16 foot-shock, 0.5 s, 1 mA	Yes, tone	Latency to reach activity level	24 h	Contextual conditioning and retention in infants at PDs 17 and 19, potentiated by the CS, and in this case, greater than in adult rats
Weber et al., 2006	PD18	Fear conditioning	Chamber with three black and white striped walls and one transparent	1 foot-shock, 1 s, 0.6 mA	No	Freezing (%)	1 min, 24 h and 7 days	Contextual conditioning in infant rats, retention 1 min, but not 24 h or 7 days after training. Naloxone alleviated contextual amnesia.
Esmoris-Arranz et al., 2008	PD17	Fear conditioning	Black Plexiglas chamber (with odor)	8 foot-shocks, 1 s, 1 mA	Yes, tone	Latency to reach activity level	23 h	Contextual conditioning and retention in infants, potentiated by the CS
Foster and Burman, 2010	PD17	Fear conditioning, CPFE	Clear Plexiglas chamber	1 foot-shock, 2 s, 1.5 mA	No	Freezing (%)	24 h	Contextual learning but not context-foot-shock association in infants
Raineki et al., 2010	PD21	Fear conditioning	Clear Plexiglas chamber, 1 aluminum side	10 foot-shock, 1 s, 0.5 mA	Yes, odor	Time in freezing (sec)	24 h	No evidence of contextual conditioning in infant rats
Schiffino et al., 2011	PD17	Fear conditioning, CPFE	Clear Plexiglas chamber	1 or 2 foot-shocks, 2 s, 1.5 mA	No	Freezing (%)	24 h	No evidence of contextual conditioning in infant rats
Pisano et al., 2012	PD17	Fear conditioning, CPFE	White Plexiglas chamber	1 foot-shock, 2 s, 0.5 or 1.5 mA	No	Freezing, grooming, exploration, fecal boli	24 h	Contextual conditioning and retention in infants, even in the immediate-shock group
Jablonski et al., 2012	PD17 and PD19	Fear conditioning, CPFE	Clear Plexiglas chamber	2 foot-shocks, 2 s, 1.5 mA	No	Freezing (%)	Immediate and 24 h	No evidence of contextual conditioning or retention on PD17 or PD19, mild effect on PD21 when compared with PD23
Quinn et al., 2014	PD17 and PD18	Fear conditioning	Two chambers with a white plastic back wall, aluminum sidewalls, and clear Plexiglas ceiling and front door (with odors)	15 foot-shock, 1 s, 1 mA in context A, 1 foot-shock, 1 s, 1 mA in context B	No	Freezing (%)	24 h	Contextual conditioning and retention in infant rats, with 15 but not with 1 foot-shock
Burman et al., 2014	PD17	Fear conditioning, CPFE	Chamber with black walls or a chamber with three white walls with a transparent cylinder (24 cm diameter) inside	1 foot-shock, 1.5 mA	No	Freezing (%), locomotion and latency to the first freezing	24 h	No evidence of contextual conditioning in infant rats

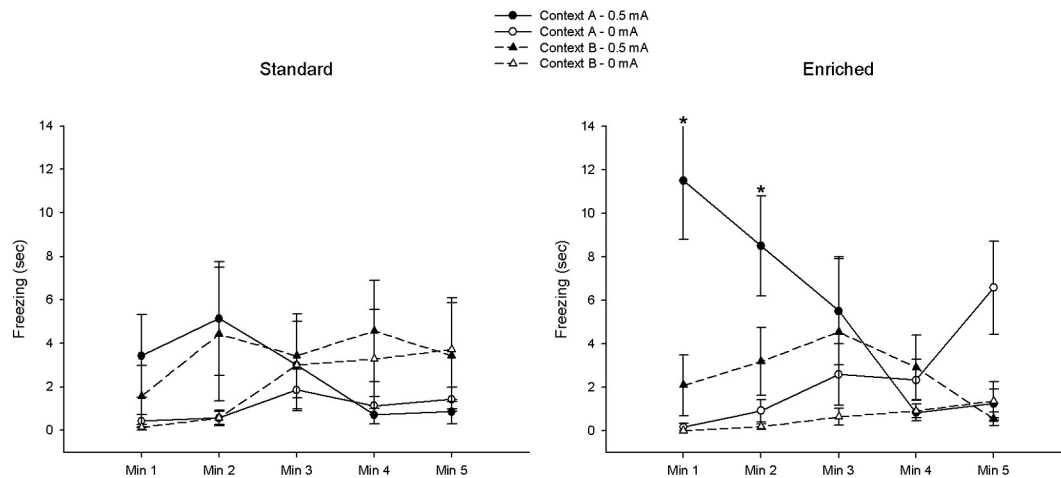
Contrary to these reports, several other studies failed to find any evidence of contextual fear conditioning in the infant rat. In general, their procedures included shorter exposures to the context than those described above, with fewer foot-shocks, and the context employed was usually a standard one (transparent Plexiglas chamber), without explicit odors. Their conclusions were also based on direct comparisons of raw freezing scores from preweanling (around PD17) and weanling rats (around PD23) [32,65,141,142,146,148]. Several explanations have been suggested to account for the divergent results across studies, some of which are based on ontogenetic differences in memory capacity rather than on procedural factors. A more detailed discussion of these explanations is provided in the following paragraphs.

