Title

Contextual enhancement on binge-like overconsumption of palatable sugar in mice.

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Abstract

Binge eating disorder is an eating disorder characterized by the excessive intake of food within a short period, often beyond physiological needs. Studies using animal models have shown that binge eating animals consume food in quantities that surpass physiological necessity, and that the neural mechanisms underlying this behavior overlap with those involved in habit formation. Habitual behaviors are thought to be automatic responses acquired through extended behavioral training and are dependent on the context in which they were learned. Therefore, this study hypothesized that binge eating has a context-dependent component. We investigated whether the excessive palatable sugar intake observed in an animal model of binge eating is triggered by an associated context as a learned behavior. To test this, mice were trained to develop binge-like sugar consumption in a specific context. During the test phase, we reduced the animals' hedonic needs for sugar solution by providing a two-hour satiety period. Sugar solution was then presented in both the training context and a novel context. The results showed that in the training context, the mice continued to consume sugar solution at levels similar to those observed at the onset of the satiation. In contrast, this context-induced sugar consumption was not observed in the novel context. These findings suggest that, like habitual behaviors, binge eating is induced under in the context-dependent manner and insensitive to the consequence of the behavior.

keywords: binge, overconsumption, contextual conditioning, habitual behavior

Introduction

Binge eating disorder is a behavioral disorder characterized by the inability to control the consumption of large amounts of food in a short period (Brownley, Berkman, Sedway, Lohr & Bulik, 2007; Mathes, Brownley, Mo & Bulik, 2009). With a global prevalence ranging from 0.3% to 1.8% in adults, this disorder persists even after physiological hunger has been satiated, leading to significant impairments in psychological well-being and quality of life

(Giel et al., 2022). Furthermore, binge eating disorder is often associated with obesity and food addiction, exacerbating its impact on individual health (Cassin & von Ranson, 2007; de Zwaan, 2001). The environmental and behavioral factors, along with the neural mechanisms underlying this disruption of feeding regulation, are actively explored (Keski-Rahkonen, 2021).

To investigate the mechanisms underlying binge eating, rodent models have been proposed (Oswald, Murdaugh, King, & Boggiano, 2011; Rossetti, Spena, Halfon, & Boutrel, 2014; Yasoshima & Shimura, 2015). For instance, in the protocol proposed by Yasoshima & Shimura (2015), mice were induced to develop binge-like excessive sugar intake through a regimen of successive restricted feeding. In their study, the animals were allowed access to normal chow and palatable sugar (sucrose solution) for only 4 hours each day over a period of 10 days. This repeated restricted feeding led the animals to consume significantly larger quantities of the sugar in a short time than they would normally. Notably, their study also revealed that this feeding behavior persisted even after the animals' physiological need for nutrition had been met, demonstrating that the model successfully mimics clinical characteristics associated with binge eating disorder.

The nature of binge eating, marked by unnecessary feeding behaviors, resembles habitual behavior. In psychology of learning, the habits are understood as the acquired automaticity of behaviors (Ciria, Watson, Vadillo & Luque, 2021). In the literature of instrumental learning, habitual behavior is operationally defined as decrement of sensitivity to the outcome produced by behavior (e.g., foods obtained via lever press). The instrumental behavior is typically sensitive to the outcome. For example, the lever press response is reduced by the taste aversion learning or satiation by free access to the reinforcer (‘outcome devaluation'; Adams, 1982; Adams & Dickinson, 1981). This mode of behavior is called ‘goal-directed' (Dickinson & Balleine, 1994). It has been considered that the goal-directed behavior is emitted based on the current value of the reinforcer to fulfill the specific needs. In contrast, habitual behavior develops via extensive repetition of instrumental behavior, leading to being insensitive to the outcome (Dickinson et al., 1985; Dickinson, Balleine, Watt, Gonzalez & Boakes, 1995).

There may be a similarity between habits and overeating in that both involve seemingly automated behaviors, which are insensitive to the immediate needs of animals. Indeed, Furlong and Balleine (2017) demonstrated that the dorsolateral striatum is involved in binge-like behavior, which has been known to play a role in habitual actions, revealing a common neurophysiological basis. The maladaptation of corticostriatal circuits were also found in human neuroimaging (Kessler, Hutson, Herman, & Potenza, 2016).These similarity between binge eating and habitual behavior lead to the hypothesis that if similar mechanisms underlie both habits and binge eating, the factors that control habitual behavior might also apply to overeating.

