

Impaired Associative Learning with Food Rewards in Obese Women

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Summary

Obesity is a major epidemic in many parts of the world. One of the main factors contributing to obesity is overconsumption of high-fat and high-calorie food [1], which is driven by the rewarding properties of these types of food [2, 3]. Previous studies have suggested that dysfunction in reward circuits may be associated with overeating and obesity [4–8]. The nature of this dysfunction, however, is still unknown. Here, we demonstrate impairment in reward-based associative learning specific to food in obese women. Normal-weight and obese participants performed an appetitive reversal learning task in which they had to learn and modify cue-reward associations. To test whether any learning deficits were specific to food reward or were more general, we used a between-subject design in which half of the participants received food reward and the other half received money reward. Our results reveal a marked difference in associative learning between normal-weight and obese women when food was used as reward. Importantly, no learning deficits were observed with money reward. Multiple regression analyses also established a robust negative association between body mass index and learning performance in the food domain in female participants. Interestingly, such impairment was not observed in obese men. These findings suggest that obesity may be linked to impaired reward-based associative learning and that this impairment may be specific to the food domain.

Results

Studies of reward processing in obesity typically examine the static representations of previously acquired reward values and ignore the constant need to update these values based on new information from one's internal state and external environment. This adaptive learning may be deficient in obese individuals. For instance, behavioral treatments that seek either to alter existing negative eating behavior by rewarding the adoption of new positive behaviors or to modify responses to cues that trigger inappropriate eating have only had limited success [7]. These observations suggest that impaired reward-based learning may be closely associated with overeating and obesity.

To test the ability of normal-weight and obese individuals to acquire and modify cue-reward associations, we administered an appetitive reversal learning paradigm to human participants. The task consisted of an acquisition stage, followed by an unsignaled transition to a reversal stage (Figure 1A). Two colored squares (blue and purple) were used as conditioned stimuli. During acquisition, color A was followed by a reward image in one-third of the trials (conditioned stimulus [CS+]), whereas color B was never followed by a reward (unconditioned stimulus [CS–]). During reversal, the reward contingencies switched, such that color B was now followed by a reward in approximately one-third of the trials (new CS+), and color A was never followed by a reward (new CS–). The designation of blue and purple as colors A and B was counterbalanced across participants. To assess reward expectancy, we prompted participants to indicate the degree to which they expected to receive a reward upon CS presentation in each trial, using a scale of one to nine (Figure 1B). To test for possible domain specificity of any observed effects, we used two kinds of reward—food (peanut M&M'S or pretzels) and money—in a between-subject design. Normal-weight and obese participants were recruited based on body mass index (BMI). The experiment was approved by the Yale University School of Medicine Human Investigation Committee. The crossing among body weight status (normal weight or obese), reward modality (food or money), and gender (male or female) yielded eight experimental groups. There was no significant difference in BMI among the normal-weight groups or among the obese groups (three-way ANOVA: $p < 0.001$ for main effect of body weight status, $p > 0.44$ for all other main effects and interactions; post hoc Tukey tests between groups: $p > 0.99$ for all pairs of normal-weight groups, $p > 0.92$ for all pairs of obese groups; Table S1 available online; Supplemental Experimental Procedures). There was also no significant difference in age, income, education, and self-reported hunger level among the eight groups (separate one-way ANOVAs: age $p = 0.89$, income $p = 0.95$, education $p = 0.46$, hunger $p = 0.33$; see Table S1).

Learning Strength in Obese and Normal-Weight Individuals

To quantify the degree of learning in the task and to facilitate a direct group comparison, we used the ratings (Figure S1) to derive three learning indices capturing different components of the associative learning processes involved in the task. Acquisition strength (ACQ) was defined as the difference between the mean ratings of CS+ (color A) and CS– (color B) in the second half of the acquisition stage (late acquisition). In this measure, positive indices indicate learning of the proper associations (higher rating of CS+ compared to CS–), zero indicates no learning (similar ratings for both stimuli), and negative indices indicate learning of the wrong contingencies (higher rating of CS– than CS+).