The first hypothesis is that infants can show short-term but not long-term contextual conditioning [145]. This account was proposed after the authors observed that the freezing response elicited by the context in preweanling, but not in weaning rats, was significantly higher soon after conditioning (e.g. 1 min) than 24 h later [145,170]. Rudy and Morledge (1994) ran specific experiments to exclude some alternative interpretations of these results, for example, ontogenetic differences in the sensitivity to the foot-shock or lack of capacity to express the freezing response during the preweanling period. The authors ruled out these possibilities by showing the preweanling and weaning rats did not differ when they were tested in retention of a fear memory to an auditory CS. Hence, the lack of responding to the context by the preweanling group 24 h after training was interpreted in terms of a long-term memory deficit; i.e. the infant rat was not able to consolidate the context-foot-shock association [145]. This interpretation is not compatible with results from the studies described above showing retention of contextual fear conditioning in the infant rat at least 24 h after training [29,30,48,90], although there are numerous procedural differences between them, including, for example, the number of foot-shocks delivered, the salience of the context and the amount of exposure to the context. However, in a following study, Pugh and Rudy [115] reported evidence of contextual learning with similar conditioning parameters to those that led to the original observation of weak retention 24 h after conditioning [145]. Interestingly, the only difference between these two studies was the color of the context walls, i.e. the retention deficit was observed when the context was built with transparent walls [142], but not when the authors used a context with black walls [115]. In the latter case, the freezing response was similar 1 and 24 h after conditioning, a result that led the authors to conclude that maybe there are no qualitative developmental differences in long-term contextual fear conditioning between preweanling and weaning rats, and that the ontogenetic differences in performance observed in previous studies using contexts with transparent walls may reflect ontogenetic perceptual differences. Moreover, another study found that the apparently weak contextual memory observed 24 h after conditioning in infant rats could successfully be retrieved as long as 7 days after training by means of a pre-training treatment with an opioid antagonist (Naloxone) [170], suggesting that the weak response may be due to a deficit in retrieval rather than a deficit in memory consolidation. Finally, several other studies have reported long-term retention of context conditioning during the preweanling period even when using clear Plexiglas chambers, and in some cases, the magnitude of the response in infant and adult rats was statistically equivalent [11].

It has been also suggested that the lack of contextual fear conditioning in this ontogenetic period is due to the low intensity of the US or to the reduced number of USs delivered [117]. Nevertheless, other authors failed to observe any evidence of contextual conditioning even with repeated and very intense foot-shocks (2 foot-shocks, 1.5 mA) [65], while still others observed the same magnitude of contextual fear conditioning in adults and infants with a low intensity foot-shock (2 foot-shocks, 0.4 mA) [11] or even stronger conditioning in infants than in adults using the same foot-shock treatment [30]. Therefore, it is clear that the intensity of the US cannot, by itself, explain the diversity of results observed, and that this factor necessarily interacts with other

procedural variables such as, for example, the salience of the context. For instance, in a recent unpublished study from our laboratory, we tested contextual fear conditioning in preweanling rats using a simple contextual fear conditioning task, consisting of two phases. In the first one, on PD18 subjects were exposed for 3 min to context A or B, and at the end of this period they were given a single foot-shock (1 s, 0.5 mA). In the second phase, which took place 24 h later, all subjects were tested during 5 min in context A. In one experimental condition (which we labeled *standard*) context B was a Plexiglas chamber (29 cm × 17 cm × 20 cm) with white opaque walls, except for the front one which was transparent, while context A was similar to the first one, but with vertical black lines (2 cm wide, 5 cm apart) all along the white walls. In the alternative condition (*enriched*) context B was again a Plexiglas chamber (29 cm × 17 cm × 20 cm) with white opaque walls, except for the front one that was transparent. In this case, a small piece of cotton located at the top of this chamber was used to scent the context with almond odor (0.5 ml of pure almond scent, Esencias del Boticario, Cordoba, Argentina). Context A consisted of a similar Plexiglas chamber (29 cm × 17 cm × 20 cm) with black opaque walls, scented with orange odor (0.5 ml of pure orange scent, Esencias Bangladesh, Buenos Aires, Argentina). In both conditions (*standard* and *enriched*), the contexts were placed in the same room, illuminated with a dim light and with a constant low noise generated by an air extractor. In this experiment we also included a non-shocked control group in the design. The mixed ANOVA training context (A or B) by foot-shock (0 or 0.5 mA) and by minute (1–5 min) revealed a significant interaction between the three factors,  $F(4, 332) = 4.17, p < 0.05$ , but only in the *enriched* condition. In the *standard* condition, no significant effects or interactions were revealed by the ANOVA. Post-hoc tests with scores from the *enriched* condition indicated that subjects trained in the same context used in testing (training context A) showed higher freezing scores than the remaining groups on minutes 1 and 2 (Fig. 1). Two main conclusions can be drawn from these results. Firstly, contextual fear conditioning (in terms of an increased freezing response) was clearly observed in infant rats using a single foot-shock of low intensity, demonstrating that a low intense foot-shock is not a limiting factor for observing contextual fear conditioning during infancy. Secondly, this effect was only observed in the sensory enriched condition. Hence, when the design includes a control group receiving a foot-shock in an alternative context, it seems necessary to use enriched contexts in order to foster discrimination. It is also worth noting that the conditioning effect was detected during the first minutes of testing, a result that we also observed using a different protocol in preweanling rats, but employing a stronger foot-shock (1.5 mA) [113]. This is important, because the assessment of contextual fear conditioning in the infant rat usually lasts 5 (for example, [65,148]) or even 8 min [117], and the most common dependent variable is a single score representing the percentage of time engaged in freezing behavior throughout the entire testing period. This measure may weaken the sensitivity of the analysis for detecting evidence of learning in this ontogenetic period.

Another hypothesis suggests that while infants can show long-term contextual conditioning by means of associations between representations of independent elements of the context and the US, they cannot construct a unitary and configural representation of the context [65, 145,148]. According to some authors, the hippocampus specifically participates in the formation of this configural representation involving different elements of the context [52,144]. To test the configural hypothesis, a specific three-phase task was designed [the context preexposure facilitation effect (CPFE) [52,79,144,148]]. In the preexposure phase (Phase 1), only half of the rats are exposed to the training context (preexposed group). Twenty-four hours later, at conditioning (Phase 2), all subjects receive a footshock immediately after being placed in the training context, and are then quickly removed from the context. Finally, on the testing day (24 h after conditioning), rats are placed once again in the training context for 5 min. The common result is that non-preexposed subjects show a low freezing response, the so-called “immediate shock-