Once a behavior becomes habitual, it is not necessarily irreversible. Recent research has shown that habitual behavior can be sensitive to the context in which it was developed (Steinfeld & Bouton, 2020, 2021; Thrailkill & Bouton, 2015). For example, Steinfeld & Bouton (2021) trained rats to perform a goal-directed instrumental response in one context (context-A) and then extended the training in a different context (context-B) to develop a habit. Devaluation through taste aversion learning was applied in both contexts, followed by an extinction test. The results showed that the instrumental response remained intact in context-B but not in context-A, indicating that habitual behavior is expressed in the context where it was acquired. Given the parallels between overeating and habits, it is plausible that overeating could also be understood as a context-dependent learned behavior.

The present study, therefore, investigated whether context could facilitate overconsumption by combining appetitive contextual conditioning with restricted feeding training to induce this behavior. The study consisted of two experiments: Experiment 1 examined whether binge-like overconsumption would be facilitated by the trained contexts after sensory-specific satiation. Experiment 2 assessed whether animals that underwent contextual conditioning but did not receive binge eating training would not show overconsuming palatable sugar after satiation.

Materials and Methods

Subjects and housing conditions: Thirty-four C57BL/6J male mice (CREA Japan, Osaka) were utilized for this study, with 17 mice assigned to each of the two experiments. Mice were purchased at eight weeks old and acclimated to the housing room for one week. They were housed individually in Plexiglas cages maintained at 22 °C under a 12L/12D cycle, with lights on at 7:00. Prior to the experiments, the mice had ad libitum access to water and a standard chow diet. The standard chow consisted of a pelleted commercial rodent diet (MF, Oriental Yeast Co., Ltd.: 3.6 kcal/g), which was used throughout the experiments. At the onset of the experimental procedures, the animals were 9 weeks old. All experimental procedures were conducted during the light cycle. All animals were treated in accordance with the NIH Guidelines for the Care and Use of Laboratory Animals. The study's rationale, design, and experimental protocols were approved by the Institutional Animal Care and Use Committee of the Graduate School of Human Sciences, Osaka University (approval number: R6-3-0).

Experimental procedure

Experiment 1: the experiment consisted of training and test phases, and both performed in the home cage. The restricted feeding procedure was utilized for shaping binge-like overconsumption (Yasoshima & Shimura, 2015; Figure 1a, top). All animals were maintained on a 20-h food deprivation schedule followed by 4-h access to the sucrose solution, water, and chow starting at 09:00 h every morning (2-h after lights on). The two bottles were presented side-by-side (two-bottle method): one bottle for the sucrose solution and another for water. The water bottle was provided to ensure that the mice's consumption of the sucrose solution was driven by the sucrose's incentive rather than merely by thirst.

These 4-hour feeding occasions ran under the visual ‘context’. The context was as vertical or horizontal stripe walls made of acrylic plates. It was positioned to enclose all four sides of the home cage. Given that the context was always paired with palatable sugar and normal chows, the appetitive contextual conditioning was applied, where the context functions as the conditioned stimulus (CS) to signal the sugar/food presentation (US). The context was set just before beginning of the training, and immediately removed after 4-hour periods of food access. The vertical or horizontal patterns were balanced for arranging the groups in the test phase described below. The restricted-feeding training continued 10-days.

The test was conducted the day after the last training session (day-11; Figure 1b). Prior to testing, all animals were given 2-hour access to the sucrose solution to achieve sensory-specific satiation. The water bottle was likewise positioned in the same manner as during the training sessions. The satiation session was undertaken without the context. Consumption was measured at one-hour intervals. After the satiation, the animals were given the access to the sucrose solution under the context: trained or novel. The satiation procedure was performed to determine whether the mice would consume sucrose solution in excess of their hedonic needs within the trained context.

Thus, immediately after satiation, animals were again granted access to the sucrose solution for 20 minutes in either a trained or novel context. After each feeding trial, the context was switched, allowing the animals another opportunity to feed. This procedure was repeated for three trials in each context, totaling six trials. Thus, the cumulative access time to the sucrose solution in each context was 1 hour. The animals were divided into two groups based on whether they started the test in the trained or novel context: the half of animals initially exposed to the trained context (i.e., trained -> novel -> trained -> novel -> trained -> novel), and another half of animals following in the reversed sequence.Group assignment was matched according to the sucrose solution intake on training day-10 to ensure no biases between the groups.