Two learning indices were defined in the reversal stage to capture the change in rating of color A (ΔA) and color B (ΔB). To adapt to the switch in reward contingencies in the reversal stage, one needs to decrease the reward expectancy in response to color A and increase the reward expectancy in response to color B (see Supplemental Experimental Procedures). Note that these three indices (ACQ, ΔA , and ΔB) form

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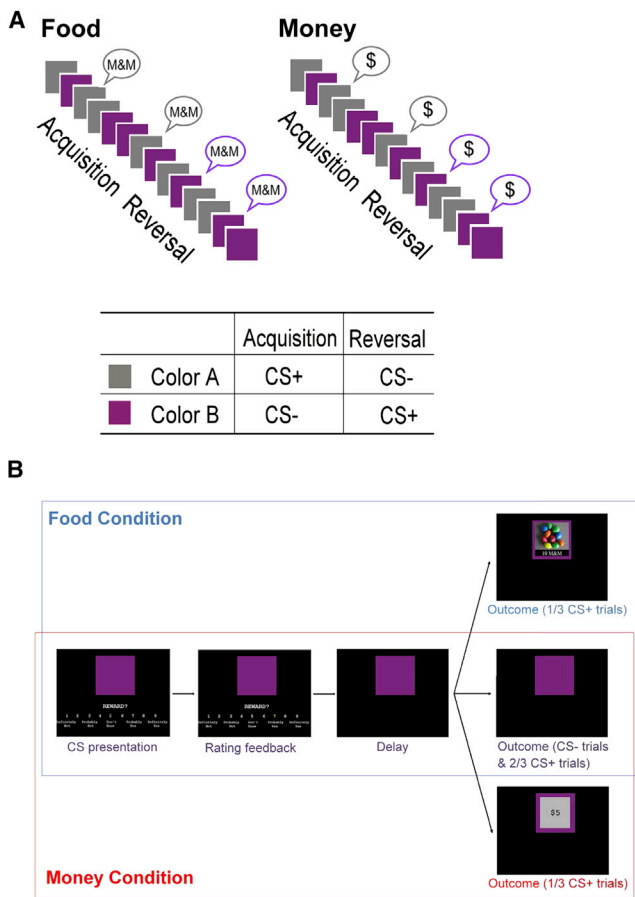


Figure 1. The Appetitive Reversal Learning Paradigm

(A) Overall timeline. Participants were randomly assigned to the food or money condition. The acquisition stage consisted of presentations of two colored squares on a partial reinforcement schedule. Color A was associated with reward in about one-third of the trials (CS+), whereas color B was not (CS−). In the reversal stage, the reward contingencies were switched, such that color B was now paired with reward (new CS+), and color A was not (new CS−). The first trial in which color B was followed by a reward marked the beginning of the reversal stage. Blue and purple were the actual colors used in the experiment, and the assignment of colors to color A and color B was counterbalanced across subjects.

(B) Within-trial timeline. Stimuli were presented in pseudorandom order together with a rating scale for a maximum of 3 s. After the participant provided the rating, the appropriate number was highlighted on the screen for 0.5 s. In one-third of the CS+ trials, a reward image was then superimposed on the colored square, indicating the reward received on that trial. Trials were separated by a 4 s intertrial interval. Before starting the task, it was made clear to the participants that at the end of the experiment, they would receive the accumulated money or food reward they saw during the experiment. Mean reward expectancy ratings in different phases of the task by the eight experimental groups are presented in Figure S1.

a complete description of the learning process. In particular, the difference in the ratings of the two conditioned stimuli in late reversal is a linear combination of these three indices.

Taken together, the scores of any participant on these three learning indices form a vectorial measure in the 3D space of her learning performance in our task. We performed a three-way multivariate analysis of variance (MANOVA) on the composite learning vector of all participants, with body weight status, reward modality, and gender as factors. There was a significant two-way interaction between body weight status

and reward modality ($p = 0.018$) and a nearly significant three-way interaction among all three factors ($p = 0.072$), and there were no main effects (all $p > 0.16$) or any other interactions (all $p > 0.64$). This suggests that, at the composite level, there was indeed difference between normal-weight and obese individuals and that the magnitude and/or the direction of the difference was also affected by reward modality and gender.

