



## Changes in sucrose and quinine taste reactivity patterns in infant rat pups after exposure to the other tastant



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### ABSTRACT

The taste reactivity test is considered as an objective measure to assess the hedonic impact of tastes. Both the appetitive and aversive pattern of responses are plastic and can change based on previous experience. The present study assessed the repertoire of taste responses elicited by sucrose and quinine in preweaning rats, and described changes in these taste reactivity patterns after exposure to the other tastant. We exposed infant rats (17 days old at the start of training) to sweet (2% sucrose) or bitter (0.01% quinine) tastants during 4, 10-min trials in two different random sequences. The subjects were weighed before and after each trial to provide a measure of percent body weight gained. The following taste reactivity responses were registered: duration of mouthing and paw lick, frequency of chin rub, head shake and flailing of the forelimbs, frequency and duration of face washing, wall climbing and paw tread. The consummatory and affective taste responses changed depending on the order in which the solutions were administered. The order of exposure to the tastants did not affect the levels of sucrose intake. Conversely, rat pups showed more ingestive, and fewer aversive, responses to the sweet tastant when access to the solution followed the intraoral infusion of quinine. Likewise, intraoral delivery of quinine elicited a more aversive taste reactivity pattern when delivered after the access to sucrose than when presented to sucrose-naïve pups. This research contributes to the analysis of taste reactivity responses during the early ontogeny of the rat and highlights the importance of previous experiences on the subsequent assessment of rewards.

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### 1. Introduction

Since its inception (Grill & Norgren, 1978a), the taste reactivity test (TRT) has gained importance and significance as an objective measure to assess the hedonic impact of tastes. Two main groups of taste response patterns have been described (Ganchrow, Steiner, & Daher, 1983; Grill & Norgren, 1978b; Jankunis & Whishaw, 2013; Kiefer, Hill, & Kaczmarek, 1998; Steiner & Glaser, 1984; Steiner, Glaser, Hawilo, & Berridge, 2001; Ueno, Ueno, & Tmonagac, 2004; Van den Bos, Meijer, & Spruijt, 2000). Appetitive/ingestive responses are usually evoked by sweet tastes (e.g., sucrose, saccharin, milk); whereas aversive responses facilitate rejection of bitter, sour

or highly salty solutions (Jankunis & Whishaw, 2013; Ueno et al., 2004; Van den Bos et al., 2000). These evolutionarily conserved behaviors may reflect “like” or “dislike”, this is, an emotional or hedonic value assigned to rewards, preserved across a wide range of species (Berridge, 2000; Steiner et al., 2001).

The appetitive pattern involves ingestive mouth movements (i.e., rhythmic movements of the jaw and mouth) and tongue protrusions. The aversive pattern involves gaping (triangular opening of the mouth) and body movements such as chin rubbing (rub the chin against the floor, driving the body forward), head shaking (quick shake of the head to the sides), paw pushing (also called paw treading –successive movements of one of the paws forward on the floor while the other one retracts), face washing (circular movements of the paws on the snout) and flailing of the forelimbs (quick shake of the forepaws). Some studies (Arias & Chotro, 2005a, 2005b, 2006b; Parker, Rana, & Limebeer, 2008) restricted the set of aversive responses to gaping, paw pushing and

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chin rubbing, and added paw licking to the appetitive pattern. Wall climbing (resting the forelimbs on the wall) and passive drips (the rat remains motionless, allowing the solution to leak from the mouth) also belong to the disgust set of responses, yet they are more often observed in preweanling than in older rats (Arias, Pautassi, Molina, & Spear, 2010; Díaz-Cenzano & Chotro, 2010b, 2010a).