Experiment 2: most of the procedure was the same as Experiment 1 unless otherwise noted Figure 1a, bottom). The normal chow was ad libitum throughout the training periods unlike Experiment 1. The sucrose solution was presented in the same way as Experiment 1, from 9:00 to 13:00. Thus, the animals were exposed with paring of the context and sucrose solution. This protocol was adopted because Yasoshima & Shimura (2015) previously revealed that ad libitum to normal chow hindered the development of binge-like overconsumption. The test was performed completely the same as Experiment 1.

Data Analysis

The increase in food intake during training was analyzed using ANOVA. The Greenhouse-Geisser method was applied to adjust the degrees of freedom for within-subject factors. In the tests, sucrose intake was compared across four conditions: the first and second hours of satiation, and the trained and novel contexts, using pairwise t-tests. Multiple comparisons were reported with p-values corrected using Holm's method (Holm, 1979).

For the trial-by-trial fluctuation of sucrose consumption during the test sessions, we adopted a linear mixed model to estimate the effect of trials and the context conditions, because the data is not complete; it is obvious that one animal could not simultaneously receive foods under different contexts (e.g., an animal which experienced the trained context in the first trial cannot receive the novel context in that trial). The conditions of contexts and trials were treated as fixed effects, and individual differences were accounted for as random effects.

All analysis and visualization were performed under R version 4.1.0 using the packages including 'lme4' v1.1-27.1 and 'car' v3.1-2 for linear mixed model and the likelihood ratio test (lmer() and Anova() function), 'rstatix' v0.7.0 for ANOVA (anova_test() function), and 'tidyverse' v1.3.1for data handling and processing.

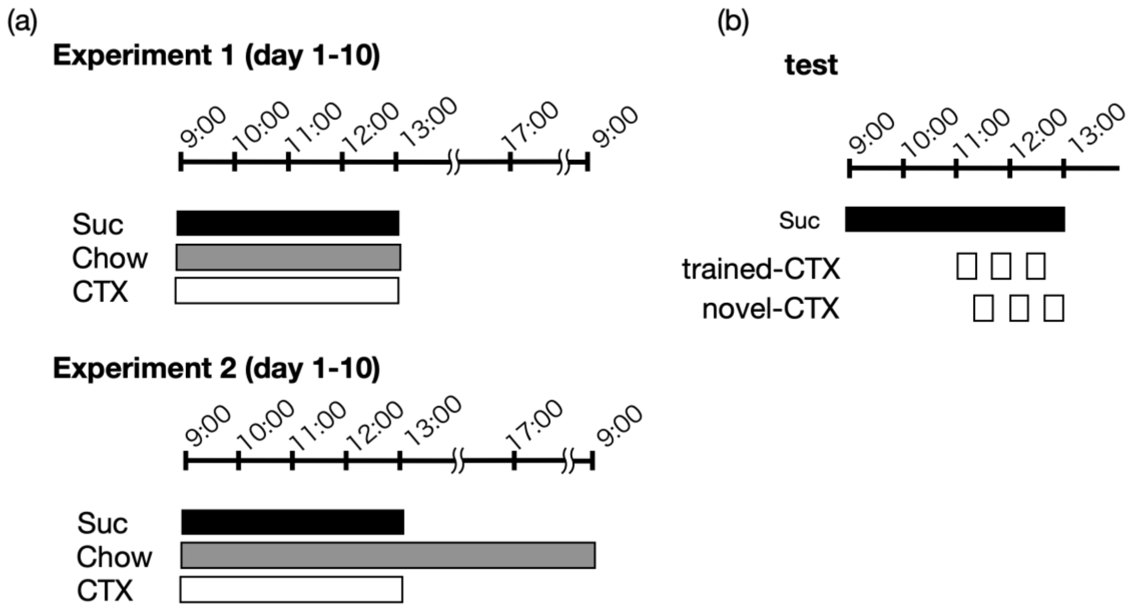

Figure 1. The timeline of the study included (a) a training phase and (b) a test. (a) Training was conducted over 10 consecutive days. (b) Testing took place immediately after the 10th day of training. Half of the animals were first exposed to the trained context after a 2-hour period of satiation, while the other half were initially placed in a novel context. The illustration in the figure represents the time course of the group that started with the trained context. Suc: sucrose, Chow: standard chow, and CTX: context.

