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Pavlovian-to-instrumental transfer in Anorexia Nervosa: A pilot study on conditioned learning and instrumental responding to low- and high-calorie food stimuli

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Abstract

Anorexia Nervosa is characterized by persistent restraint eating despite severe negative consequences and often a chronic course of the disease. Recent theoretical models suggest that abnormalities in reward processing and incentive salience of disorder-compatible stimuli as observed in addictive behaviours contribute to the development and maintenance of Anorexia Nervosa. The aim of the present study was to investigate the process of the acquisition of food-related conditioned responses and the influence of conditioned low-calorie and high-calorie food stimuli on instrumental responding for different foods. A *Pavlovian-to-instrumental transfer paradigm* and questionnaires on eating disorder psychopathology (*EDE-Q*, *EDI-2*) were administered to patients with Anorexia Nervosa ($n = 39$) and healthy controls ($n = 41$). Results indicated that patients with Anorexia Nervosa showed deficits of the acquisition of knowledge of the experimental contingencies. Nevertheless, in patients with Anorexia Nervosa and healthy controls instrumental responding for low- and high-calorie food rewards was affected by stimuli conditioned to these rewards; no group differences were observed. Importantly, in Anorexia Nervosa, instrumental responding for low-calorie food increased with increasing severity of eating disorder psychopathology suggesting weight-loss directed behaviour. Future studies are warranted to enhance our understanding of deficits of reward-associated learning and to replicate and extend findings with regard to the impact of conditioned stimuli on instrumental responding. At present, our findings suggest that cognitive treatment interventions might be warranted that challenge dysfunctional beliefs about weight loss.

KEYWORDS

appetitive conditioning, eating disorders, goal-directed behaviour, instrumental responding, PIT effect

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1 | INTRODUCTION

Anorexia Nervosa (AN) is an eating disorder that often has its onset in early adolescence and is for many patients characterized by a chronic progressive course of the disease (Arcelus, Mitchell, Wales, & Nielsen, 2011). Thus, it is important to enhance our understanding of the mechanisms that contribute to the development and maintenance of AN. Recently, several authors suggested that mechanisms of addictive behaviour might be crucial in AN (e.g. Godier & Park, 2014; O'Hara, Campbell & Schmidt, 2015; Steinglass & Walsh, 2006; Walsh, 2013). Theories on addictive behaviour assume that stimuli that are regularly associated with the use of a drug become conditioned stimuli and elicit conditioned stimulus-related responses (i.e. "wanting") that promote instrumental drug seeking behaviour (e.g. Berridge & Robinson, 2016). With regard to AN, several authors (e.g. Godier und Park, 2014; O'Hara et al., 2015; Steinglass & Walsh, 2016; Uniacke, Walsh, Foerde & Steinglass, 2018; Walsh, 2013; Wierenga et al., 2014) suggested that disorder-compatible stimuli (e.g. low-calorie food, underweight bodies and physical activity) could acquire incentive salience and promote restraint eating and other eating disorder-related symptoms. In line with this assumption, there are a number of studies demonstrating incentive salience of disorder-compatible stimuli. Thus, Fladung and colleagues demonstrated that the presentation and self-referring processing of stimuli displaying pictures of underweight bodies were associated in patients with AN compared to healthy controls with a higher activation of the ventral striatum, a central structure of the dopaminergic mesolimbic reward system (Fladung et al., 2010; Fladung, Schulze, Schöll, Bauer & Grön, 2013). In addition, O'Hara et al. (2016) assessed the affect-modulated startle reflex and found an increased appetitive response to disorder-compatible stimuli (i.e. underweight body pictures and pictures of active female bodies). Further evidence for an aberrant function of the reward system in AN can be derived from studies investigating the processing of food stimuli (e.g. Godier, Scaife, Braeutigam & Park, 2016a; Holsen, Lawson, Christensen, Klibanski & Goldstein, 2014; Horndasch et al., 2018; Paslakis et al., 2016; Rothemund et al., 2011; Scaife, Godier, Reinecke, Harmer & Park, 2016). Thus, while in obese individuals, the presentation of high-caloric food stimuli is associated with an activation of the reward system (e.g. Grosshans et al., 2012), opposing results have been observed in AN. For example, Cowdrey, Finlayson and Park (2013) reported that both current and weight-restored patients with AN demonstrated significantly less implicit "wanting" for high-calorie foods and more implicit "wanting" for low-calorie foods compared with healthy controls. Taken together, these findings suggest that on the one hand, patients with AN seem to have a reduced response to stimuli that are not compatible with pursuing the goal of weight loss (i.e. high-caloric food stimuli), while disorder-compatible stimuli (i.e. low-calorie food underweight or active bodies, etc.) have acquired incentive salience and might function as conditioned appetitive stimuli that trigger, as in addictive behaviours, pathological behaviour like restraint eating.