The taste and orofacial responses are plastic and can change based on previous experience. Adult or infant rats trained in a conditioned taste aversion protocol (e.g., saccharin-gastric discomfort association) exhibited rejection responses toward a sweet tastant, a result probably shown first by Spector, Breslin, and Grill (1988; also see Arias et al., 2010; Grant et al., 2012; Itogaa, Berridge, & Aldridge, 2016). Furthermore, prenatal exposure to ethanol is associated with greater emission of appetitive responses, and reduced emission of aversive responses towards ethanol, as assessed during postnatal life (Arias & Chotro, 2005a, 2005b, 2006a; Díaz-Cenzano & Chotro, 2010a). Suárez, Pautassi, Mustaca, and Kamenetzky (2014) gave three-week old rats alternating stimulation with 12% and 2% sucrose. These animals exhibited significantly greater emission of aversive responses towards 2% solution than control (i.e., “un-shifted” animals) animals that always received the 2% solution. Conversely, preweanling rats stimulated with 0.01% quinine (the prototypical aversive solution) after exposure to 0.1% quinine exhibited decreased aversive, and increased appetitive, responses than counterparts always stimulated with 0.01%. The studies reviewed highlight, by carefully changing the magnitude of a given reward, the important role that expectancies play in the hedonic assessment of tastants. It has been less explored, however, how previous experience with a given taste affects the palatability of another taste.

In taste reactivity studies, a difference can be made between “wanting” and “liking”. The latter is related to the palatability of a sapid reinforcer (i.e., the perception on how pleasant or unpleasant is), whereas the former encompasses the motivation to approach that reinforcer, including preparatory, approach and consummatory behaviors. Although they often go together, these components can be dissociated (Limebeer & Parker, 2000; Parker, 1995; Pautassi, Arias, Molina, & Spear, 2008; Suárez et al., 2014). The brain systems involved with wanting are widely distributed in the brain and exhibit overlap with those implicated with liking (see Berridge, Robinson, & Aldridge, 2009; Castor & Berridge, 2014).

The present study assessed the repertoire of taste responses elicited by sucrose and quinine in preweanling rats, and described changes in these taste reactivity patterns after exposure to the other tastant. More in detail, we assessed if a sweetened solution becomes more palatable after consumption of a bitter solution, and if the bitter solution becomes more aversive after stimulation with the sweet tastant. The study of the early reactivity responses towards sweet and bitter solutions is important for many reasons. The hedonic response to basic tastants is subjected to early fetal or perinatal programming. For instance, Ayres et al. (2012) observed that the hedonic, ingestive responses towards a sweet solution – but not towards water – were diminished in human neonates with intrauterine growth restriction. These results may explain the higher propensity for obesity in subjects that experienced intrauterine growth restriction. Also, when compared to adult counterparts, preweanling rats exhibit significantly greater consumption of ethanol (Truxell, Molina, & Spear, 2007), known to be perceived as a mixture of sweet and bitter components. The second week of life in the rat is also a critical developmental window, in which specific, stimulus-dependent, appetitive and disgust reactions emerge. It has been shown (Hoffmann, Hunt, & Spear, 1991) that 15-day-old, but not 5-day-old, rats exhibited qualitatively different conditioned disgust reactions when stimulated

with a lithium-chloride paired taste, than when stimulated with a footshock-paired taste.

## 2. Method

### 2.1. Subjects

Twenty-eight naïve female Wistar rats, representative of 10 litters, were used. The rats, seventeen days-old at the beginning of the training, were bred at Instituto de Investigaciones Médicas Dr. Alfredo Lanari (IDIM-CONICET, Argentina), in a vivarium kept in a reversed 12:12 h light:dark cycle, with lights on at 0700. Room temperature was  $23^{\circ}\text{C} \pm 1$ . The day of birth was considered postnatal day 0 (PDO). Pups were housed with the dam until training with ad libitum access to water and food (Cooperación, Buenos Aires, Argentina). We followed the guidelines for animal care and use established by the National Research Council (1996).