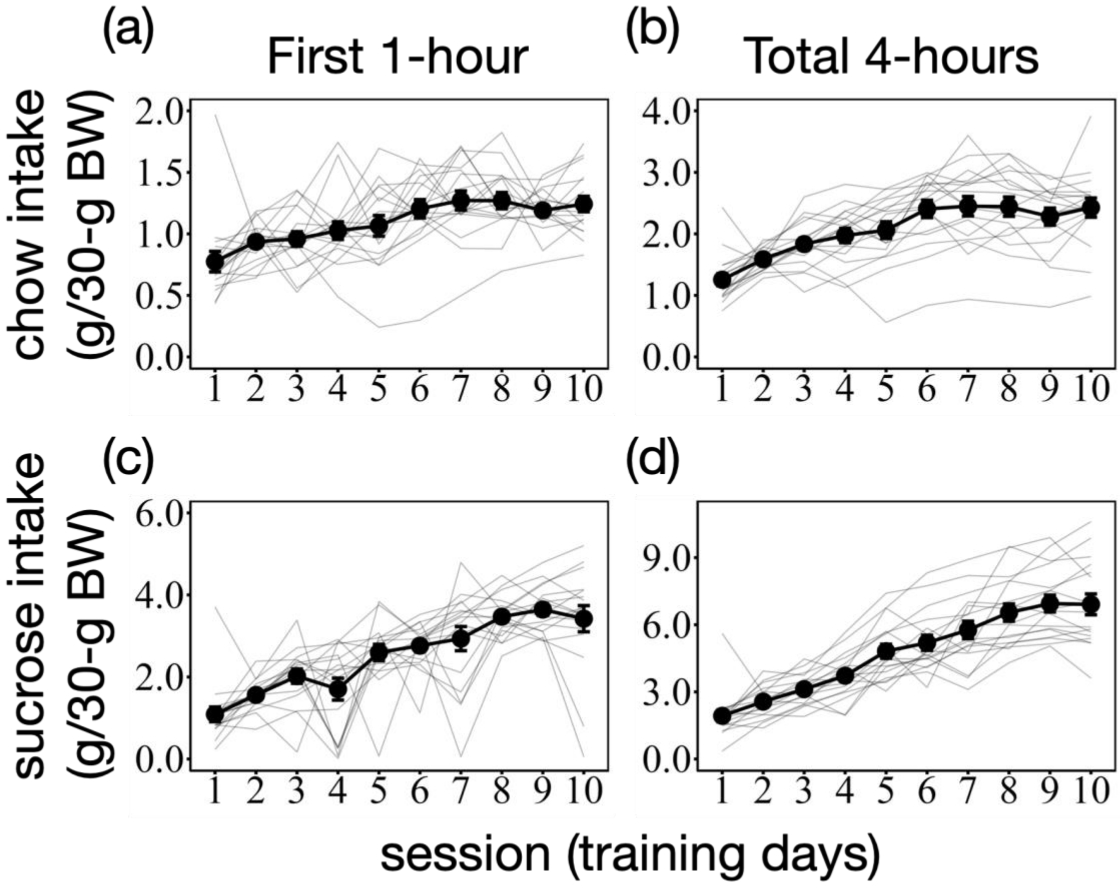

Figure 2. The average food consumption increased as the session proceeded and reached asymptotic levels. The thin gray lines represent individual data. The error bars denote standard errors. (a) 1-hour consumption of normal chow. (b) Total consumption of normal chow up to 4-hour daily feeding sessions. (c) 1-hour consumption of sucrose solution given as palatable substance. (d) The 4 hours total consumption of sucrose solution.

Results & Discussion

Experiment 1: contextual enhancement on the overconsumption of palatable sugar

The animals increased the feeding amount across the training periods, and reached the asymptotic levels in both normal chows and sucrose solution (Figure 2), replicating the previous binge-like consumption (Yasoshima & Shimura, 2015). A one-way analysis of variance (ANOVA) revealed the significant effect of 1-hour consumption of sucrose solution ($F(4.05,64,86) = 21.21$, $p < .0001$), that of total 4-hours ($F(3.23,51.63) = 71.33$, $p < .0001$), 1-hour consumption of chow ($F(4.93,78.87) = 7.85$, $p < .0001$), and that of total 4-hours ($F(4.12,65.92) = 24.72$, $p < .0001$). On average, the animals consumed sucrose solutions more than 20% of animals' body weights in the later sessions, whereas less than 10% in the initial sessions.