There are several studies that used the *Pavlovian-to-instrumental transfer (PIT) paradigm* to investigate the influence of Pavlovian conditioned stimuli on instrumental responding with regard to addictive behaviours (e.g. Garbusow et al., 2014; Garbusow et al., 2016; Hogarth & Chase, 2011; Hogarth & Chase, 2012; Martinovic et al., 2014; Vogel et al., 2018) or food-related behaviour (e.g. Colagiuri & Lovibond, 2015; Watson, Wiers, Hommel, Gerdes & de Wit, 2017). A specific PIT effect is characterized by an increase of instrumental responding for a reward outcome in the presence of a conditioned stimulus associated with that outcome. For example, Watson et al. (2017) found for obese individuals that a stimulus associated with high-calorie food increased responding for high-calorie foods demonstrating that aberrant eating behaviour may be influenced by conditioned food-related stimuli. Consequently, the PIT paradigm seems to be a useful tool to investigate whether in AN, the confrontation with conditioned disorder-compatible stimuli triggers pathological behaviour to achieve the goal of weight loss. To the best of our knowledge, no studies to date have addressed this research topic. However, this seems to be an important research question given that such a learning theory based approach can spread new light on the mechanisms involved in the maintenance of AN and stimulate the development of new treatment approaches.

Against this background, we administered in the present study a PIT paradigm with high-calorie and low-calorie food rewards and aimed firstly to investigate in female patients with AN compared to age- and gender-matched healthy controls (HC) Pavlovian learning (as indicated by the acquisition of knowledge of the association of different abstract stimuli with either low-calorie or high-calorie food rewards; first part of the PIT paradigm). To control for confounding effects due to possible malnutrition-related cognitive deficits of patients with AN compared to HC (e.g. Decker, Figner & Steinglass, 2015; Steward et al., 2019), the Trail Making Test was also administered. We further aimed to investigate the impact of the stimuli conditioned to low-calorie and high-calorie food rewards on instrumental responding for different food rewards (third part of the PIT paradigm). In addition, we aimed to explore whether severity of eating disorder-related pathology and the duration of AN would affect instrumental responding for food in the task.

2 | MATERIALS AND METHODS

2.1 | Participants

Eighty female participants aged between 14 and 34 years (M = 22.46, MD = 21.00, SD = 4.61) were recruited for the study. These were 39 patients who fulfilled the DSM-5-diagnostic criteria (American Psychiatric Association, 2013) of AN based on a structured clinical interview and 41 matched healthy controls (HC). All patients underwent inpatient psychotherapeutic treatment at one of three treatment centres, which offer cognitive-behavioural treatment for eating disorders. HC were recruited from the university student and general population of Bamberg, Germany. Exclusion criteria were substance use disorder, severe psychiatric (with the exception of AN for patients) or neurological disorder, affective and psychotic disorders. The ethics committees of the University of Bamberg and of the Medical Faculty of the University of Erlangen-Nuremberg approved the study. All study participants signed written informed consent and were compensated with 15€ for their study participation.

2.2 | General procedure

Testing comprised a single individual test session in which the PIT paradigm, different questionnaire measures on demographic and psychopathological characteristics, and the Trail Making Test to control for cognitive function were administered. The test session lasted about 90 minutes in total.

2.3 | Pavlovian-to-instrumental transfer (PIT) paradigm

A PIT paradigm as developed in our previous research (Vogel et al., 2018) was used and adapted to study the influence of conditioned stimuli on instrumental responding for food. In short, participants were seated in front of a Dell Latitude E5470 (14") laptop with a Fujitsu optical mouse connected to it. To the left of the participants, two grey metal boxes (107 × 73 × 28 mm; height, width, depth) with their lids open were placed. One box contained the low-calorie food reward (i.e. vegetable; symbolized by green coins showing a carrot symbol) while the other box contained the high-calorie food reward (i.e. chocolate, symbolized by purple coins showing a chocolate symbol). To the right of the participant, two identical boxes that were empty and labelled either *"Your vegetable points"* or *"Your chocolate points"* were placed.

The PIT paradigm comprised three different phases (see Figure 1). During *Pavlovian training*, two of four abstract stimuli were presented in each trial and participants had to learn through feedback that one of the stimuli (CS^V; that is conditioned stimulus related to vegetable) predicted the display of a vegetable-related picture, while another stimulus (CS^C; that is conditioned stimulus related to chocolate) predicted the display of a chocolate-related picture. Vegetable-related and chocolate-related pictures were selected from the *food-pics database* (Blechert, Meule, Busch, & Ohla, 2014) and matched by valence ratings (t_{31} = 0.56 and p = .581); in each trial, a different picture of vegetable or chocolate was presented. The two other stimuli (X, Y) served as control stimuli. As dependent variable, expectancy ratings ("Do you think you will see a vegetable- or a chocolate-picture? 1 = vegetable, 9 = chocolate"; anchors counterbalanced across participants) were assessed in each trial. Participants completed four blocks of sixteen trials (64 trials in total); each block contained eight CS^C- and eight CS^V-trials.

Then, *instrumental training* started with the purpose to establish two reward-related responses. Thus, by pressing either "G" or "S" (the first letter of the German word for "vegetable"

