



# Individual differences in anticipatory activity to food rewards predict cue-induced appetitive 50-kHz calls in rats



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## HIGHLIGHTS

- Individual differences in anticipatory activity to food predict cue-induced USVs.
- Re-exposition to reward cues elicits USVs and invigorated appetitive behaviors.
- Reward-experienced rats show behavioral cross-tolerance on amphetamine-induced USVs.
- Rats prone to attribute incentive salience to cues respond weakly to DAergic drugs.
- Prone rats still emit USVs to food cues even after being totally sated.

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## ABSTRACT

Reward-related stimuli come to acquire incentive salience through Pavlovian learning and become capable of controlling reward-oriented behaviors. Here, we examined individual differences in anticipatory activity elicited by reward-related cues as indicative of how animals attribute incentive salience to otherwise neutral stimuli. Since adult rats can signal incentive motivation states through ultrasonic vocalizations (USVs) at around 50-kHz, such calls were recorded in food-deprived rats trained to associate cues with food rewards, which were subsequently devalued by satiation. We found that the extent to which animals developed conditioned anticipatory activity to food cues while food deprived determined the level of cue-induced appetitive USVs while sated. Re-exposure to reward cues after a free-testing period reinstated USVs, invigorated reward seeking and consumption, and again, increases in calling occurred only in animals with high levels of cue-induced anticipatory activity. Reward-experienced rats systemically challenged with the catecholamine agonist amphetamine or with the dopamine receptor antagonist flupenthixol showed attenuated responses to these drugs, especially for USVs and in subjects with high levels of cue-induced anticipatory activity. Our results suggest that individuals prone to attribute incentive salience to reward cues showed heightened reward-induced USVs which were reliably expressed over time and persisted despite physiological needs being fulfilled. Also, prone subjects seemed to undergo particular adaptations in their dopaminergic system related with incentive learning. Our findings may have translational relevance in preclinical research modeling compulsive disorders, which may be due to excessive attribution of incentive salience to reward cues, such as overeating, pathological gambling, and drug addiction.

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## 1. Introduction

In Pavlovian experimental preparations, a localizable visual stimulus usually evokes approach and consumption behaviors directed toward the reward cue itself (for review see: [1]), whereas diffuse or non-localizable stimuli such as a tone or a testing context would instead enhance behavioral exploration [2–7]. Both types of non-contingent

conditioned responses, although quite consistent, are nevertheless moderated by individual differences [1,8–11]. It has been widely demonstrated that variations in cue-induced conditioned behaviors indicate how animals attribute incentive salience to otherwise neutral stimuli [1, 4,9,10,12]. From these conditioned responses, anticipatory activity in the presence of reward-related cues has also traditionally been taken as evidence of incentive motivation [4,5].

Juvenile and adult rats have a complex repertoire of ultrasonic vocalizations (USVs) which differ in their fundamental peak frequencies and in the contexts where they are usually emitted (for review see: [13]). Out of these, high-frequency calls (i.e., 50-kHz calls) are normally

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produced in naturalistic rewarding situations such as mating, and rough-and-tumble play, or triggered by non-naturalistic stimuli such as hetero-specific play simulated by tickling [14–16], electrical stimulation of the mesolimbic dopamine (DA) and norepinephrine (NE) pathways [17], or by psychostimulatory drugs like amphetamine and cocaine [12,18–26]. The production of spontaneous [16,27,28], and reward-induced USVs is highly dependent on individual differences [29–33]. It has been consistently shown that reward-induced USVs exhibit great individual variability [25,29,30], which may rely upon differences in the way mesolimbic DAergic and NEergic systems encode information about rewards and their predicting cues [17,29,34,35]. However, the analysis of individual differences has focused on variations in the utterance of 50-kHz calls, especially using the tickling paradigm. The inherently biological background of such inter-individual variability has been demonstrated by breeding rats selectively for their levels of tickling-induced appetitive 50-kHz calls [31,34–37]. At the behavioral and neural levels, high and low callers have been compared based on diverse parameters relevant for reward, positive affect, and social behavior [14,17,31–33,38]. In this regard, subjects with high levels of 50-kHz USVs have been found to show greater reward sensitivity, as indicated by intra-accumbens and systemic amphetamine-increased calling [29,34], higher sensitization to cocaine-induced 50-kHz calls [35], and higher electrical [17] and cocaine self-administration rates [30]. However, the question of whether animals that already differ in their reward-related behaviors also show heightened appetitive 50-kHz calls has not been fully addressed. Efforts have been made toward gauging USV variability by using screening tests of exploratory activity and unconditioned anxiety [16,21,28,39], however not through the use of tests related to learning and motivation. In the present study, therefore, we asked whether individuals with high levels of conditioned anticipatory activity – elicited by food-related cues – show high rates of 50-kHz calls, especially when food rewards were devalued by satiation. We analyzed individual differences in food-deprived rats that had been trained to anticipate food rewards (normal rat chow vs. sweetened condensed milk) under certain cues (experiments 1 to 3), and in rats that had been instrumentally conditioned to access their daily feeding ration by running down a runway maze (in experiment 4). In experiment 5, rats were previously trained in the same Pavlovian conditioning paradigm as in experiments 1 to 3, and after a free-training week, they were re-exposed to food cues in order to evaluate firstly, the ability of reward cues to reinstate calling and secondly, to determine whether preceding individual differences in anticipatory activity still affect rates of USVs. Finally, reward-experienced rats were challenged with the DAergic (and NAergic) agonist amphetamine (experiment 6) or with the DAergic receptor antagonist flupenthixol (experiment 7). In these cases, reward-experienced rats were expected to show a diminished response to the particular effect of each drug, with such an effect indicating the occurrence of behavioral cross-tolerance between Pavlovian incentive learning and DAergic-related drugs [40–42]. Secondly, we asked whether the effects of these DAergic drugs on psychomotor activity and 50-kHz calls vary along with individual differences in anticipatory activity developed during previous incentive training. This assumption arises from evidence suggesting that individual differences in attribution of incentive salience to reward predicting cues are highly dependent on mesolimbic DA activity [8,9,43].