Based on these results, we constructed hypothesis-driven contrasts to test which groups were different from each other. Considering the significant interaction between body weight status and modality, we first compared obese individuals (both male and female) in the food condition to all other groups. This comparison revealed a significant difference ($p = 0.028$, step-down Bonferroni corrected, same for p values below), indicating a food-specific learning deficit. Given the trend toward significance of the three-way interaction, we next examined each gender separately. In women, the same contrast remained significant ($p = 0.039$), whereas in men, it did not ($p = 0.840$). Finally, we tested whether the performance of obese women in the food condition differed from the other seven groups. Indeed, the corresponding contrast was significantly different from zero ($p = 0.040$), suggesting that the impairment only existed in obese women.

After identifying this general impairment in associative learning with food reward in obese women, we turned to examine each individual learning index separately. The mean ACQ, ΔA , and ΔB scores of men and women are presented in Figure 2. The ACQ scores were significantly different from zero (separate two-tailed one-sample t tests against zero, all $p < 0.02$) for all groups except obese females performing the task with food reward ($p = 0.72$), indicating that the latter was the only group that, on average, failed to learn the reward contingencies in the acquisition stage. Following up on the MANOVA, post hoc Tukey tests showed that this group indeed had a significantly lower mean ACQ score (mean \pm SEM: -0.26 ± 0.71) than the normal-weight females in the food condition (2.16 ± 0.68 ; $p = 0.048$) and the obese females in the money condition (2.46 ± 0.57 ; $p = 0.027$), whereas the other seven groups did not differ from each other (all $p > 0.90$).

The inability to distinguish between the predictive values of the two conditioned stimuli could result from an underestimation of the CS+ value, an overestimation of the CS− value, or both. We therefore also examined the absolute ratings that produced the observed differences in ACQ scores between the experimental groups. Interestingly, whereas all eight groups provided almost identical ratings for the CS+, obese females in the food condition rated the CS− higher than the other groups (Figure S2). This suggests a generalization effect in which the high predictive value of the CS+ was erroneously spread to the CS− or a failure in inhibitory learning of the cue that was not reward predictive.

In the reversal stage, similar to ACQ, ΔA and ΔB scores were significantly different from zero or nearly so (separate two-tailed one-sample t tests: ΔA , all $p < 0.05$; ΔB , all $p \leq 0.05$) for all groups except obese females in the food condition (ΔA , $p = 0.39$; ΔB , $p = 0.32$; Figures 2A and 2B, middle and right). Whereas post hoc pairwise Tukey tests showed no significant difference in ΔA (all $p > 0.32$), obese females in the food condition had significantly lower ΔB scores than both normal-weight females in the same condition ($p = 0.003$; Figure 2A, right) and obese females in the money condition ($p = 0.013$). Conversely, normal-weight and obese males showed comparable performance in either reward modality