**Fig. 1.** Contextual freezing as a function of training context (A or B), foot-shock (0 or 0.5 mA) and testing minute (1 to 5). Left panel: subjects from the “standard” condition; right panel: subjects from the “enriched” condition. Subjects received the foot-shock treatment in the same (A) or in a different (B) context than the one used at testing. All subjects were tested on context A. Contextual conditioning was only evident in the “enriched” condition: training context  $\times$  foot-shock  $\times$  min [ $F(4.332) = 4.17, p < 0.05$ ]; post-hoc (Newman–Keuls) analysis indicated that freezing scores from subjects trained in the testing context (context A) were significantly higher than those from the remaining conditions during the first two testing minutes. The ANOVA conducted with freezing scores from the “standard” condition did not reveal any significant effect or interaction. \* indicates significant differences from the remaining groups,  $p < 0.05$ . Vertical lines illustrate standard errors of the mean. Number of subjects: 8–10 per group.

deficit”, which is alleviated by the preexposure treatment [144]. Hypothetically, this facilitation of conditioning by the preexposure treatment requires the formation of a configural representation of the context [65, 144, 148]. Given that in some studies preweaning, although not weaning rats, failed to show said effect, some authors have concluded that infants can show long-term contextual conditioning based on elemental associations, but not on the configural representation of the context [65, 148].

However, a recent study found evidence of the CPFE in preweaning rats using a comparable procedure [113]. Interestingly, this CPFE disappeared when subjects were tested in a novel context different from the one used at conditioning, a finding which corroborates that the CPFE was due contextual learning [113]. It is also worth noting that if weaning and preweaning rats are compared on the basis of the magnitude of their raw freezing scores (percentage of time) for the whole 5-min testing period, the response is stronger in older subjects than in younger ones (Fig. 2a). However, the magnitude of the effect is comparable between both ages. We calculated a z-score comparing the raw freezing scores of preexposed subjects to scores from their corresponding age-matched non-preexposed controls, and these z-scores were statistically similar (see Fig. 2b). These data analyses question whether it can really be concluded beyond question that learning in the infant is weaker than in the weaning rat, based exclusively on a comparison of the raw freezing scores obtained by both age groups.

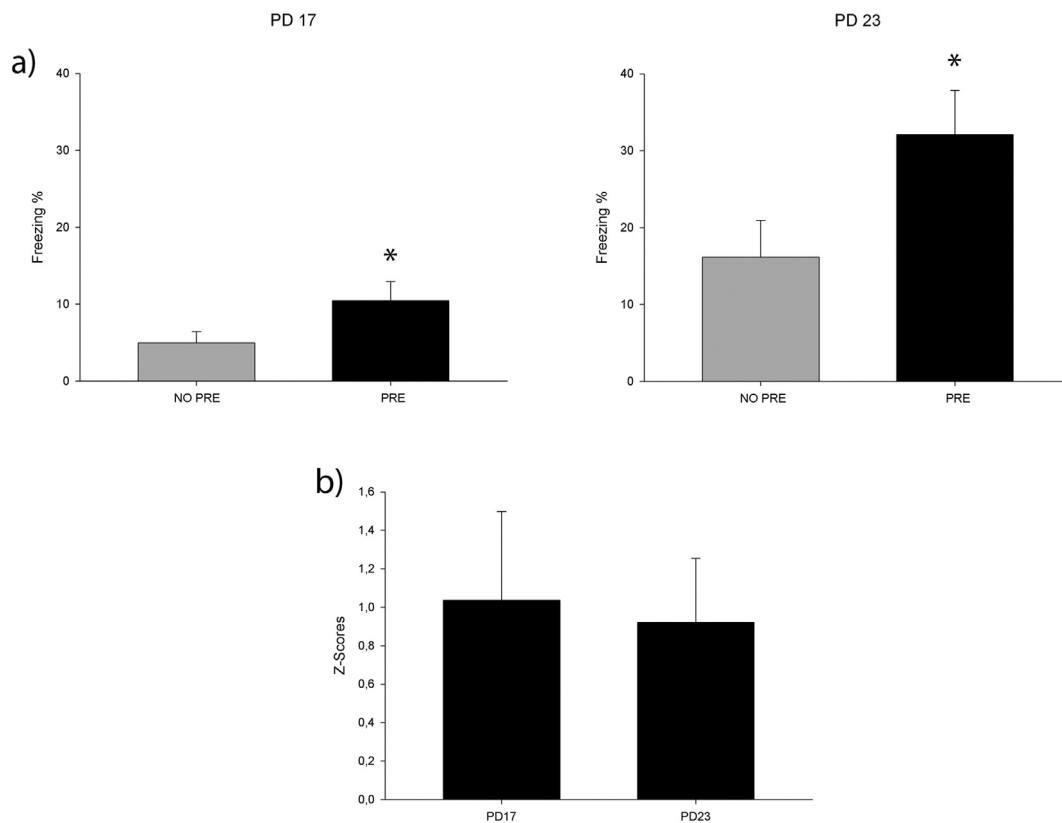
One question that remains unanswered is why, in some studies that did not find the CPFE during infancy, the freezing response in preexposed and non-preexposed subjects was statistically equivalent [65, 148]. Although it may be overly speculative, we can suggest here several possible accounts, with the aim of stimulating further research. For example, in these studies, during Phase 1 non-preexposed subjects were usually preexposed to a different context from the one used at conditioning and testing, while in the study conducted by Pisano et al. non-preexposed subjects remained in their home-cage. The CPFE reflects what the preexposed subjects learned about the context in Phase 1, but this effect also depends on non-preexposed subjects discriminating between the preexposure and conditioning contexts. One way of corroborating whether or not subjects do indeed discriminate between the contexts is to determine whether they respond differently to them after conditioning. In the study by Pisano et al., this discrimination was evident, since at testing the freezing response was higher in preexposed than in non-preexposed rats, while the lack of differences observed between these groups in other studies may be indicative of an absence of discrimination (or even generalization) between the

contexts. This may possibly be congruent with results showing the importance of the sensory content of the context for discrimination between contexts in preweaning rats ([124]; see also Fig. 1). The possible generalization between the preexposure and conditioning contexts in non-preexposed subjects may explain why, in studies in which the CPFE was not observed, the freezing response displayed by non-preexposed subjects was usually higher than in the study by Pisano et al., while the response of preexposed subjects seems to be equivalent.