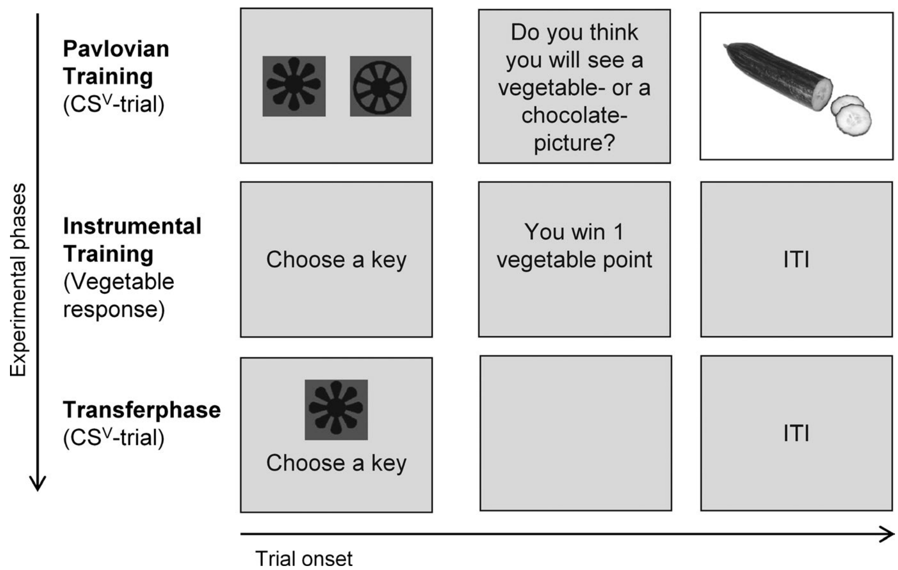

FIGURE 1 The Pavlovian-to-instrumental transfer Paradigm with food-related stimuli. The paradigm comprises three experimental phases. Displayed is a Pavlovian trial in which a vegetable-related stimulus is presented (left picture); in instrumental training, the participant has pressed the vegetable-related key and receives feedback; in the transfer phase, no feedback is provided

or "chocolate", respectively) participants were able to earn the coins provided in the metal boxes. Participants were informed that they should press in each trial only one of the two keys and that they should press repeatedly to increase their chances. Either the feedback "You win one vegetable point." or "You win one chocolate point." was presented if participants pressed one of the keys at least once during the two-second response window (if participants did not press at all, the feedback "You win nothing." was presented). In each trial, only one outcome was available at random thus that over the course of each block, the chocolate-related and the vegetable-related responses were reinforced with a 50% contingency. Instrumental training consisted of four blocks of 12 trials. After each block, a summary of the winnings was presented, and participants placed the coins they had won in their boxes.

The final phase, the *transfer phase*, appeared as a continuation of instrumental training as participants could still earn vegetable-related or chocolate-related coins by pressing either "G" or "S". However, in 1/3 of the trials, a grey square was presented, while in the remaining 2/3 of the trials, either the CS^C or the CS^V were presented in random order in the position of the grey square. Key presses were still reinforced with a 50% contingency, whereas feedback about the winnings was provided only at the end of the transfer phase to preclude new learning (see e.g. Jeffs & Duka, 2017; Martinovics et al., 2014; Vogel et al., 2018). The transfer phase comprised four blocks, each with 12 trials (total of 48 trials).

An *emotional evaluation* of the different abstract stimuli was conducted before and after Pavlovian training. Participants rated each stimulus twice in random order on a nine-point Likert scale (counterbalanced across participants) with regard to the questions: "How pleasant do you find this picture?" (pleasantness) and "How arousing do you find this picture?" (arousal).

Presentation® software (Version 18.1, www.neurobs.com) was used for the experimental procedures and recording of responses.

2.4 | Questionnaires

The *Eating Disorder Examination Questionnaire* (*EDE-Q*; Hilbert, Tuschen-Caffier, Karwautz, Niederhofer & Munsch, 2007) was used to assess disturbed eating behaviour. Eating disorder psychopathology can be measured through four different subscales as well as a total score (Hilbert, Brähler, & De Zwaan, 2012). In the current sample, internal consistency was good to excellent for the different subscales as well as the total score (Cronbach's $\alpha \geq 0.86$).

The short version of the *Eating Disorder Inventory-2* (*EDI-2*; Paul & Thiel, 2005) was used in addition as a measure of cognitive and behavioural aspects associated with eating disorders validated in adolescents and adults. The *EDI-2* is a self-rating inventory with 64 items on eight scales in its short version. Internal consistency for the different subscales and the total score was good or excellent in the current sample (Cronbach's $\alpha \geq 0.84$).

2.5 | Trail making test

The *Trail Making Test* (*TMT*; Reitan, 1992) is a valid measure to assess attention and executive control abilities (e.g. Kortte, Horner, & Windham, 2002; Sánchez-Cubillo et al., 2009) and was administered to control for deficits of cognitive flexibility in AN as a possible confounding factor. We calculated the TMT-B to TMT-A ratio (B/A) as an indicator of deficits of cognitive flexibility, especially task switching (Arbuthnott & Frank, 2000).

2.6 | Data analyses

Expectancy ratings in CS^V- and CS^C-trials during Pavlovian training were averaged for the four blocks, and a repeated measures analysis of variance was calculated with category (vegetable and chocolate) and block (1, …, 4) as repeated measures factors. Following the procedure previously described (e.g. Loeber & Duka, 2009; Vogel et al., 2018), we coded participants as explicitly aware of the experimental contingencies if expectancy ratings in CS^V- and CS^C- trials differed significantly in the final block of Pavlovian training and indicated higher expectancy of vegetable-related pictures in CS^V- trials.

Changes of the emotional evaluations (pleasantness, arousal) of the CS^V, CS^C and control stimuli X, Y were entered into an ANOVA with time (before and after Pavlovian training) and stimuli (CS^V/CS^C, X and Y) as the repeated measures factors. This analysis was run with aware participants only and counterbalance was added as a covariate.