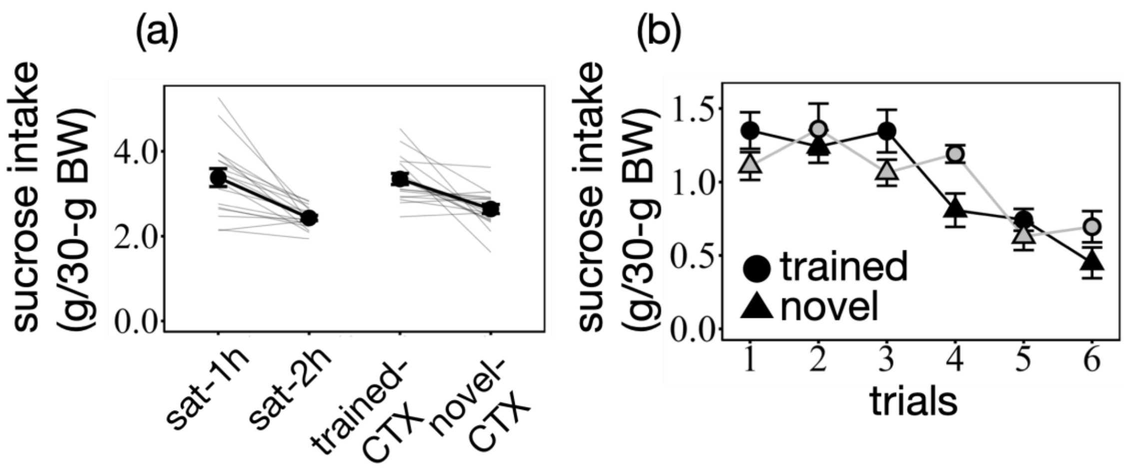

Figure 3. The contextually-induced binge-like consumption is resistant to sensory-specific devaluation by satiation of sucrose solution. (a) The consumption of sucrose solution on the test day. The 'sat' and 'CTX' represent satiation and context, respectively. (b) The trial-by-trial fluctuation of sucrose solution consumption under the trained and novel contexts revealed the context-specific elicitation of feeding behavior in the sated animals. The circles and triangles represent the trained and novel contexts, respectively. The black marker and line represent the group that began with the trained context, while the gray markers and line indicate the group that started with the novel context. The error bars represent SEM.

In the next day after accomplishing restricted feeding training (i.e., day-11), animals were tested the following procedure: at first, the animals were given 2-hours free access to the sucrose solutions to satiate (i.e., sensory-specific devaluation) without the context. The satiation has been commonly used in experiments of habit to judge a target instrumental behavior is sensitive to the values of an outcome (Dickinson & Balleine, 1994), and our results revealed the consumption of sucrose solution decreased during the 2 hours devaluation session (Figure 3a, left side, $t(16)=4.80$, adjusted $p = .001$).

After the 2-hours free access to the sucrose solution, we asked whether binge-like overconsumption is resistant to devaluation of the palatable sugar. For that purpose, after the satiation, the animals were given access to sucrose solutions under the trained context or novel context. Each access continued 20 minutes, and the access was given in another context (trained-> novel or novel -> trained). Three alternations of context conditions (trained or novel) were conducted, resulting in a total of six trials and 1 hour eating occasion in the respective contexts. The total amounts of consumption given contexts were statistically significant (Figure 3a, right side, t(16) = 3.75, adjusted p = .007). The consumption under the trained context was comparable to that during the initial 1 hour of satiation (t(16)=.125,adjusted p=.90). Similarly, the consumption under the novel context was on par with that during the last 1 hour (t(16) = 1.50, adjusted p = .31).

It can be observed that feeding behavior is influenced by specific contexts in the trial-by-trial fluctuation of consumption (Figure 3b). The linear mixed model revealed that both the trial and context was significant ($\chi^2(5) = 75.46$, $p < .0001$ for trials and $\chi^2(1) = 12.77$, $p= .0004$), while the significant interaction was not observed ($\chi^2(5) = 2.09$, $p = .84$).

Taken together, these results indicate that contextual enhancement can lead to the overconsumption of palatable food, even after 2 hours of satiation. However, it is important to consider whether this observation is specific to the binge-like behavior model. Since animals were trained with contextual appetitive conditioning over 10-days, with consistent pairing of context and food, the context itself might acquire a controlling effect that elicits feeding behavior beyond hedonic needs. In other words, mere contextual conditioning might be sufficient to influence excessive food intake. Experiment 2 was designed as a control experiment to investigate this possibility.