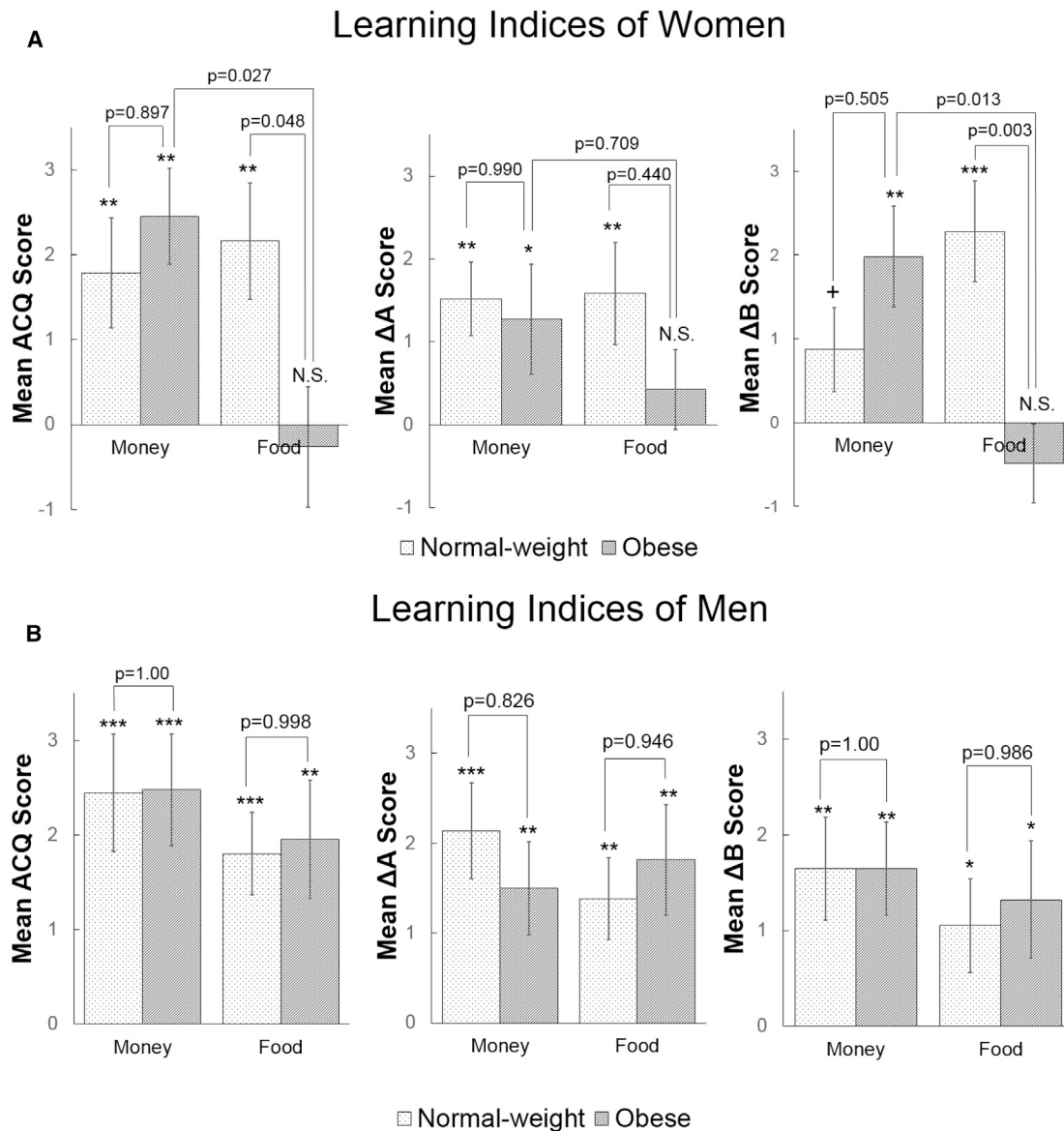


Figure 2. Learning Indices of Women and Men

Learning indices of women (A) and learning indices of men (B). Average learning indices of the normal-weight and obese participants performing the task with money and food reward are shown separately. Error bars represent SEM. The significance of two-tailed one-sample t tests against zero are shown above the error bars: + $p < 0.05$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. The significance of selected post hoc Tukey tests for pairwise comparisons is also presented with the exact p values. Obese females in the food condition failed to learn the initial associations in the acquisition stage (mean ACQ score versus zero, $p = 0.72$). They were also unable to decrease the reward expectancy upon seeing color A (mean ΔA score versus zero, $p = 0.39$) or increase the reward expectancy upon seeing color B (mean ΔB score versus zero, $p = 0.32$). Compared with normal-weight females in the same condition, their ACQ and ΔB scores were significantly lower (post hoc Tukey tests, ACQ $p = 0.048$, ΔB $p = 0.003$). They also performed significantly worse than obese females learning about money reward (post hoc Tukey tests, ACQ $p = 0.027$, ΔB $p = 0.013$). No difference in learning performance between normal-weight males and obese males was observed. Obese women's failure to learn the initial discrimination in the food condition can be described as a generalization effect (see Figure S2).

(Figure 2B). Because women tend to like and crave chocolate more than men [9], we also examined those participants who received pretzels rather than M&M'S, separately. The same pattern of behavior was observed, with obese women scoring lower on ACQ and ΔB compared to normal-weight women (six obese, five normal weight; ACQ: $p = 0.012$, ΔB : $p = 0.046$).