Performance of the instrumental response to achieve the reward outcome in the instrumental training and the transfer phase was assessed by two different outcome measures. Firstly, we assessed the percentage of choice of the vegetable-related versus chocolate-related key (i.e. response choice). Secondly, we calculated the response rate (in Hz) which indicated the number of presses per second on the vegetable-related or chocolate-related key. For the transfer phase, response choice and response rate were calculated separately for trials in which the CS^V, CS^C or grey square was presented. Differences with regard to response choice and response rate were analysed using repeated measures analyses of variance with stimulus (CS^V, CS^C, grey square) as repeated measures factor; awareness was entered as between-group factor for responses in the transfer phase.

Correlation analysis (Pearson correlation, no Bonferroni correction applied) for aware AN and HC and stepwise multiple linear regression analysis for AN were calculated to explore the influence of eating disorder-related psychopathology on performance of the instrumental response. For the analysis of predictors of the magnitude of the "vegetable-PIT" and the "chocolate-PIT" effects (i.e. the difference scores to responding after presentation of the grey square), all variables were mean centred. Knowledge of the experimental contingencies (as indicated by the difference in expectancy ratings in CS^V- compared with CS^C-trials in the final block of Pavlovian training) was entered as control variable in the first step. Then, the total scores of the *EDE-Q* and the *EDI-2* and duration of AN were entered as predictor variables.

The assumptions of all statistical procedures applied were checked. In the case of violation of the assumption of sphericity, the Greenhouse–Geiser adjustment was applied and adjusted degrees of freedom are reported. Effect size statistics (partial eta^2, η_p^2) are reported for the main outcome measures. A significance level of $\alpha \leq 0.05$ was considered as significant. For significant main effects, post hoc analyses with Bonferroni-corrected *t* tests were used. All analyses were performed using IBM SPSS Statistics (version 24).

3 | RESULTS

3.1 | Sample characteristics

Patients reported a mean illness duration of 4.60 years (*SD* = 4.33, range 0–16). Twenty-four patients with AN (62%) had a diagnosis of the restrictive subtype, eight patients (21%) of the binge-eating/purging subtype while for seven patients (20%) no subtype was defined. As expected, patients scored significantly higher than HC with regard to eating disorder psychopathology and had a lower BMI. However, the groups did not differ with regard to age, and no deficits of cognitive flexibility were observed in patients with AN compared to HC (see Table 1 for details).

3.2 | Knowledge of the experimental contingencies and emotional evaluation of the stimuli

3.2.1 | Expectancy ratings and awareness of the experimental contingencies

Figure 2 shows that as training progressed *expectancy ratings* differed between the trials predicting a vegetable- or a chocolate-related picture, respectively (see Figure 2). A repeated measures ANOVA indicated a significant main

TABLE 1 Demographic characteristics and psychopathology of patients with a diagnosis of Anorexia Nervosa (AN) and healthy control participants (HC)

Variables	AN (*n*=39)	HC (*n*=41)	Statistics (*t*/*P*)
Age (years) [Mean/MD (*SD*)]	22.74/21.00 (5.10)	22.20/21.00 (4.15)	−0.53/0.60
BMI (adults[a]) [Mean (*SD*)]	17.88 (2.77)	22.20 (3.10)	6.13/<0.001
BMI age percentile (adolescents[a]) [Mean (*SD*)]	18.34 (17.25)	50.80 (35.31)	1.85/0.10
Duration of AN (years) [Mean (*SD*)]	4.60 (4.33)	n/a	
Duration of present treatment (weeks)[Mean (*SD*)]	3.71 (3.90)	n/a	
EDE-Q (restraint) [Mean (*SD*)]	3.39 (1.87)	1.99 (0.98)	−4.19/<0.001
EDE-Q (eating concern) [Mean (*SD*)]	3.59 (1.40)	1.52 (0.53)	−8.70/<0.001
EDE-Q (weight concern) [Mean (*SD*)]	4.57 (1.52)	2.18 (1.02)	−8.25/<0.001
EDE-Q (shape concern) [Mean (*SD*)]	5.33 (1.35)	2.48 (1.04)	−10.54/<0.001
EDE-Q (total) [Mean (*SD*)]	4.22 (1.40)	2.04 (0.77)	−8.57/<0.001
EDI−2 (DT) [Mean (*SD*)]	31.26 (7.96)	16.88 (5.91)	−9–14/<0.001
EDI−2 (total) [Mean (*SD*)]	247.74 (41.83)	158.44 (29.40)	−11.00/<0.001
TMT ratio (B/A)	2.39 (0.51)	2.46 (0.82)	0.47/0.64

Abbreviations: *EDE-Q*, Eating Disorder Examination Questionnaire; *EDI-2*, Eating Disorder Inventory-2; *EDI-2* (DT), subscale "drive for thinness"; n/a, not applicable.