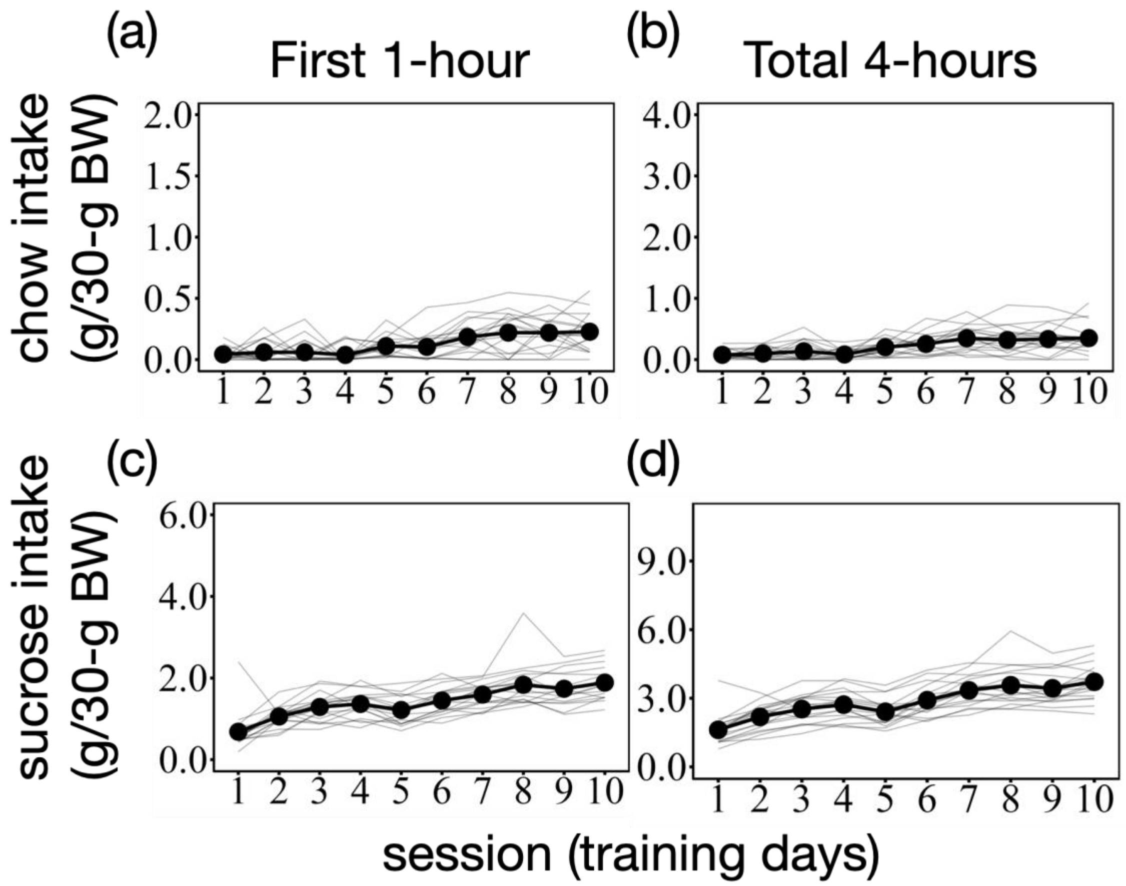

Figure 4. The average food intake remained at a lower level compared to Experiment 1. The thin gray lines represent individual data. The error bars denote standard errors. The ranges of the vertical axis were set the same as Figure 2. (a) 1-hour consumption of normal chow. (b) Total consumption of normal chow up to 4-hours daily feeding sessions. (c) 1-hour consumption of sucrose solution given as palatable food. (d) The 4 hours total consumption of sucrose solution.

Experiment 2: specificity of contextual control in the binge-eating model

The sucrose and chow consumption were developed across days (Figure 4). A one-way analysis of variance (ANOVA) revealed the significant effect of 1-hour consumption of sucrose solution ($F(3.44,55.11) = 33.85$, $p < .0001$), that of total 4-hours ($F(2.37,37.97) = 36.77$, $p < .0001$), 1-hour consumption of chow ($F(9.0,144.0) = 11.22$, $p < .0001$), and that of total 4-hours ($F(9.0,144.0) = 13.27$, $p < .0001$). Even though chow was ad libitum in the experiment 2, both chow and sucrose consumption were significantly increased as the session proceeded.

However, when food consumption between experiment 1 and 2 was compared using two-way ANOVA (session × experiment), all measures in Figure 2 and 4 showed significant difference between experiment and interaction: 1-hour consumption of sucrose solution (experiment: $F(1.00,32.00) = 85.89$, $p < .0001$, the interaction: $F(4.51,144.39) = 7.69$, $p < .0001$), that of total 4-hours (experiment: $F(1.00,32.00) = 45.30$, $p < .0001$, the interaction: $F(3.18,101.9) = 25.01$, $p < .0001$), 1-hour consumption of chow (experiment: $F(1.0,32.0) = 552.71$, $p < .0001$, the interaction: $F(5.43,173.88) = 2.93$, $p = .012$), and that of total 4-hours (experiment: $F(1.0,32.0) = 305.91$, $p < .0001$, the interaction: $F(4.48,143.51) = 12.62$, $p < .0001$). These results demonstrate that the amount of food consumption grew up far more in the restricted feeding than under the free access to the chow. Thus, binge-like food consumption was notable in Experiment 1, but not in Experiment 2.