### 2.2. Apparatus

An infusion pump (Apema S.R.L., Buenos Aires, Argentina), equipped with four Prexajet syringes, delivered the sweet (2% sucrose, 58.42 mM) or bitter (0.01% quinine, 0.308 mM) tastants. Following previous work (Pautassi et al., 2008), the total amount of liquid delivered in each trial was equivalent to 2.5% of the pup's body weight. Sucrose and quinine solutions were prepared by diluting 2 gr of sugar (Ledesma, San Luis, Argentina) or 0.01 gr of quinine (Saporiti S.A., Buenos Aires, Argentina) in 100 ml of water, respectively. The syringes were connected to a polyethylene tube (PE-50), connected to a cannula previously positioned in the cheek of the animal. Cannulas were fabricated by creating a small flange in one end of the device. Training chambers were two mirrored trapezoid boxes ( $34 \times 18 \times 18$  cm) divided in two equal compartments. The side and back walls were made of mirror glass. The front was made of a transparent glass and the dividing wall of opaque glass. All tests were recorded (Sony, DCR-SR47) and subsequently processed by two observers, which were unaware of the taste sequence assignment of each animal, via the JWatcher software.

### 2.3. Procedure

Each day, the pups were separated from the dams and cannulated as described by Pautassi et al. (2008). Cannulation was made by attaching the unflanged end of a PE10 cannula to a metal needle (30G C-KJECT, CK Dental Industries, Buenos Aires, Argentina). The needle was pulled through the medial internal surface of the cheek of the animal, leaving the unflanged end inside the cavity of the pup. This procedure did not require more than ten sec per animal and does not induce major stress on preweanling rats (Spear, Specht, Kirstein, & Kuhn, 1989).

The cannulation was alternated between the left and right cheek of the animal to preserve the tissue of the area. Three hours after the cannulation, the pups' anogenital region was stroked with cotton to stimulate defecation and/or urination. Then the PE10 cannula was attached to the PE50 cannula, which was connected to the infusion pump. Training took place on PD 17 (Session 1) and PD18 (Session 2), between 10:00 and 17:00 h, and consisted of two daily trials, separated by three hours. This is, a total of 4 trials were conducted. During each trial, the animals were intraorally infused with either sucrose or quinine (2.5% of the body weight), for 10 min. To counterbalance the order of treatments, approximately half of the animals ( $n = 13$ ) were given the sequence sucrose-quinine-quinine-sucrose during trials 1 to 4, whereas the remaining animals ( $n = 15$ ) were stimulated with quinine-sucrose-sucrose-quinine during trials 1 to 4, respectively (see the experimental

**Table 1**  
Scheme of the experimental design.

N	Session 1		Session 2	
	Trial 1	Trial 2	Trial 3	Trial 4
13	Sucrose	Quinine	Quinine	Sucrose
15	Quinine	Sucrose	Sucrose	Quinine

design in Table 1). The subjects were weighed before and after each trial to provide a measure of percent body weight gained [(post-weight – pre-weight)/pre-weight] × 100. (post-weight). The chambers were cleaned with a wet cloth after each trial.