Finally, some authors have suggested that it may be that infants can learn about the context (including its configural representation) but cannot associate this representation with the US [55]. This possibility is based on results from two experiments in which the CPFE was observed in subjects that were preexposed to the context on PD17, conditioned on PD24 and tested on PD25 [55]. Moreover, more recently these same authors also suggested that cue-fear conditioning might be impaired in the infant rat [32]. However, this possibility is not compatible with the large body of evidence showing tone and contextual fear conditioning in preweaning rats (for example, [29, 145]; see also Table 1).

We have presented here a compilation of evidence indicating contextual fear conditioning during the preweaning period. In some cases, the effect was absent or weak in comparison with that found in older subjects (at least in terms of the magnitude of the CR), but in others, the magnitude of the effect was stronger in the infant than in the adult rat. The divergent results seem to depend on the conditions under which infants and adults are compared. The observation of contextual fear conditioning during infancy seems to be facilitated by signaling the US, which is compatible with the hypothesis that infants are less selective than adults during learning, although studies that supported this conclusion used protocols involving long exposures to the context and many foot-shocks. The salience of the context seems to be also an important factor contributing to detection of contextual learning during infancy. While these procedural variables are important, they are not necessary for detecting this effect, although when the foot-shock is delivered in a control group, detection of conditioning may require the different contexts to be salient enough for the infant rat. Finally, the duration of the test, or the sensitivity of the behaviors used to infer conditioning, may be also important factors to take into consideration during this ontogenetic stage. Overall, these data do not support the assumption that difficulties in finding contextual fear conditioning in infants reflect exclusively the immaturity of the contextual learning capacity and the non-functionality of the hippocampus during the third postnatal week of life. Rather, the difference between studies





**Fig. 2.** a) Contextual freezing scores (%) from subjects trained on PD17 or PD23 with a context preexposure facilitation effect (CPFE) procedure, as a function of the preexposure treatment (preexposed Vs non-preexposed) and Age (PD17 Vs PD23). Foot-shock intensity: 1.5 mA. Freezing scores were collected at testing. The ANOVA preexposure by age revealed significant main effects of preexposure [ $F(1,51) = 6.26, p < 0.05$ ] and age [ $F(1,51) = 14.59, p < 0.05$ ] while the interaction of preexposure by age was far from significance ( $p > 0.20$ ). \* indicates significant differences from the non-preexposed group,  $p < 0.05$ . Vertical lines illustrate standard errors of the mean. b) Figure b represents z-scores corresponding to the same data from the a) panel. These z-scores were calculated referring freezing scores from preexposed subjects to the corresponding age-matched non-preexposed controls. As can be observed, when the raw freezing scores are converted to z-scores, values from each group of age were equivalent. These figures are based on data from [113].

which find or fail to find evidence of contextual fear conditioning in this ontogenetic period may lie in the extent to which their procedures were sufficiently adapted to the overall maturational (perceptual and behavioral) capacities of the experimental subjects. This is compatible with the ecological view as well as with the idea that the behavioral expression in a theoretically hippocampus-dependent task may depend on the interaction between the developmental status of the hippocampus itself and the different behavioral and perceptual systems involved in the task [160].

#### 4.3. Context-dependent interference learning in the infant rat

Context can also be used to disambiguate conflicting information [26]. This role of context has been widely studied in adult rats, for example, with interference learning paradigms, in which subjects are exposed to conflicting information in different phases of the experiment [22–24]. We shall now focus on two such effects, specifically those that have received most attention in the infantile period: Latent inhibition, an effect consisting of an attenuation of the CR as a consequence of pre-conditioning exposure to the CS [84]; and Extinction, a reduction of the CR as a consequence of post-conditioning exposure to the CS [111]. One feature that is common to both these and other interference learning effects is that they are considered highly context-dependent, because they can be attenuated by a contextual change between the different phases of the experiment [23]. Interestingly, this context-dependence also requires an intact hippocampus [63,67]. The context-dependence of extinction is commonly observed in renewal procedures, in which conditioning and extinction are carried out in different contexts. The expression of the extinction learning depends on the presence of the extinction context, because when subjects are tested

in the conditioning context (ABA renewal) or in a novel context (ABC renewal) the extinguished CR is recovered (for example, [77,167]). The renewal effect, together with other procedures allowing recovery from extinction, such as reinstatement, spontaneous recovery or rapid reconditioning, support the hypothesis that the extinction effect involves new learning, and that the memory trace acquired at conditioning survives, at least partially, the extinction training [25,28].

The neuromaturational hypothesis predicts that some complex forms of learning (such as higher order conditioning) emerge after simpler forms of conditioning (such as simple excitatory conditioning). For example, in relation to contextual learning, it has been suggested that direct associations between the context and the US should (ontogenetically speaking) be observed before the context is able to enter into more complex functions, such as, for example, the disambiguation of conflicting learned information [142]. Based on some results that were compatible with the idea that infant rats are not able to retain contextual conditioning, it was hypothesized that interference learning effects would not be affected by a context change during infancy. If this were correct, one additional interesting prediction would be that, if the extinction effect is not context-dependent during infancy, then the extinguished CR would not be reinstated by a context change. This implies that extinction during infancy may be due to a weakening or even an erasure of the memory trace acquired at conditioning [70].

Supporting these predictions, the first set of studies exploring the possible context-dependency of latent inhibition and extinction in the infant rat revealed that a context change did not attenuate these interference learning effects [69,142,172,173]. These results are compatible with the neuromaturational model. In a follow-up series of studies, some other results were found in support of this hypothesis, with no evidence of recovery from extinction being observed with reinstatement

or spontaneous recovery procedures [70]. These results led the authors to conclude that extinction during infancy may involve different mechanisms than in adulthood. Extinction in adulthood would be a flexible learning effect, involving, hypothetically, the acquisition of new inhibitory learning in which the extinction context would predict the absence of the US. In contrast, extinction during infancy may be an example of inflexible learning, involving the erasure of the associative memory acquired at conditioning [70].