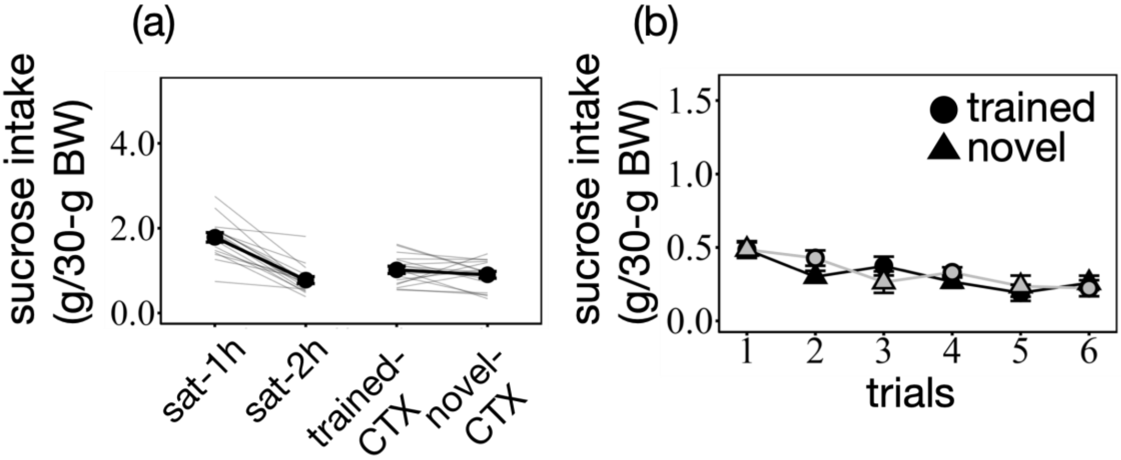

Figure 5. The mere contextual conditioning did not facilitate feeding behavior resistant to the satiation. The ranges of the vertical axis were set the same as Figure 3. (a) The consumption of sucrose solution on the test day. The 'sat' and 'CTX' represent satiation and context, respectively. (b) The trial-by-trial fluctuation of sucrose solution consumption under the trained and novel contexts revealed the context-specific elicitation of feeding behavior in the sated animals. The circles and triangles represent the trained and novel contexts, respectively. The black marker and line represent the group that began with the trained context, while the gray markers and line indicate the group that started with the novel context. The error bars represent SEM.

The test was conducted the next day after 10 days training, and the testing procedure was completely the same as experiment 1. Similarly to Experiment 1, the 2-hours satiation decreased the sucrose consumption (the left of Figure 5a; $t(16) = 8.80$, adjusted $p < .0001$), revealing that the satiation effectively reduced the sucrose consumption. However, unlike Experiment 1, the sucrose consumption under the trained or novel context did not produce the significant difference (the right side of Figure 5a; $t(16) = 1.14$, adjusted $p = .39$). The animals consumed less sucrose under the trained context than in the initial 1-hour of satiation ($t(16)=7.52$, adjusted $p < .0001$). Thus, the satiation was still at work to reduce the consumption of sucrose even in the trained context.

The trial-by-trial fluctuation also demonstrated that the sucrose consumption did not differ between the trained and novel context (Figure 5b). Indeed, the linear mixed model revealed that only the trial was significant ($\chi^2(5) = 39.38$, $p < .0001$), while the significant effect of the context was not observed ($\chi^2(1) = 1.67$, $p = .20$). The interaction between these neither significant ($\chi^2(5) = 5.61$, $p = .35$). These results indicated that the contextual enhancement was not found in the animals that did not develop the binge-like consumption of the palatable food.

General Discussion

The present study aimed to determine whether binge-like consumption in a mouse model is subject to contextual enhancement of palatable sugar intake and whether feeding behavior beyond satiation depends on the context in which binge eating is developed. To investigate these possibilities, we employed a restricted feeding protocol to induce overconsumption within a specific context and subsequently assessed whether the mice would seek sucrose solutions even after a 2-hour period of satiation.