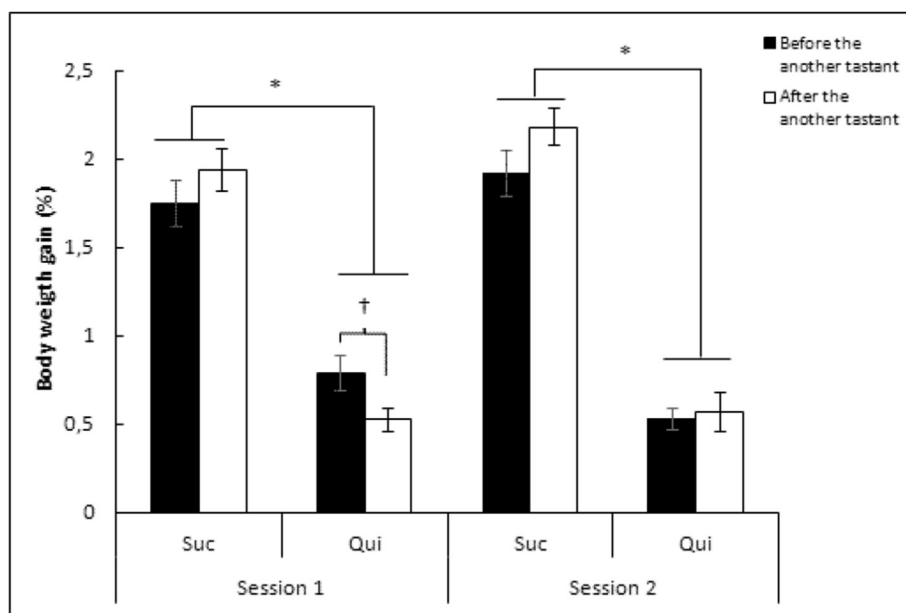
The following taste reactivity responses were registered: duration of mouthing and paw lick, frequency of chin rub, head shake and flailing of the forelimbs, frequency and duration of face washing (circular movements of the paws on the snout), wall climbing and paw tread (successive movements of one of the paws forward on the floor while the other one retracts, as in an attempt to dig). Inter-observer reliability was >85%, across behaviors.

#### 2.4. Statistical analysis

Percent body weight gained (% BWG) and frequency or duration of each taste reactivity behavior were analyzed via the independent-samples *t*-test. For each session (i.e., day), we compared the responses towards sucrose (average of trials 1 and 2) vs the responses towards quinine (average of trials 1 and 2). The same variables were compared based on the order of administration of sucrose (i.e., whether sucrose was given on trial 1 (Suc1) or on trial 2 (Suc2)), for each individual session, or quinine (Qui1 vs Qui2). Hedges' *g* effect size for intake and taste reaction responses was analyzed. The data was analyzed via SPSS 18 and the alpha level was set at 0.05.

### 3. Results

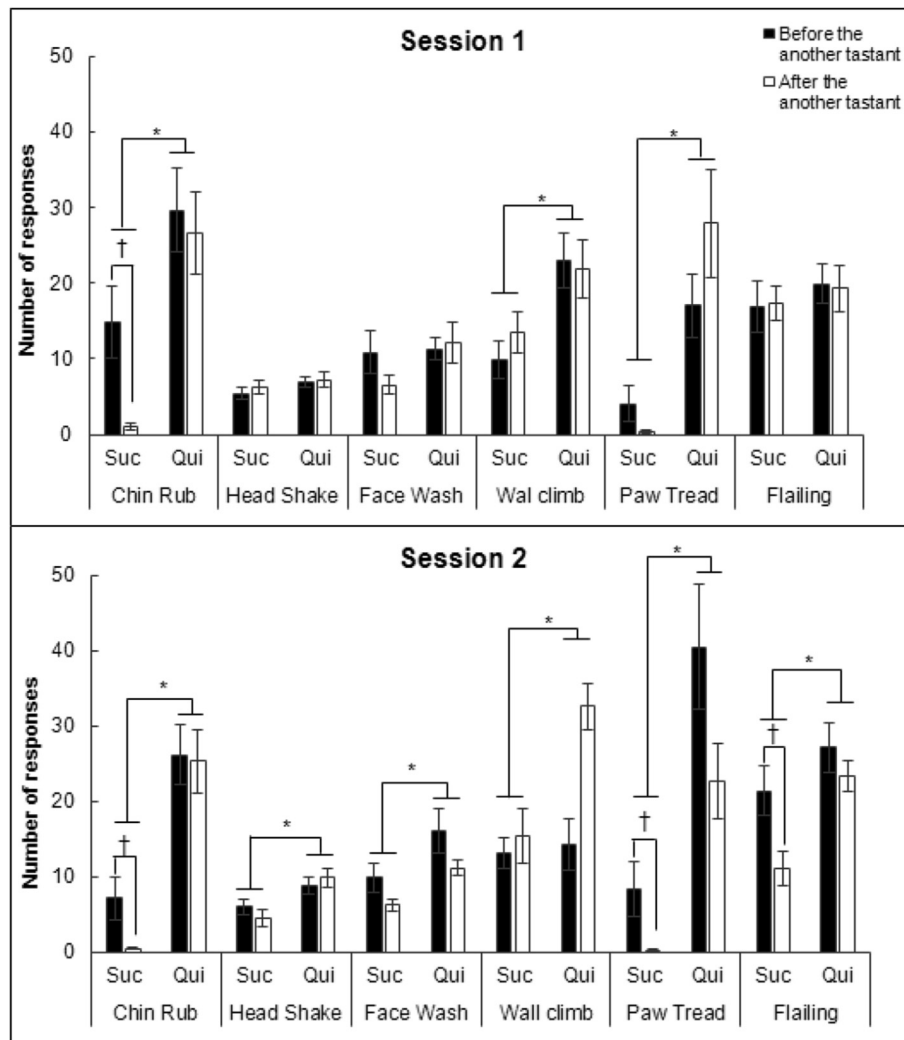
Fig. 1 shows the %BWG after the consumption of sucrose and quinine, in trials 1 (black bars) and 2 (white bars), for both sessions.