[a] *n* = 5 participants of the AN group and *n* = 5 participants of the HC group were aged below 18 and BMI percentiles were calculated instead of the BMI.

effect of stimulus ($F_{1,78} = 73.43$, $p < 0.001$, $\eta_p^2 = 0.49$) which was qualified by a significant stimulus by block interaction ($F_{2,156} = 28.95$, $p < 0.001$, $\eta_p^2 = 0.27$). In addition, a small, albeit significant, stimulus by block by group interaction was found ($F_{2,156} = 3.40$, $p = 0.04$ and $\eta_p^2 = 0.04$). All other effects were not significant (all $F \leq 3.44$, all $p \geq 0.07$). Post hoc tests revealed that for patients with AN and HC, the expectancy of the vegetable-related stimuli was significantly higher in CS^V- than in CS^C-trials in all four blocks of Pavlovian training (all $t \geq 4.79$, all $P_{corrected} \leq 0.001$). Descriptive analysis of Figure 2 further indicates that the difference in expectancy ratings in CS^V- compared to CS^C-trials was greater for HC compared to patients with AN from the second to the final block; however, these differences were not significant and only approached significance in the final block as indicated by Bonferroni-corrected post hoc tests ($t_{78} = 2.43$ and $P_{\text{corrected}} = 0.07$).

With regard to the number of participants who were classified as *aware* of the experimental contingencies according to their expectancy ratings in the final block of Pavlovian training, we found that a significantly lower proportion of patients ($N = 12$, 31%) compared with HC ($N = 23$, 56%) were classified as aware ($\chi_1^2 = 5.21$ and $p = 0.03$). Aware and unaware patients did not differ significantly with regard to eating disorder-related psychopathology as indicated by the duration of AN as well as the total scores achieved in the *EDE-Q* and the *EDI-2* (all $t \leq |0.91|$, all $p \geq 0.37$).

3.2.2 | Changes of emotional ratings of stimuli

With regard to changes in pleasantness ratings for aware participants, results indicated neither significant main effects of time or stimulus nor a significant time by stimulus interaction (all $F \leq 1.52$, all $p \geq .22$). The main or interaction effects of group were also not significant (all $F \leq 1.34$, all $p \geq 0.26$). Similar results were observed with regard to arousal ratings (all $F \leq 1.85$, all $p \geq 0.18$).

3.3 | Instrumental responding and eating disorder-related psychopathology

3.3.1 | Instrumental responding

During instrumental training, participants responded on average in 95.00% of the trials ($SD = 5.30$ and range 70.83–100.00). For *response choice*, descriptive analysis indicated that the vegetable-related key was pressed more often; however, the main effect of category only approached significance ($F_{1,78} = 3.67$, $p = 0.06$ and $\eta_p^2 = 0.05$). No significant main effect of group ($F_{1,78} = 0.02$, $p = 0.89$ and $\eta_p^2 = 0.00$) or group by category interaction effect was observed ($F_{1,78} = 1.17$, $p = 0.28$ and $\eta_p^2 = 0.02$).

With regard to *response rate*, the main effect of category ($F_{1,78} = 0.66$, $p = 0.42$ and $\eta_p^2 = 0.01$) and group ($F_{1,78} = 0.00$, $p = 0.97$ and $\eta_p^2 = 0.00$) was not significant, but a significant category by group interaction ($F_{1,78} = 5.70$, $p = 0.02$ and $\eta_p^2 = 0.07$) emerged. However, post hoc *t* tests indicated that this effect was not reliable (all $t \leq 2.64$, all $P_{\text{corrected}} \geq 0.05$).

In the transfer phase, participants responded in 96.90% of the trials ($SD = 5.20$, range 72.92–100). With regard to the influence of the conditioned stimuli on *response choice* of the vegetable-related key, a repeated measures analysis of variance indicated a significant main effect of stimulus ($F_{2,152} = 33.73$, $p < 0.001$, $\eta_p^2 = 0.31$) that was qualified by a significant stimulus by awareness interaction ($F_{2,152} = 35.75$, $p < 0.001$, $\eta_p^2 = 0.32$). All other effects were not significant. Post hoc tests revealed that aware participants chose more often to press the vegetable-related key when the CS^V was presented compared with presentation of the CS^C ($t_{34} = 12.38$, $P_{corrected} < 0.001$) or the grey square ($t_{34} = 6.75$, $P_{corrected} \leq 0.001$) (''vegetable PIT' effect') while response choice of the vegetable-related key after presentation of the CS^C was significantly lower compared with presentation of the grey square ($t_{34} = -8.69$, $P_{corrected} < 0.001$) indicating that presentation of the CS^C increased responding on the chocolate-related key (''chocolate PIT' effect'). This pattern was observed for patients with AN and HC (see Figure 3 for an illustration). No significant differences emerged for unaware participants (all $t_{34} \leq 1.89$, all $P_{corrected} \geq 0.20$).

With regard to *response rate,* similar results were observed. A main effect of stimulus ($F_{2,\,152} = 29.37$, $p < 0.001$, $\eta_p^2 = 0.28$) that was qualified by a significant stimulus by awareness interaction ($F_{2,152} = 22.80$, $p < 0.001$, $\eta_p^2 = 0.23$) indicated that aware participants pressed the vegetable-related