## 2. General materials and methods

### 2.1. Subjects

Adult male Wistar rats (Harlan-Winkelmann, Netherlands) served as subjects. In experiment 1, 30 experimentally naïve rats weighing 277–351 g on arrival were used. These rats were used later in experiment 4. Experiment 2 included 24 experimentally naïve rats (weight on arrival: 231–256 g), which also served as subjects in experiments 5 and 7. In experiment 3, 20 experimentally naïve rats (weight on arrival: 240–265 g) were used, which were also the subjects of experiment 6.

Upon arrival all animals were housed 4–5 per cage (Macrolon type-IV) in a climate-controlled room with a 12:12 h light–dark schedule (light on at 07:00 h), where they remained undisturbed during one week before testing. Food and water were freely available unless otherwise specified. All procedures were conducted in accordance with the ethical regulations for animal experimentation at the Philipps-University of Marburg. In all experiments, animal order was counterbalanced within and across days and experiments to the fullest extent possible.

### 2.2. Screening cage test

Rats were screened for their levels of spontaneous USVs as recently described [26]. The test, which was conducted on two consecutive days (5 min each), consisted of recording spontaneous USVs while a given rat explored a clean cage with fresh bedding [16,21,28]. According to the number of 50-kHz calls emitted on both days, experimental groups were counterbalanced without excluding subjects.

### 2.3. Appetitive cage test

As recently described [44], a given rat was put into a clean cage with bedding, which was then placed on a desk under the microphone, where the recording session immediately started. Two loudspeakers (Avemaster 60 PC stereo system, Germany) connected to a personal computer were placed on either side of the cage. As the conditioned stimulus (CS), a 3-kHz tone (49.2 dB inside the cage) was used. The unconditioned stimulus (UCS) was either normal rat chow (about 20 g) or sweetened condensed milk (10% fat content diluted 1:3 in tap water, Milbona, Germany). For the reward groups, the CS predicted either the start of each daily feeding session (1.5 h access to food per day) or a 30 min-drinking time (milk). Throughout the whole experiment, reward intake took place in the same testing cage used for a given rat. During the first 120 s, animals were left undisturbed (“context” phase), then the CS was presented over another 120 s, subsequently followed by the UCS (food or milk). The overlapping CS–UCS period lasted 30 s once reward intake started. When the tone ended, the animal was allowed to continue consuming the reward for another 60 s before being transported back (in the same testing cage) to the adjacent animal room. A matched control rat was tested simultaneously in a test cage, where it received the same pairing schedule as the matched reward rat, except that food or milk was never delivered there. Afterwards, the pair of control and reward animals was brought back to the animal room and placed on a rack, with controls on odd and reward rats on even rows, so that cages from each group were never side by side. Each control rat remained in its own testing cage while the matched reward rat completed either the 1.5 h-feeding session or 30-min drinking time. At least 3 h after all controls rats had been brought back into their own group cages, namely once the night cycle entered, their 1.5 h-daily feeding session began. In the experiments using milk as reward (2 and 5) all animals were first habituated to the sweetened condensed milk for one week. During this period, control rats had milk in the evening together with their daily food, whereas reward rats had milk in the light period, coinciding exactly with the time of the day during which they would be going to be tested. In experiment 3, both during habituation and testing phases, reward rats had access to their daily food ration only in the testing room, so that the fact of being fed after a 22.5-h FD period was specially linked to this environment. Control rats remained in the testing room during the same time period as reward rats and they were fed only in the animal room hours later.

### 2.4. Runway maze

The apparatus was a single U-shaped runway maze constructed of black acrylic, which consisted of two arm alleys (50 cm L × 20 cm W × 24 cm H) connected by a 20 cm L corridor. The start box (40 cm L) was equipped with a guillotine door that could be manually lifted from afar using a pulley

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