**Fig. 1.** %BWG after the consumption of sucrose and quinine, in trials 1 (before the another tastant - black bars) and 2 (after the another tastant - white bars), for Session 1 and Session 2. \* indicates *p* values < 0.05.

Sucrose intake was significantly greater than quinine consumption, both in session 1 [ $t(56) = 10.976, p < 0.0001$ ] and 2 [ $t(55) = 13.491, p < 0.0001$ ]. We then evaluated if the order of exposure affected intake patterns. The question under analysis was whether sucrose intake changed depending on whether it was experienced before or after quinine; and, vice versa, whether quinine intake changed depending on whether it was experienced before or after sucrose. The level of intake (i.e., %BWG) of each solution was analyzed via an independent-samples *t*-test [grouping variable: Sucrose in trial 1 (Suc1) vs. Sucrose in trial 2 (Suc2), and Quinine in trial 1 (Qui1) vs. Quinine in trial 2 (Qui2)], one for each session. The order in which the sucrose solution was received did not affect the consumption in either of the two sessions ( $ps > 0.05$ ). Intake of quinine during the first session, on the other hand, significantly decreased after the animals had been stimulated with sucrose [ $t(27) = 2.202, p < 0.037$ ].

Fig. 2 shows the frequency of chin rubbing, head shaking, face washing, paw treading and flailing of forelimbs, in pups stimulated with sucrose or quinine, in Trial 1 (black bars) and Trial 2 (white bars), and during the first and second session (Panels A and B, respectively). Fig. 3 depicts duration of mouthing, paw lick, face washing, wall climbing and paw tread. Duration of mouthing [ $t(28.29) = 7.83, p < 0.0001$ ] and paw licking [ $t(31.08) = 4.08, p < 0.0001$ ] was significantly higher in animals stimulated with sucrose, which also exhibit significantly lower emission of chin rubbing [ $t(47.12) = -4.43, p < 0.0001$ ] and wall climbing [ $t(48.33) = -3.11, p < 0.003$ ], and lower frequency and duration of paw tread [ $t(31.52) = -4.36, p < 0.0001$ , and  $t(30.74) = -4.23, p < 0.0001$ , respectively]. Similar results were found in session 2: pups stimulated with sucrose exhibited higher duration of mouthing [ $t(28.93) = 10.62, p < 0.0001$ ] and paw licking [ $t(27.47) = 5.13, p < 0.0001$ ], lower frequency of chin rubbing [ $t(43.62) = -6.55, p < 0.0001$ ], head shaking [ $t(54) = -3.58, p < 0.001$ ], face washing [ $t(54) = -2.78, p < 0.007$ ] and flailing of forelimbs [ $t(54) = -2.90, p < 0.005$ ], and lower duration and frequency of paw tread [ $t(10.24) = -3.02, p < 0.012$  and  $t(10.73) = -3.11, p < 0.01$ , respectively] and wall climbing [ $t(54) = -2.78, p < 0.0$  and  $t(44.85) = -2.67, p < 0.01$ ].