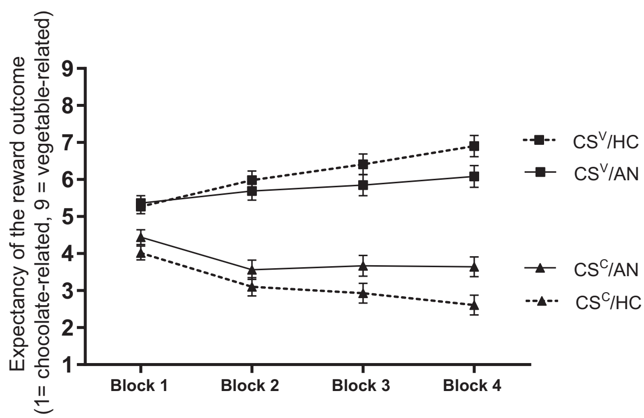

FIGURE 2 Expectancy ratings (mean and *SEM*) of the vegetable-related outcome increased in CS^V trials and decreased in CS^C-trials during Pavlovian training across blocks of trials. No reliable group differences emerged. CS^V, conditioned stimulus related to vegetable and CS^C, conditioned stimulus related to chocolate

key more often when the CS^V was presented compared to presentation of the CS^C ($t_{34} = 11.45$, $p < 0.001$) or the grey square ($t_{34} = 6.33$, $p < 0.001$). Response rate on the vegetable-related key was significantly lower when the CS^C was presented compared with the grey square ($t_{34} = -6.69$, $p < 0.001$). For unaware participants, no significant differences emerged (all $t \leq 2.13$, all $P_{corrected} \geq 0.11$).

3.3.2 | Instrumental responding and its association with eating disorder-related psychopathology

Correlation analysis with aware participants only indicated that for patients with AN, eating disorder-related psychopathology was significantly positively related with responding on the vegetable-related key. As shown in Table 2, in AN, the total score of the *EDE-Q* and the total score of the *EDI-2* were related to the more frequent choice of the vegetable-related key after presentation of the grey square. While these variables were not significantly associated with the ‘‘vegetable PIT’ effect’, they were positively associated with the ‘‘chocolate PIT’ effect’ suggesting that more severe eating disorder symptoms were related with a greater difference in responding on the vegetable-related key after presentation of the grey square compared with presentation of the CS^C. For healthy participants, no significant associations emerged (all $r \leq |0.33$, all $p \geq 0.15$; data not shown).

Regression analysis to enhance our understanding of variables affecting the “vegetable-PIT” and the ‘‘chocolate PIT’ effect’s in AN was run. When we entered the magnitude of knowledge of the experimental contingencies as a control variable in the first step to predict the magnitude of the *‘‘vegetable PIT’effect’*, the model was not significant (see Table 3, upper panel). However, when we entered the variables related to AN in the next step, the model was now significant. As shown in Table 3, the severity of eating disorder-related psychopathology as assessed with the total score of the *EDE-Q* was significantly negatively associated with the magnitude of the “vegetable-PIT” effect.

Contrary to these findings, knowledge of the experimental contingencies was a significant predictor of the magnitude of the ‘‘chocolate PIT’ effect’ as indicated by a significant model in the first step (see Table 3, lower panel). Entering the variables related to AN did not significantly improve the model ($\Delta R^2 = 0.03$ and $p = 0.67$).

4 | DISCUSSION

Given the discussion that disorder-compatible stimuli might acquire incentive salience and contribute to the development and maintenance of AN by triggering pathological behaviour (e.g. restraint eating, physical activity), we investigated Pavlovian learning and the impact of stimuli conditioned to low-calorie and high-calorie food rewards on instrumental responding for different food rewards. Our findings suggest that patients with AN might have more difficulties than HC to acquire stimulus-response-outcome associations, even though set-shifting (as assessed with the Trail Making Test) may be not impaired. Thus, as Pavlovian training progressed, all participants learned to discriminate between the stimulus that predicted low-calorie food pictures (CS^V) and the stimulus that predicted high-calorie food pictures (CS^C). However, a small, albeit significant interaction effect of stimulus by

TABLE 2 Results from correlation analysis (*r*/*P*) for aware patients with Anorexia Nervosa with regard to instrumental responding in the transfer phase

Variables	Overall choice vegetable key (%)	Choice vegetable key after square (%)	Choice vegetable key after CS^V (%)	Choice vegetable key after CS^C (%)	Magnitude ‘‘vegetable PIT’ effect’	Magnitude ‘‘chocolate PIT’ effect’
EDE-Q (restraint)	0.23/0.46	0.60/0.04*	-0.19/0.56	-0.24/0.46	-0.47/0.12	−0.60/0.04*
EDE-Q (eating concern)	0.52/0.09	0.75/0.01*	0.08/0.81	-0.43/0.17	-0.39/0.21	−0.81/<0.01*
EDE-Q (weight concern)	0.44/0.15	0.72/0.01*	0.02/0.96	-0.44/0.15	-0.44/0.15	−0.77/<0.01*
EDE-Q (shape concern)	0.61/0.04*	0.71/0.01*	0.20/0.53	-0.40/0.20	-0.30/0.34	−0.75/0.01*
EDE-Q (total)	0.48/0.12	0.75/0.01*	0.02/0.96	-0.40/0.19	-0.45/0.14	−0.79/<0.01*
EDI−2 (DT)	0.47/0.12	0.74/0.01*	0.09/0.78	-0.57/0.05	-0.41/0.19	−0.84/<0.01*
EDI−2 (total)	0.43/0.17	0.68/0.01*	-0.01/0.97	-0.32/0.32	-0.44/0.15	−0.71/0.01*

Note: r, Pearson correlation coefficient; *P*, *p*-value without Bonferoni correction applied.
*$p < 0.05$; CS^V, vegetable-related stimulus; CS^C, chocolate-related stimulus; Magnitude ‘‘vegetable PIT’ effect’, increase in responding on the vegetable-related key after presentation of the CS^V relative to presentation of the square (CS^V - grey square); Magnitude ‘‘chocolate PIT’ effect’, decrease in responding on the vegetable-related key after presentation of the CS^C relative to presentation of the square (grey square - CS^C); EDE-Q, Eating Disorder Examination Questionnaire; and *EDI*-2, Eating Disorder Inventory-2.