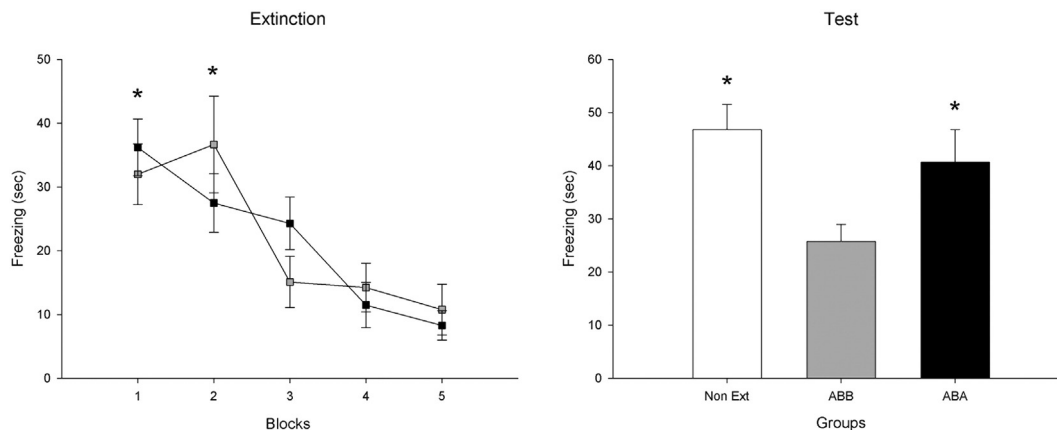
However, in some cases, the ABA-renewal procedure was also ineffective in recovering an extinguished response in adult rats. Thomas et al. demonstrated that the number of features differentiating contexts A and B, along with the salience of these contexts, is critical to enabling recovery from extinction [167]. Following this result, and considering the importance of context salience for observing context effects and contextual fear conditioning during infancy, we ran a series of experiments aimed at determining whether it was possible to find evidence of context-dependent interference learning during infancy by increasing the salience of the contexts. The results were consistent throughout a variety of procedures. For example, using a conditioned taste aversion protocol we recently reported the effectiveness of a context change in attenuating the latent inhibition effect in preweanling rats [123]. In another series of experiments, we found evidence of ABA-renewal using also a conditioned taste aversion procedure, and in the same study we also found evidence of reinstatement and rapid reconditioning [122]. All of these results indicate that extinction during infancy may also involve new learning (similar to during adulthood). More recently, we extended this result to a fear conditioning procedure, observing clear evidence of spontaneous recovery from extinction [125] and ABA-renewal in infant rats when contexts A and B differed in their odor content, and not merely in their visual cues [124]. Finally, in an unpublished experiment in which we used the same contexts (enriched with explicit odors) as those used in the Revillo et al. study [124] we found ABA-renewal in preweanling rats using a light as a CS, and a foot-shock as a US (Fig. 3). In this experiment, conditioning (PD18) took place in context A and consisted of 8 trials of a 10-s light- CS followed by a 1-s 0.6 mA foot-shock (US) after 1 min of context exploration. The extinction phase (PD19) was carried out in context B, in which rats were allowed to explore the context for 1 min before being exposed to 30 CS (10-s light) presentations with an ITI of 10 s (5 blocks of 60 s). Finally, on PD20, subjects' freezing response to a single 2 min CS presentation was registered after 1 min of context exploration. Half of the subjects were tested in the extinction context (ABB-group,  $n = 8$ ), while the

others were tested in the training context (ABA-group,  $n = 10$ ). A non-extinction group was included in the design. Half of the subjects of this group were tested in context A while the remaining half in context B ( $n = 10$ ). As shown in Fig. 3, and consistent with previous results from our laboratory, when the contexts employed differed in more than one characteristic and included distinctive odors, a context change was effective in recovering the extinguished CR. The ANOVA with testing scores revealed a significant main effect of group [ $F(2, 25) = 4.29$ ,  $p < 0.05$ ]. According to post-hoc tests (Newman-Keuls), at testing, freezing scores from the ABA group were statistically similar to those from the non-extinction group, while scores from the ABB group were significantly lower than those from the remaining conditions (see Fig. 3).

The summarized results indicate that by using salient contexts including explicit odors, context-dependent interference effects can be observed in this ontogenetic period. In all of the aforementioned studies in which the authors found renewal, no evidence of context-induced CRs was observed, indicating that the renewal effects were not caused by the excitatory strength of the context potentiating the response induced by the CS. This in turn indicates that infants are capable of using contextual information to disambiguate conflicting information about the relationship between the CS and the US. Interestingly, in two of these experiments, procedures started on PD13, suggesting that by this age, subjects may already be acquiring and retaining contextual information.

### 5. Functional development of the hippocampus

The hippocampus seems to be the main brain structure involved in contextual learning, to the extent that contextual learning has been proposed as a behavioral test for hippocampal function [85]. Consistent with this idea, when this structure is not functional, either because it has been inactivated or lesioned, major deficits are observed in context learning and context-effects [42–44,63,67,68,72,86,116,148]. Because the hippocampus is one of the brain structures that completes its anatomic maturational process later in ontogeny, it was suggested that there must be an ontogenetic stage during infancy in which subjects are unable to encode contextual information [102]. The first set of studies that approached this question explored spatial memory in infant rats using the Morris water maze (for example, [147]), observing that preweanling rats were unable to orientate themselves using distal visual cues until PD20 (although other authors reported evidence of spatial



**Fig. 3.** This figure represents extinction (left panel) and testing (right panel) freezing scores in response to a light-CS. Subjects were trained on PD18, extinction was carried out on PD19 and testing on PD20. The ABB group was tested in the same context than the one used during extinction, while the ABA group was tested in the same context than the one used at training, but in a different one than the extinction context. Subjects from the non-extinction group received the same training than the remaining two groups, and during extinction were exposed to the context (B) but not to the CS. Half of the subjects from this group were tested in context A while the remaining half in context B. The ANOVA with extinction scores revealed a significant main effect of block [ $F(4,64) = 20.48$ ,  $p < 0.05$ ], indicating that freezing scores progressively decreased during the extinction session. At testing, the ANOVA revealed a significant main effect of group [ $F(2,25) = 4.29$ ,  $p < 0.05$ ]. According to the post-hoc tests (Newman-Keuls), scores from the ABB group were significantly lower than those from the remaining conditions, while scores from the ABA and non-extinction group were statistically equivalent. \* indicates significant differences from the ABB group,  $p < 0.05$ . Vertical lines illustrate standard errors of the mean. Contexts (A and B) used in this experiment were similar to those that were used in a previous study demonstrating renewal in the infant rat [122].