**Fig. 2.** Frequency of chin rubbing, head shaking, face washing, paw treading and flailing of forelimbs, in pups stimulated with sucrose or quinine, in Trial 1 (before the another tastant - black bars) and Trial 2 (after the another tastant - white bars), and during the first and second session (Panels A and B, respectively). \* indicates  $p$  values < 0.05.

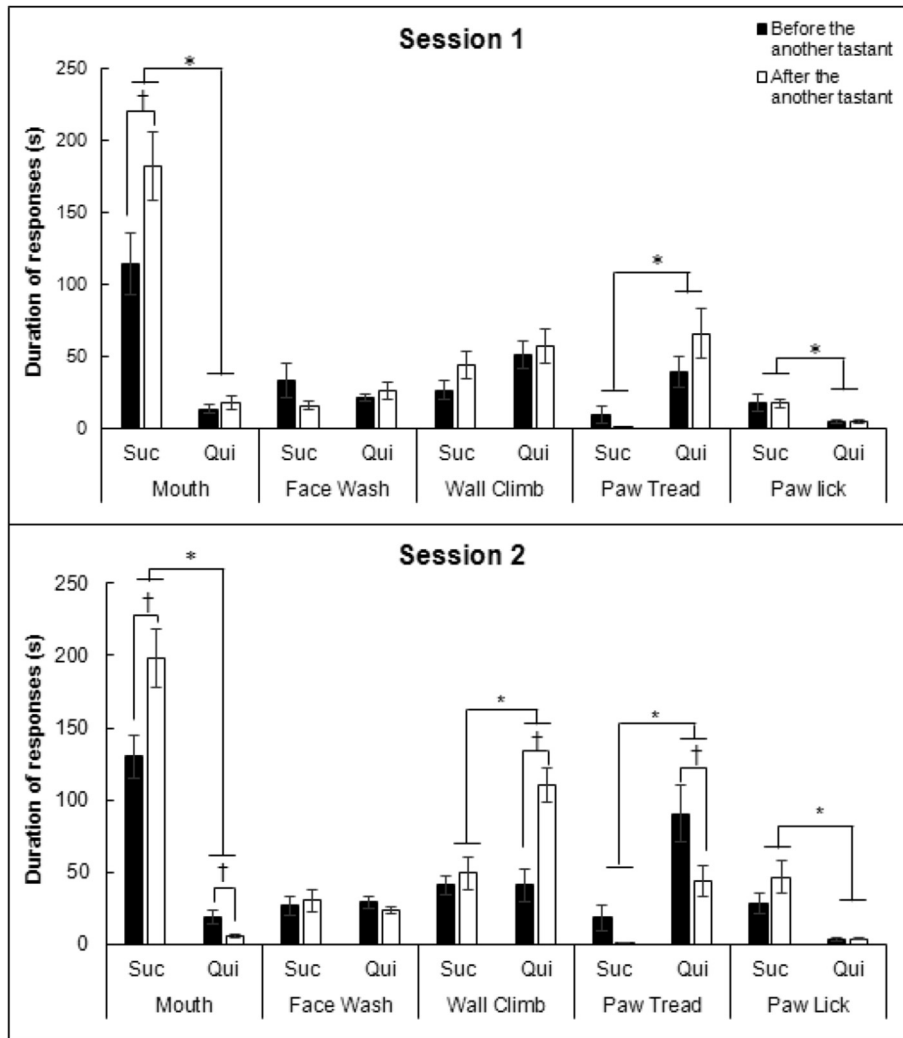
When we compared the responsivity to each solution as a function of the order of stimulation (i.e., Suc1 vs Suc2 and Qui1 vs Qui2) we found that mouthing duration for sucrose was significantly higher when the animals received the solution in the second trial, on both sessions, than when it was administered for the first time [Session 1:  $t(26) = -2.13$ ,  $p < 0.043$ , Session 2:  $t(26) = -2.72$ ,  $p < 0.011$ ]. Conversely, chin rubbing frequency after quinine was significantly lower in the second than in the first trial [Session 1:  $t(12.17) = 2.94$ ,  $p < 0.012$ , Session 2:  $t(14.23) = 2.30$ ,  $p < 0.037$ ]. Additionally, during session 2 the animals displayed significantly fewer paw tread [ $t(14.02) = 2.20$ ,  $p < 0.045$ ] and flailing of forelimbs [ $t(26) = 2.47$ ,  $p < 0.02$ ] when sucrose was administered on the second trial. There were no significant differences for the rest of the measurements ( $p > 0.05$ ). The analysis for quinine responses indicated that pups exhibited, during session 2 and when the bitter solution was given in second place (i.e., after sucrose), a significantly lower duration of mouthing [ $t(13.79) = 2.66$ ,  $p < 0.019$ ] and paw tread, [ $t(26) = 2.18$ ,  $p < 0.038$ ] and a significantly higher frequency and duration of wall climbing [ $t(26) = -4.10$ ,  $p < 0.0001$  and  $t(26) = -4.26$ ,  $p < 0.0001$ , respectively]. These data suggest that the order of taste stimulation affects the expression of some, yet not all, taste reactivity responses. All results are summered in [Table 2](#). [Table 3](#) indicates