TABLE 3 Results of the stepwise hierarchical linear regression analysis to predict the ‘‘vegetable PIT’ effect’ and the ‘‘chocolate PIT’ effect’

	Magnitude of the ‘‘vegetable PIT’ effect’					
	Step 1			Step 2		
Variables and steps	β	T	p	β	T	p
Diff expectancy ratings Pt	0.2	1.24	0.22	0.22	1.43	0.16
EDE-Q (total)				−0.34	−2.18	0.04*
EDI−2 (total)				0.19	0.92	0.37
Duration of AN				0.19	1.19	0.24
R^2	0.04		0.22	0.11		0.05*
	Magnitude of the ‘‘chocolate PIT’ effect’					
	Step 1			**Step 2**		
	β	T	P	β	T	P
Diff expectancy ratings Pt	0.5	3.55	0.00*	0.52	3.55	0.00*
EDE-Q (total)				0.12	0.57	0.57
EDI−2 (total)				−0.11	−0.55	0.59
Duration of AN				−0.14	−0.95	0.35
R^2	0.25		0.00*	0.27		0.02*

Note: β, standardized regression coefficient; ‘‘vegetable PIT’ effect’, the difference in responding on the vegetable-related key after presentation of the vegetable-related stimulus (CS^V) compared with presentation of a grey square (CS^V - grey square); ‘‘chocolate PIT’ effect’, the difference in responding on the vegetable-related key after presentation of grey square compared to presentation of the CS^C (grey square - CS^C); PT, Pavlovian training; and AN, Anorexia Nervosa.
*$p < 0.05$.

block by group emerged suggesting differences between patients with AN and HC. Although post hoc tests indicated that this effect was not reliable, group differences are supported by a significantly lower percentage of participants in the AN group (31%) compared with the HC group (56%) who were classified as aware of the experimental contingencies based on expectancy ratings in the final block of Pavlovian Training. Importantly, the percentage of aware HC was in the range of previous research (e.g. Jeffs & Duka, 2017; Vogel et al., 2018) indicating that this finding was not due to a higher difficulty of the task compared with previous non-food-related versions. While no study to date has directly assessed deficits of Pavlovian learning in AN, there are some studies that reported an impairment in AN with regard to learning from feedback, implicit learning or deficits of reward processing (e.g. Park, Godier & Cowdrey, 2014; Shott et al., 2012; Wagner et al., 2007). Although we administered the Trail Making Test and thus controlled for an impairment of set-shifting as possible confounding variable, from the results of the present study we cannot further elucidate whether the observed impairment is due to other cognitive deficits associated with malnutrition or already existed before the onset of AN. Thus, to enhance our understanding of such a possible deficit of Pavlovian learning seems an important aspect in the framework of research on reward processing in AN.

Our results further indicated in aware patients with AN and HC a clear “vegetable-PIT” and a ‘‘chocolate PIT’ effect’. Thus, responding on the vegetable-related key increased after presentation of the vegetable-related stimulus compared with presentation of the chocolate-related stimulus and the grey square, while presentation of the chocolate-related stimulus, compared with the grey square, decreased responding on the vegetable-related key. Importantly, this impact of the stimuli conditioned to either low- or high-calorie food rewards on instrumental responding was, however, observed in patients with AN and HC with no significant group differences. Only recently, Hogarth and colleagues reported lacking differences between drug users and healthy controls with regard to the PIT effect and interpreted this finding as indicating intact goal-directed behaviour in patients (Hogarth et al., 2018). The present findings thus suggest that instrumental responding in AN is modulated by conditioned stimuli signalling the availability of different food rewards—even if they are high-caloric. Interestingly, our further results indicated that increasing severity of eating disorder-related psychopathology affected performance in the task by increasing choice of the low-calorie food reward. This finding is also in line with research on addictive behaviour as there are a number of studies which found that severity of dependence does not affect the PIT effect, but is associated with preferential choice of the drug (Hardy, Parker, Hartley 2018 & Hogarth, 2018; Hogarth & Chase, 2011; Hogarth & Chase, 2012; Hogarth et al., 2018). In the present study, severity of eating disorder-related psychopathology as indicated by weight, shape and