navigation on PD19 but not on PD18 [31]). Results from these and other behavioral studies were compatible with the idea linking the emergence of the hippocampal function and context learning, and it was predicted that, during the infantile period (before PD20), the hippocampus was not sufficiently mature to support some types of learning, including contextual learning and context effects [102]. However, as described in the previous section, during the 80s and 90s, a considerable number of studies reported results which contradicted this hypothesis, showing clear evidence of contextual learning and context effects in rats younger than 20 days of age. Stanton [160] reviewed the literature analyzing the emergence of learning capacities theoretically dependent on the hippocampus, and he concluded that the age in which these capacities emerge is very variable, from the second postnatal week of life to the beginning of adolescence, depending, probably, on the behavioral system involved in the task (see Table 1 in [160]).

More recently, it was suggested that the hippocampus may be responsible for the formation of the configural representation of the context, while other forms of context learning involving elemental associations may be hippocampus-independent [65,71,112,144,148], and that infants may be impaired in contextual learning based on this configural representation [65,148]. This hypothesis should be taken cautiously for two main reasons. Firstly, as shown earlier, the CPFE, an effect that theoretically requires the configural representation of the context, has been observed in subjects trained during the preweaning period [55,113], although it still needed to confirm whether this effect in young rats was mediated by a configural representation of the context and whether it depends on the hippocampus. Secondly, almost all the contextual learning effects described in Section 4 can be enhanced during the preweaning period by using salient contexts, usually containing explicit odor cues, while those studies that found no evidence of the CPFE during infancy used contexts without explicit odors. The weak response to contexts distinguished mainly by visual cues may reflect perceptual rather than memory limitations [30,115]. It can be argued that the explicit odor may be a contextual cue, but that this does not necessarily imply that it is encoded by the hippocampus, although this possibility needs to be experimentally tested, especially in light of some results with adult rats showing that the hippocampus is also involved in encoding olfactory information. For example, the hippocampus has been found to successfully process olfactory cues allowing spatial learning, especially in the absence of salient visual cues [174]. These authors suggest that olfactory information may help stabilize place fields in the hippocampus when other sensory modalities are not salient enough. Furthermore, the hippocampus seems also to participate in encoding olfactory contexts [108]. In this study, the context consisted of an explicit odor presented for several minutes, during which subjects received signaled or unsignaled foot-shocks. The authors found that when the hippocampus was lesioned, subjects were able to learn cue-fear but not contextual-fear conditioning. When the odor was presented during a shorter period of time, the hippocampal lesion did not affect odor-fear learning, suggesting that in this case, the odor may be acting as a cue (hippocampus-independent) [108]. Interestingly an intact dorsal hippocampus is necessary for both unimodal (olfactory) contextual fear conditioning [108,110] and the CPFE [148]. These findings may imply that the hippocampus in the infant rat may also encode contextual odor cues, although this possibility needs to be experimentally tested. In keeping with such a possibility, one study used a spatial learning task involving contextual learning for which subjects needed to use olfactory, tactile or auditory stimuli to show that the hippocampus is activated in rat pups during the second postnatal week of life (before they even opened their eyes) [109].

Interestingly, only a few studies have focused directly on exploring the hippocampal function in contextual learning during infantile development. Foster and Burman found evidence of the CPFE when preexposure took place on PD17, conditioning on PD24 and testing on PD25 [55]. Interestingly, a pre-training lesion to the hippocampus (on PDs 15–16) prevented the expression of the CPFE [55]. This result is

compatible with the hypothesis which holds that the hippocampus is functional by at least PD17 and can support contextual learning, although it is not conclusive because the lesion could be affecting conditioning or testing that in this experiment occurred after the weaning period. In another report, Raineki et al. [118] tested rats on PD21 and PD24 in cue and contextual fear conditioning procedures. The authors found evidence of contextual fear conditioning only in the older group of rats, while cue conditioning was found in both age groups. They also showed that only PD24 rats exhibited an increase in hippocampal neuronal activation measured by c-fos expression after training. In view of the wealth of evidence showing contextual fear conditioning in infant rats (even younger than 21-days-old), we suggest that the ontogeny of the hippocampal function during contextual learning should be studied using procedures that allow the expression of contextual fear conditioning in infant rats.

The hippocampus is in continuous development during the first four postnatal weeks of life, although clear evidence of functionality has been observed before PD21. For instance, by the beginning of the third postnatal week of life, infant rats already have functional head direction cells, grid cells and place cells in the hippocampus [1,80], and by at least PD17 the hippocampus is activated, together with other brain structures, during the extinction of an instrumental response. Its function in this case may possibly be to allow reinforcement schedules to influence the extinction rate [103,104]. Additionally, long term potentiation can be measured in CA1 by at least PD17 [12]. The fact that the hippocampus is involved in behavioral inhibition through the activity of endogenous corticosterone hormones on glucocorticoid receptors in this brain structure, may also be relevant for ontogenetic contextual fear conditioning [165]. Interestingly, by the end of the second postnatal week of life infant rats are able to freeze in response to the presence of a threat [40,163,164], and the number of glucocorticoid receptors in the rat hippocampus continues to increase until the end of the third postnatal week [91–93], which could result in differences in the expression of freezing behavior during the third postnatal week of life. With all these examples of the functional activity of the hippocampus during, at least, the third postnatal week of life, it would not be surprising to learn that this brain structure is responsible for the context learning effects summarized in the present review, although this possibility has yet to be explored in detail.

## 6. Context effects in the human infant

The function and development of the different memory systems during human infancy have been discussed in much the same terms as in animal research. According to the neuromaturation model, a basic memory system, consisting of associative memory, procedural memory and pre-explicit memory, becomes functional very early on in newborn human infants, although it is not until the age of 6 to 12 months that a more complex explicit memory system, involving “memory representations” and conscious awareness, emerges [105].