Hedges'  $g$  effect size for intake and taste reaction responses according to the order of administration of tastants (sucrose after quinine or quinine after sucrose) for both sessions.

#### 4. Discussion

This research assessed consummatory and taste reactivity responses toward sucrose and quinine, in infant rats. An important question was whether these responses changed depending on the history of exposure to the different tastes. As expected, the pups emitted significantly more appetitive (i.e., mouthing and paw lick) yet significantly less aversive (i.e., chin rubbing, head shaking, paw tread, face washing and flailing forelimbs) responses towards sucrose than towards quinine. This replicates the results found on adult rats and mammals in general (Berridge, 2000).

The main finding was that the consummatory and affective taste responses changed depending on the order in which the solutions were administered. Specifically, pups stimulated with sucrose after quinine exhibited, when compared to peers given sucrose before quinine, a significant increase in the hedonic response of mouthing and a significant decrease in the dislike responses of chin rubbing, paw treading and flailing of forelimbs. Interestingly, the order of exposure to the tastants did not affect the levels of sucrose intake.



**Fig. 3.** Duration of mouthing, paw lick, face washing, wall climbing and paw tread in pups stimulated with sucrose or quinine, in Trial 1 (before the another tastant - black bars) and Trial 2 (after the another tastant - white bars), and during the first (Panel A) and second session (Panel B). \* indicates *p* values < 0.05.

**Table 2**

Summary of the results on consumption and taste reactivity responses according to the order of administration of tastants (sucrose after quinine or quinine after sucrose) for both sessions. ↑ indicates that this behavior increased, ↓ indicates that this behavior decreased and - indicates no modification of this measure.

		Session 1		Session 2	
		Suc after qui	Qui after suc	Suc after qui	Qui after suc
Intake	%BWG	—	↓	—	—
Hedonic Pattern	Mouthing	↑	—	↑	↓
	Paw Licking	—	—	—	—
	Chin rubbing	↓	—	↓	—
Aversive Pattern	Head Shaking	—	—	—	—
	Face Washing	—	—	—	—
	Wall Climbing	—	—	—	↑
	Paw Treading	—	—	↓	↓
	Flailing of forelimbs	—	—	↓	—

Conversely, when pups received sucrose before quinine, the consumption of the latter significantly decreased, the emission of mouthing and paw treading was reduced as well, and wall climbing significantly increased.