Association between BMI and Learning

So far, we have demonstrated that as a group, obese women were impaired in reward-based associative learning with

food. This impairment may have been driven by demographic, physiological, or psychological factors associated with obesity rather than the obesity status itself. To address this issue, we conducted stepwise multiple regressions with several candidate predictive variables in addition to BMI. These variables consisted of our demographic measures (age, income, and education), hunger level, and selected scores from three widely used self-report questionnaires on reward and punishment sensitivity (behavioral inhibition system/behavioral activation system [BIS/BAS] scale [10]),

Table 1. The Models for ACQ, ΔA , and ΔB Generated by Stepwise Regression for the Food Female Group

Dependent Variable	Variables Entered	Standardized Coefficients	Significance	Variables Removed
ACQ	BMI	-0.594	<0.001	income, age, education, BIS-11 perseverance, BIS-11 nonplanning impulsivity, TFEQ hunger
	hunger level	0.293	0.040	
	BIS-11 cognitive complexity	-0.690	<0.001	
	TFEQ disinhibition	0.514	0.002	
ΔA	BMI	-0.350	0.046	income, age, education, BIS-11 perseverance, BIS-11 nonplanning impulsivity, TFEQ hunger, TFEQ disinhibition
	hunger level	0.346	0.058	
	BIS-11 cognitive complexity	-0.433	0.02	
ΔB	BMI	-0.623	0.002	income, age, education, hunger level, BIS-11 nonplanning impulsivity, BIS-11 perseverance, TFEQ hunger
	BIS-11 cognitive complexity	-0.359	0.039	
	TFEQ disinhibition	0.433	0.026	

For each learning index, the variables entered, their standardized coefficients, and significance are presented. A list of removed variables is also included for each index, respectively. BMI entered the models of all three learning indices, and the standardized coefficients were all negative, indicative of a negative relationship between body weight status and associative learning with food reward. Hunger level, the cognitive complexity score from BIS-11, and the disinhibition score from TFEQ also entered the models of some indices. For the other three groups (food male, money female, and money male), BMI did not enter the model of any learning index. See [Table S2](#) for details.

impulsivity (Barratt impulsiveness scale [BIS-11] [11]), and eating behavior (three-factor eating questionnaire [TFEQ] [12]). The selected scores were those that were modulated by body weight status (see [Supplemental Experimental Procedures](#) for details). Separate regressions were conducted in each combination of gender and reward conditions (money male, money female, food male, and food female), collapsing across body weight status.

The results for the group of most interest, food female, are presented in [Table 1](#). For all three learning indices, BMI entered the model with high significance level (ACQ: $p < 0.001$; ΔA : $p = 0.046$; ΔB : $p = 0.002$). The regression coefficients for BMI in all three models were invariably negative, meaning that higher BMI was associated with poorer learning performance if other variables in the model were held constant. Among other candidate variables, disinhibition scores (from TFEQ), cognitive complexity scores (from BIS-11), and hunger level also entered the models for one or more learning indices (see [Table 1](#) for details). Conversely, BMI was not selected by the stepwise regression procedure to enter the model for any learning index in any of the three other groups (food male, money male, and money female; see [Table S2](#)). These results corroborated what we saw in the analysis of group means and provided strong support for the negative association between BMI and learning performance only in the food domain and only in women.

Discussion

Our results show that women classified as obese based on BMI are impaired in their ability to flexibly acquire and modify the predictive reward value of food cues. When food was used as reward, obese women were not, on average, able to discriminate the food predictive cue from the other cue. They also did not update the stimulus values after the switch in reward contingencies. Conversely, when money was used as reward, obese and normal-weight women exhibited comparable learning abilities. These findings provide the first evidence in humans for an association between obesity and a deficit in dynamic value learning specific to the food domain.

Obesity is a highly heterogeneous disorder that stems from a complex interaction of a myriad of causes, ranging from genetic [13], metabolic [14], and behavioral [15] factors at the individual level to economic [16] and cultural [17] factors at the societal level. Critically, the eight groups of participants

(normal weight/obese \times money/food \times male/female) were carefully matched for age, income, education, and self-reported hunger level, which are all factors that may influence reward-based associative learning and affect task performance. Follow-up analyses using stepwise regression also formally tested the validity of the link between BMI and learning performance by taking into account all these factors, as well as a range of personality traits and day-to-day eating habits. Crucially, the effect of BMI was enhanced in stepwise regressions that controlled for various demographic and personality factors. Moreover, BMI is a convenient but imperfect proxy for body weight status [18], and, thus, the observed association of reward learning with BMI is most likely an underestimation of its actual association with body weight status. This association was not driven by a single type of food item because comparable patterns of behavior were observed for both peanut M&M'S and pretzels. Finally, the potentially higher incentive value of the monetary reward compared to the food reward could not account for the results because there was no main effect of reward modality on the composite learning measure or on individual indices.