Since some studies found no evidence of complex, adult-like, explicit memory until late in infancy, it was assumed that the neural network underlying adult memory systems became functionally mature around the 9th postnatal month of life [10,99,105,136]. Anatomical post-mortem evidence is consistent with the idea that late maturation of the hippocampus precludes the development of an explicit memory system early in infancy. These studies show high levels of anatomical maturation in the hippocampus and related brain areas from birth, but adult-like neuronal connectivity is not reached until some time between the 2nd and 8th year of life [10,150]. The verbal nature and motor requirements of many explicit memory tasks limit our ability to explore the development of this type of memory in early infancy, since results must be inferred from non-verbal behavioral analysis. One of the most commonly used tasks is the deferred imitation task, which requires higher order memory skills [61,95]. The first developmental studies that used this task concluded that infants were able to

solve it at 9-months of age, but not earlier [94]. At the same time, the data showed that the retention of memory increased with age, following the maturation rate of the hippocampus [133,134,136,138]. Nevertheless, more recent studies have demonstrated that infants are able to respond correctly in the deferred imitation task at the age of 6 months [7,8,39,60,82,83], and moreover, if appropriate reminders were provided periodically, even 3-month-olds are capable of retaining this kind of learning for a three month period (until they are 6 months old) [34].

Another approach that has been proposed for studying hippocampal dependent declarative memories in preverbal infants is to explore the contextual dependency of memories. The neuromaturational model predicted that in the human newborn, similar to in the infant rat, learning would be context-independent before the 8th or 9th month of age [101]. Curiously, it is very difficult to find empirical evidence of context-independent learning in human infants, while there are a large number of studies showing the importance of the context for learning and memory during this ontogenetic period (see Table 2). The contextual-change effect was consistently observed with different procedures (the mobile conjugate reinforcement paradigm, the train task or the puppet imitation task) and at a variety of ages within the first year of life (see [133] for a description of the procedures). For example, the contextual-change effect was observed in 3-month-old infants, and depending on the components of the context, the effect was also observed as long as 7 days after training [33,46,49,50,53,62,107,135,137,140,149,162]. In an attempt to analyze the evolution of memory skills during the first year of life, Hartshorn et al. [58] compared the performance of infants at 3, 6, 9 and 12 months of age in an operant task, finding that a context change affected retention at long intervals, but not one day after training at 3, 9 and 12 months of age. The opposite pattern was found in 6-month-old infants, in which the context change affected retention 24 hs after training but not after longer delays [13,19,21]. A similar profile was found using an imitation task, in which 6-month-olds (but not older infants) performed more poorly if they were evaluated in a novel context 24 h after demonstration [60]. These results indicate that sensitivity to the context change effect does not necessarily vary monotonically during early development. Furthermore, the contextual-change effect was attenuated in 3-month-olds by training subjects in the mobile task in multiple contexts [135], and in 6-month-olds by preexposing subjects to training and testing contexts simultaneously for seven consecutive days prior to the training phase [18].

During the first year of life, infants can also use contextual information to retrieve forgotten memories. For example, a brief experience with the mobile was an effective reminder for reactivating learned responses, enabling extraordinary long term retention [8,20,56,59]. Interestingly, the effectiveness of the reminder was found to be context-dependent in young infants and to become less context-dependent with age, for example some studies shown that infants between 3 and 9 months of age, recovered a forgotten response when the reminder was presented in the training context, but not when it was presented in a novel context [21,33,57], whereas 12-month-olds recovered the response after being presented with the reminder both in the training, or in a novel context [45]. Finally, it was demonstrated that infants as young as 3 months old can learn to associate a context with particular experimental contingencies, and can use a distinctive context to disambiguate conflicting information in a renewal procedure following extinction training [133].

In sum, although some authors argue the central nervous system, or at least some of its neural structures such as the hippocampus, is not mature enough to support complex learning and memory skills until 8–9 months of age, an increasing amount of evidence shows complex learning and memory skills from early on in infancy. This section has mainly reviewed studies analyzing context learning, and the results reveal that contextual information mediates the behavior and learning of human infants during the first postnatal year of life, in parallel to

what was described for the infant rat, although the role of hippocampus or medial temporal lobe function in these effects is currently unknown.

## 7. Concluding remarks

The question of whether infants (both human and rat) can encode or use contextual information is still generating research. The results of the studies reviewed here prompt a wide range of conclusions. We have described how, during the preweaning period of the rat, context can play similar roles in learning and memory as those described for adult rats. Furthermore, although in some cases contextual learning was weaker in the preweaning than in the weaning rat, other studies found the opposite profile, with, for example, stronger contextual fear conditioning (for example, [30]) or more sensitivity to the distinctive context or to contextual change effects (for example, [41,153]) in infants. This variety of outcomes produced by contextual learning tasks may be indicative of the sensitivity of contextual effects to some specific procedures (as described in Section 4), although this is not a particularity of studies with infant rats. In adult rats the observation of contextual learning and context change effects are also dependent on procedural variables.

A substantial body of evidence supports contextual learning and context effects during the third postnatal week of life in the rat. However, the question of whether context can influence learning and behavior in younger rats remains open. There is some evidence that may be indicative of context learning during the second postnatal week of life. For example, we previously found that preexposure to the context between PDs 9 and 11 attenuated the acute locomotor stimulating effect of ethanol, without producing habituation in terms of locomotor suppression [4]. During the second postnatal week of life learning and behavior of infant rats is also affected by the presence of a familiar context [152,158]. Other authors have found evidence of hippocampal activity during a spatial learning task between PDs 10 and 13 [109]. Finally, in a recent study we have shown that tolerance to the locomotor stimulating effect of ethanol is context-dependent during the second postnatal week of life, although no direct conditioned responses to the context were detected [38]. If these early evidences of contextual learning are confirmed and extended, then it would also be interesting to see whether they correlate with hippocampal activity, which could lead to a reconsideration of predictions made by the neuromaturational hypothesis regarding the age at which infants are able to encode and use contextual information. It is likely that this age depends on the behavioral and perceptual systems involved in the task used to evaluate contextual learning [160]. We think this hypothesis is not incompatible with the ecological view, and that both approaches result in similar predictions about the ontogeny of contextual learning. Specifically, if task demands are adapted to the behavioral level of the organism, the infant can respond well in theoretically hippocampus-dependent tasks.