Experiment 1 clearly demonstrated that animals were more likely to consume sucrose solutions in the context where they had developed binge-like overconsumption. This contextual enhancement was specific to the context associated with binge eating (Figure 3), as the novel context did not exert the same regulatory influence. The total sucrose consumption in the trained context was comparable to the amount consumed during the initial hour of free access to sucrose during satiation. In contrast, consumption in the novel context was similar to that observed during the final hour of satiation. Since sucrose consumption decreased over the course of satiation, it suggests that the animals had access to an adequate amount of palatable sugar. Thus, exposure to the trained context facilitated food consumption beyond satiety. This context-specific facilitation of overconsumption was not observed in Experiment 2, where animals had free access to standard chow during the training, resulting in the absence of binge-like eating.

The observed lack of sensitivity to the reinforcer resembles habitual behavior in instrumental learning (Dickinson et al., 1983). It is well-established that behaviors developed through both classical and instrumental learning are typically sensitive to the value of the reinforcer (Adams & Dickinson, 1981; Holland, 1981; Rescorla, 1973). The outcome devaluation, including satiation or taste aversion learning, are commonly used to reduce the value of the reinforcer, which is known to diminish the animal's response (Colwill & Rescorla, 1985). This mode of behavior is termed 'goal-directed' because it is motivated by the value of the outcome to fulfill specific needs (Dickinson & Balleine, 1994). In contrast, habitual behavior emerges through extended learning periods, and is characterized by insensitivity to the value of the outcome (Dickinson, 1985). For instance, instrumental responses can persist even after the reinforcer has been devalued (Dickinson et al., 1983). This form of habitual behavior has also been observed in human studies (Cushman & Morris, 2015; Tricomi, Balleine, & O'Doherty, 2009). Additionally, behavioral automaticity resulting from extended training has been documented in Pavlovian learning in crickets (Mizunami et al., 2019). In these studies, behaviors were considered automated and insensitive to the value of the behavioral consequence due to repeated exposure to specific environment-behavior cycles, similar to the contextually-induced feeding observed in our study. This view of value-insensitivity is supported by a theoretical model that describes the development of habitual behavior (Yamada & Toda, 2023).

The physiological mechanisms underlying habitual behavior involve the dorsolateral striatum, which is crucial for generating automated behaviors, whereas the dorsomedial striatum is more associated with goal-directed behavior (Gremel & Costa, 2013; Yin, Knowlton & Balleine, 2004). The dorsolateral striatum is also implicated in binge eating behavior (Furlong et al., 2014). Abnormalities in striatal function have been reported in patients with binge-eating disorder (Kessler et al., 2016; Wang et al., 2011). Striatal circuits involved in behavioral automaticity overlap with those implicated in other disorders, such as obsessive-compulsive disorder and drug addiction (Kenny, 2011; Simmler & Ozawa, 2019). For instance, striato-midbrain-striatal connectivity plays a critical role in habitual cocaine-seeking behavior (Belin & Everitt, 2008). These circuits may serve as a common pathway for executing automated behaviors driven by environmental cues, including the overconsumption elicited by contextual factors observed in our study.

The functional impairments specific to binge eating may reside in the mechanisms governing feeding regulation. Normally, feeding is terminated by detecting stimulation of the gut (Aitken et al., 2024; Kim et al., 2024). In binge eating, however, this feeding termination may be disrupted by other regulatory mechanisms that promote food intake. Recent research, indeed, has shown that exposure to food-related contexts can enhance appetite through increased activity in the lateral hypothalamus (Subramanian et al., 2023). Additionally, sympathetic nerve activity has been found to inhibit the release of glucagon-like peptides 1, further promoting appetite (Ren et al., 2024). It is possible that these top-down processes, rather than bottom-up signals from the gut, likely involve context-specific amplification of eating behaviors. However, the mechanisms by which contextual factors drive food consumption beyond satiety remain poorly understood. Further studies are needed to elucidate how environmental factors modulate feeding regulation.

In summary, the present experiments demonstrated that the context in which binge-like behavior developed facilitated feeding beyond satiety. This effect was context-specific and resembled habitual behavior in instrumental learning. However, simply establishing a Pavlovian association between the context and palatable substance was insufficient for eliciting contextual facilitation of overconsumption in our study. Instead, contextual facilitation may emerge when food restriction is combined to binge-like behavioral abnormalities.

Acknowledgements

The present research was funded by JSPS KAKENHI (24K16867 to H.M.).

Declaration of generative AI

The authors used ChatGPT 4.0 for language-proofing to refine the manuscript written by non-native English speakers.

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