The specificity of the decreased learning to the food domain and the fact that it was only observed in women suggest that it is not a learning impairment per se but rather a more complex interaction among food, gender, and learning. A few recent studies of decision making and reward processing have also reported gender specificity. Obese women, but not men, showed greater delay discounting [19] and higher preference for immediate reward in the face of longer-term negative consequences, compared to their normal-weight counterparts, and these behavioral differences were associated with structural differences in striatum and dorsolateral prefrontal cortex [20]. Women were also less able than men to inhibit the desire to eat when the desire was elicited by food stimulation [21], and the inhibition was inversely correlated with BMI [22]. Domain specificity was suggested in a study that reported an association between percent body fat and impatient and risk-averse decisions about food, but not about money, in a group of mostly female participants [23]. By examining associative learning, our study provides an insight into the behavioral mechanisms that underlie gender differences in reward processing.

Our findings echo the animal literature on feeding behavior and associative learning. The use of a nonchoice quasi-Pavlovian paradigm, in which participants were provided

with only minimal information about the task, allowed us to directly compare our results with those of animal studies. Interestingly, rats on an unrestricted high-fat and dextrose diet showed impaired reversal learning with food, whereas rats on standard chow did not show this deficit [24], compatible with our results in humans. Future research is needed to unravel the neural mechanisms underlying these observed behavioral differences. In rats, the behavioral deficit was accompanied by neural changes in the hippocampus and the prefrontal cortex [24]. In humans, imaging and lesion studies have implicated regions of the prefrontal cortex, most notably the ventromedial prefrontal cortex and the orbitofrontal cortex, in value learning and updating [25–28]. An intriguing question is whether a dysfunction in these brain regions could account for the learning impairment in obesity.

It is important to note that the present results cannot inform us about causality. The food-specific learning impairment in women may be a consequence of obesity, a cause for obesity, or both. Obese individuals often struggle with dietary restraint, impulse inhibition, and difficult tradeoffs between weight control goals and the pleasure of food. The mere presence of food cues, such as the food images in our study, could trigger concerns in obese individuals, but not in normal-weight people, and these concerns may produce additional cognitive loads for obese individuals and thus hinder their learning. Such cognitive loads could be much higher for obese women because women in general are more dissatisfied with their body images [29]. This account is in line with a recent report of reduced cognitive function in individuals of low socioeconomic status, specifically when they are induced to think about everyday financial demands [30]. Alternatively, it is also plausible that preexisting impairments in the ability to flexibly update the predictive reward value of food-related cues in accord with changes in the external environment or the individual's internal state may lead to overconsumption of food. Such individuals may also be less responsive to information promoting healthy eating. These two accounts are not, of course, mutually exclusive. It could well be that obesity first leads to impaired learning, which in turn exacerbates the tendency to overeat, resulting in a vicious cycle in which flawed learning serves both as a cause for obesity and as its effect [31].

Identifying impairments in learning that are associated with overeating bears important clinical implications for possible behavioral interventions that are gender appropriate. Instead of focusing on reactions to the food itself, our results call for shifting attention to the way obese individuals learn about the environment and how they approach or ignore cues associated with food. Rather than target these individuals' behavior with food, we suggest that a successful intervention should aim to modify their interactions with other cues that determine their eating patterns.

Supplemental Information

Supplemental Information includes Supplemental Experimental Procedures, two figures, and two tables and can be found with this article online at <http://dx.doi.org/10.1016/j.cub.2014.05.075>.

Author Contributions

Z.Z., K.F.M., D.S., and I.L. designed the study and wrote the paper. Z.Z. and K.F.M. carried out the experiments. Z.Z. analyzed the data.

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