A similar pattern of results has been reported by studies with human infants, which describe multiple functions of context in learning and memory during the first year of life. Moreover, these studies reveal the prominent role played by experience in the cognitive changes that take place during early ontogeny. Taken together, the results reviewed show more similarities than differences between infants and adults as regards their cognitive capacities. At the same time, they reveal differences in terms of what infants and adults attend to in a particular situation or the particular behavior they engage in. These results do not necessarily support a linear development of cognitive capacities and the assumption that infants are immature adults with a basic set of cognitive capacities that become more complex as the brain matures. Perhaps, as Spear suggested [157] and Rovee-Collier highlighted on many occasions [131–134,136,139], a valuable approach to studying cognitive development is to view the infant as a completely different organism from the adult, an organism that behaves and evolves in a



**Table 2**

Studies analyzing context effects in human infant rats younger than 1-year-old. Age: age of training. Procedure: task used. Context: type of context. Outcome: context-effect observed in the study.

Authors and year	Age	Procedure	Context	Outcome
Rovee-Collier et al., 1985	3-month-old human infants	Mobile conjugate reinforcement paradigm	Visual context	1 Context-dependent retention 7 days after training 2 Context-dependent reinstatement 14 days after training
Fagen et al., 1989	3-to 4-month-old human infants	Mobile conjugate reinforcement paradigm	Affective context (internal context)	1 Context-dependent retention 7 days after training
Butler and Rovee-Collier, 1989	3-month-old human infants	Mobile conjugate reinforcement paradigm	Visual context	1 Context-dependent retention 3 and 5 days after training 2 Context-dependent reinstatement 14 days after training
Ohr et al., 1990	3-to 4-month-old human infants	Mobile conjugate reinforcement paradigm	Affective context (internal context)	1 Cue-dependent retention 1, but not 3, 5 or 7 days after training 2 Context-dependent retention 7, but not 1 or 3 days after training
Borovsky and Rovee-Collier, 1990	6-month-old human infants	Mobile conjugate reinforcement paradigm	Visual context	1 Context-dependent retention 1 and 3, but not 5, 7 or 14 days after training 2 Context-dependent reinstatement
Rovee-Collier and DuFault, 1991	3-month-old human infants	Mobile conjugate reinforcement paradigm	Visual context	1 Context-dependent retention 3 days after training 2 Context-dependent reactivation 14 days after training 3 Training in multiple contexts alleviate the context dependence of retention and reactivation
Hayne et al., 1991	3-month-old human infants	Mobile conjugate reinforcement paradigm	Visual context	1 Context-dependent reactivation 14 days after training
Boller and Rovee-Collier, 1992	6-month-old human infants	Mobile conjugate reinforcement paradigm	Visual context	1 Passive exposure to an alternative context during or immediately after training disrupted the context dependence of retention (1 day) and reactivation (21 days)
Fleckenstein and Fagen, 1994	3-to 4-month-old human infants	Mobile conjugate reinforcement paradigm	Affective context (internal context)	1 Context-dependent retention 7 days after training
Boller and Rovee-Collier, 1994	6-month-old human infants	Mobile conjugate reinforcement paradigm	Visual context	1 Passive exposure to an alternative context immediately after reactivation does not alter the response reactivation or its context specificity (21 days)
Earley et al., 1995	3 and 6-month-old human infants	Mobile conjugate reinforcement paradigm	Visual context	1- Context-dependent retention 3 days after training in 3-month-olds 2- Context-dependent reactivation in 6-month-olds (21 days)
Fagen et al., 1997	3-month-old human infants	Mobile conjugate reinforcement paradigm	Auditory context	1 Context-dependent retention 7, but not 1 day after training
Hartshorn et al., 1998	9 and 12-month-old human infants	Train task	Visual context	1 Context-dependent retention at long intervals
Hartshorn and Rovee-Collier, 1997	6-month-old human infants	Train task	Visual context	1 Context-dependent reactivation 21 days after training
Boller, 1997	6-month-old human infants	Mobile conjugate reinforcement paradigm	Visual context	1 Simultaneous preexposure to distinctive contexts, eliminated the context dependence of retention (1 day after training) in 6-month-olds
Rubin et al., 1998	3-month-old human infants	Mobile conjugate reinforcement paradigm	Olfactory context	1 Context-dependent retention 1 day after training
Hayne et al., 2000	6–18-month-old human infants	Deferred imitation task	Visual context	1 Puppet-dependent retention 1 day after demonstration in 6, 12-and-18-month-olds 2 Context-dependent retention 1 day after demonstration in 6-but not 12-or-18-month-olds
Learmonth et al., 2004	6–9-12-month-old human infants	Deferred imitation task	Visual context	1 Context-dependent retention 1 day after demonstration in 6-but not p-or 12-month-olds
Learmonth et al., 2005	6–18-month-old human infants	Deferred imitation task	Social context	1 Context-dependent retention 1 day after demonstration in 6, 9, 12, 15 and 18-month-olds 2 A passive exposure to an alternative context alleviates context dependence of retention
Schroers et al., 2007	3-month-old human infants	Mobile conjugate reinforcement paradigm	Odorant context	1 Context-dependent retention 1 and 5 days after training
Suss et al., 2012	3-month-old human infants	Mobile conjugate reinforcement paradigm	Odorant context	1 Context-dependent reactivation 7 days after training

particular and changing environment, with different challenges but with all the necessary tools to survive at each moment in time. Seen from this perspective, learning and memory capacities are revealed as neither basic nor rudimentary, but rather as developed enough to allow successful interaction with the environment at each developmental stage. In light of this proposal, in our opinion, future research aimed at exploring the possible involvement of the hippocampus in contextual learning during early infancy should take special care to select procedures sensitive enough to allow the expression of this type of learning in this ontogenetic period.

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