These results suggest an experience-dependent dissociation

**Table 3**

Hedges' *g* effect size for intake and taste reaction responses according to the order of administration of tastants (sucrose after quinine or quinine after sucrose) for both sessions. \* means medium effect size (between 0.4 and 0.8). \*\* means large effect size (more than 0.8).

		Session 1		Session 2	
		Suc after qui	Qui after suc	Suc after qui	Qui after suc
Intake	%BWG	1.54**	3.14**	2.23**	0.45*
Hedonic Pattern	Mouthing	3.04**	1.14**	3.83**	3.90**
	Paw Licking	0.16	0.53*	2.06**	0.48*
	Chin rubbing	4.32**	0.54*	3.20**	0.18
Aversive Pattern	Head Shaking	0.95**	0.32	1.54**	0.84**
	Face Washing	2.03**	0.41	2.39**	2.29**
	frequency/duration	2.08**	1.13	0.54*	1.44**
	Wall Climbing	1.35**	0.28	0.78*	5.79**
	frequency/duration	2.15**	0.58*	0.92**	6.05**
	Paw Treading	2.28**	1.90**	3.01**	2.67**
	frequency/duration	2.17**	1.83**	2.79**	3.05**
Flailing of forelimbs	0.12	0.22	3.57**	1.40**	

between consumption and taste reactivity responses. This is congruent with prior work indicating that animals given pairings of a taste and the effects of a drug (e.g., amphetamine, cocaine or morphine) usually exhibit, when subsequently tested for

responsiveness to the drug-related taste, reduced intake yet greater appetitive response patterns. Similarly, Suárez et al. (2014) found that two-week old rats subjected to a devaluation paradigm (e.g., free access to sucrose was shifted from a highly – 12% – to a modestly – 2% – concentrated solution) consumed more of the solution than un-shifted animals, yet showed significantly higher frequency of chin rubbing and other aversive behaviors when stimulated with 2% sucrose.

These results also highlight the importance of previous experiences on the subsequent assessment of rewards. As mentioned, sucrose liking was greater after, as opposed to the levels observed before, the stimulation with a bitter solution. This suggests that pups in the present study may have experienced a positive hedonic contrast. We previously observed that infant pups exhibited a dislike response pattern towards an inherently appetitive taste (sucrose) that had been devaluated (e.g., from 12% to 2% of sucrose, Suárez et al., 2014), and in another study (Suárez, Pautassi & Kamenetzky, 2017) we even found a positive hedonic pattern response towards a bitter solution that had been devaluated (e.g., from 0.1% to 0.01% of quinine). To our knowledge, however, this is the first study reporting hedonic up- and down-shifts in infant rats as a result of prior exposure to another, different taste.

This research contributes to the analysis of taste reactivity responses during the early ontogeny of the rat. The few studies that thoroughly assessed these behaviors in infants only evaluated a few responses (Hoffmann et al., 1991). In contrast, we assessed a wider spectrum of responses, such as frequency and duration of wall climbing. This measurement was useful to discriminate taste sequence effects: Frequency and duration of wall climbing in pups stimulated with quinine was significantly higher when the animal had been stimulated before with sucrose, as compared to counterparts assigned to the quinine-sucrose order of stimulation. This suggests that pups in the “sucrose-quinine” condition assessed the bitter solution as “more negative” than those in the “quinine-sucrose” condition. This impression is strengthened by the fact that pups in the “sucrose-quinine” decrease the emission of mouthing responses, although the aversive response paw tread also diminished.

In summary, the present results depict – for the first time – the emergence of behaviors suggestive of consummatory successive negative and positive contrast, within a single protocol and in the same subjects. Furthermore, PD17, the age at which these behaviors emerged, is the youngest age in which negative contrast has been reported. Previously, Suárez et al. (2014) found this phenomenon at PD18, after exposing pups to different concentrations of sucrose (however in future experiments in which positive and negative contrast is assessed, control groups that always receive sucrose or quinine should be added). Overall, the study adds important new information towards understanding the early development of intake of and reactivity responses towards the basic tastants.

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