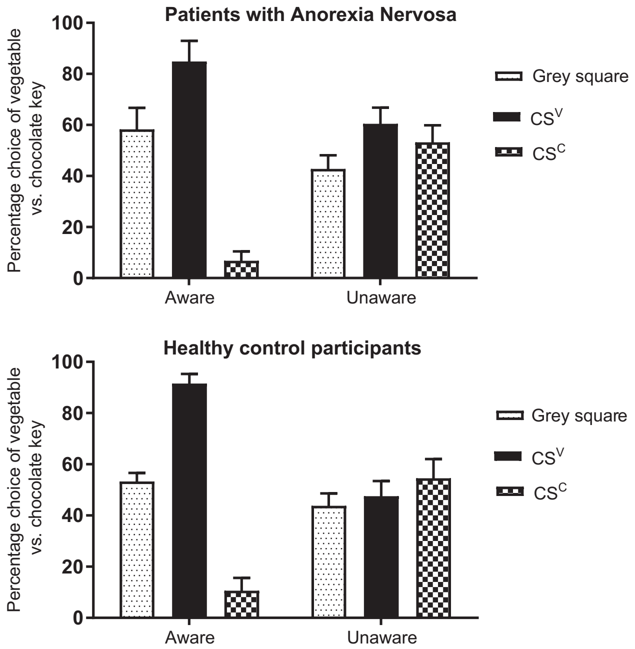

FIGURE 3 For aware patients with Anorexia nervosa (upper panel) and healthy control participants (lower panel) a "vegetable-PIT" and a "chocolate-PIT" effect were observed as indicated by percentage choice of the key associated with the vegetable-related reward after presentation of the grey square (neutral), the vegetable-related stimulus (CS^V) or the chocolate-related stimulus (CS^C) (mean and *SEM*)

eating concerns drive for thinness and restraint eating (i.e. different subscales of the *EDE-Q* and the *EDI-2*) was significantly positively correlated with responding on the vegetable-related key after presentation of the grey square. This finding suggests that with increasing severity of eating disorder pathology the preference to press the vegetable-related key increased thus favouring low-calorie foods in line with the goal of losing weight. Consequently, as the magnitude of the "vegetable-PIT" effect is calculated by subtracting choice of the vegetable-related key after presentation of the grey square from choice after presentation of the CS^V, the "vegetable-PIT" effect decreased with increasing eating disorder-related psychopathology as indicated by regression analysis. Seabrooke and colleagues (Seabrooke, Le Pelley, Hogarth & Mitchell, 2017) have recently pointed out this caveat of the interpretation of the magnitude of the PIT effect due to its calculation on difference scores. Consequently, Seabrooke et al. (2017) suggested a modified PIT paradigm with overall response choice about 50% which would be also interesting for future studies on reward processes in AN. At present, research on goal-directed behaviour in AN is very scarce and an interesting study was presented by Godier and colleagues who investigated impairment of goal-direct behaviour in favour of habitual behaviour in AN using the slips-of-action paradigm (Godier, Wit, et al., 2016b). Although compared with the present study a different assessment procedure was used and no disorder-compatible stimuli were presented, in line with the present findings, no impairment of goal-directed behaviour was found.

To further enhance our understanding of learning processes, the impact of conditioned stimuli on goal-directed behaviour and the development of habitual behaviour in AN is very important as the course of this disease is often chronic and psychotherapeutic treatment of limited effectivity. A better understanding of these processes might stimulate the development of new and more tailored treatment interventions. For example, Steinglass et al. (2018) demonstrated in a proof-of-concept study with a small sample of patients with AN that a behavioural intervention aiming at reducing habits (e.g. by implementing techniques helping to suppress habits) was associated with a significantly greater reduction in habit strength compared to a control condition, which was also reflected in pronounced clinical improvement. However, the results from the present study suggest that at least some patients show deliberate behavioural strategies in line with the goal of losing weight. These patients might benefit more from cognitive interventions focusing on dysfunctional cognitions related to their body and weight and the harmfulness of weight loss as a goal.

When interpreting the findings of the present study, a few limitations should be acknowledged. First of all, to the best of our knowledge we report here for the first time deficits in AN with regard to Pavlovian conditioning. Although these results are interesting by themselves, the observed deficits with regard to the acquisition of knowledge of the experimental contingencies resulted in a rather small sample to investigate instrumental responding to the conditioned stimuli and the PIT effect. Even though results with regard to these variables are perfectly in line with findings in addictive behaviour (e.g. lacking differences between patients and controls with regard to the PIT effect; severity of psychopathology affecting instrumental responding), future research is warranted to replicate our findings in a larger sample. These studies should consider using an adapted PIT paradigm, for example with more trials in Pavlovian training, to compensate for this deficit. In addition, it would be interesting in future studies, to investigate whether differences between the different subtypes of AN exist. Due to the small sample size, this was not possible in the present study, especially as not for all patients with AN subtypes were defined. However, it might be interesting to study whether severity of binging also affects PIT performance given its proximity to loss of control and addictive behaviours. Finally, only female patients with AN were included in the present study. Although this reflects the gender distribution often seen in clinical treatment settings, future studies should concentrate more on investigating individual differences taking also into account gender aspects.

Taken together, the results of the present study have shown that in patients with AN and HC instrumental responding for low-calorie and high-calorie food rewards is affected by stimuli conditioned to these rewards. In patients with AN, instrumental responding for a low-calorie reward increased with increasing severity of eating disorder psychopathology suggesting weight-loss directed behaviour. These findings are in line with results on addictive behaviour. However, we also observed deficits of Pavlovian learning and future studies are warranted to enhance our understanding of the observed deficits of conditioned learning and to replicate findings with regard to the impact of conditioned stimuli on instrumental responding for food rewards.

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CONFLICTS OF INTEREST

The authors have no conflict of interest.

AUTHOR CONTRIBUTIONS

SSL designed the study, analysed the data and wrote the first draft of the manuscript. VV programmed the experiment and supported the analysis of data. VV and MD collected the data. SH, OK, GP and ER supervised the clinical procedures at the treatment sites. OK, GHM and YE advised on all aspects of the study. All authors gave feedback to the manuscript.

DATA AVAILABILITY STATEMENT

Data can be requested from the corresponding author.

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