OVEREATING AND DECISION MAKING VULNERABILITIES

EDITED BY: Qinghua He, Yonghui Li, Xiao Gao and Hong Chen
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OVEREATING AND DECISION MAKING VULNERABILITIES

Topic Editor:
Qinghua He, Southwest University, China
Yonghui Li, Chinese Academy of Sciences, China
Xiao Gao, Southwest University, China
Hong Chen, Southwest University, China

Overeating is rapidly becoming a central public health challenge around the world. In this book, we assemble articles from a number of scientists who have made important contributions to this evolving field. This book dives into the basic underlying mechanism for overeating and decision-making vulnerabilities, and provides insights for weight management, treatment of overweight and obesity.

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EDITORIAL
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Editorial: Overeating and Decision Making Vulnerabilities

Qinghua He[1,2,3,4,5]*, *Xiao Gao*[1,2,4], *Yonghui Li*[3] and *Hong Chen*[1,2,4]

[1] *Faculty of Psychology, Southwest University, Chongqing, China,* [2] *Key Laboratory of Cognition and Personality, Ministry of Education, Southwest University, Chongqing, China,* [3] *Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China,* [4] *Chongqing Collaborative Innovation Center for Brain Science, Chongqing, China,* [5] *Southwest University Branch, Collaborative Innovation Center of Assessment Toward Basic Education Quality at Beijing Normal University, Chongqing, China*

Keywords: overeating, decision making, obesity, binge eating, anorexia nervosa

Editorial on the Research Topic

Overeating and Decision Making Vulnerabilities

Overweight and obesity are rapidly becoming a central public health challenge around the world (He et al., 2014a,b; He et al., 2015). For example, in the United States, nearly 65 % of adults are overweight or obese (Stein and Colditz, 2004). Overweight and obesity are associated with increased risk for cardiovascular/metabolic diseases, as well as several common adult cancers (Renehan et al., 2008). Because the fundamental cause of overweight and obesity is an energy imbalance between calories consumed and calories expended, the solution to this problem appears very simple: eat in moderation and engage in regular physical activity. However, this commonsense advice is difficult to follow for many people.

There is mounting evidence that the inability to resist calorie-rich and highly appetitive food represents a special case of addiction behavior (Chen et al.; Kelley and Berridge, 2002; Rolls, 2007; Trinko et al., 2007; Volkow et al., 2008). Similar to other drug addicts, poor decision making and impulse control may facilitate overeating, especially when faced with a constant supply of highly palatable food. This Research Topic aimed to gather a group of articles discussing the relationship between eating and decision making, including eating disorders like bulimia and anorexia.

With this scope, this research topic have assembled articles from a number of scientists who have made important contributions to this evolving field, including two Hypothesis and Theory articles (Chen et al.; Zhang and Coppin), one Protocol (Brevers et al.), and 7 original researches (Chen et al.; Lehner et al.; Li et al.; Lyu et al.; Vicario and Felmingham; Yan et al.; Zhang et al.).

HYPOTHESIS AND THEORY ARTICLES

We proposed a model of triadic neural systems for problematic eating in this research topic (Chen et al.). This model includes (a) a reward anticipation and processing system; (b) a reflective and inhibitory control system; and (c) an interoceptive awareness system. This model utilized similar tripartite neural models of Internet Gaming Disorder (Wei et al., 2017), pathological gambling and addiction (Noël et al., 2013a,b), and it had been demonstrated using fMRI techniques with dynamic causal modeling (He et al., 2019).

Zhang and Coppin analyzed the importance of memory in food valuation and choices in obese individuals (Zhang and Coppin). They described converging evidence on different forms of memory impairments accompanying obesity. Building on these findings, they formulate a general neuropsychological framework and discuss how dysfunctions in the formation and retrieval of memory may interfere with adaptive decision making for food.

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Edited and reviewed by:
Roumen Kirov,
Institute of Neurobiology (BAS), Bulgaria

Correspondence:
Qinghua He
heqinghua@gmail.com

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PROTOCOL

Brevers and colleagues proposed a research protocol aimed to explore the use of a mobile-phone application in treatment for obesity (Brevers et al.). This study protocol will run for 2 years with smartphone application collecting the 4 weeks use data, self-report measures, and participants' feedbacks.

ORIGINAL RESEARCHES

The 7 original research articles provided various angles for overeating and decision making vulnerabilities, including structural MRI (Zhang et al.), functional MRI (Chen et al.), eye movement (Lehner et al.), artificial intelligence (Li et al.), and survey/behavior assessment of patients (Lyu et al.; Vicario and Felmingham; Yan et al.).

Using structural MRI and voxel-based morphometry (VBM) method, Zhang et al. investigated the difference of gray matter volume (GMV) between obese participants and controls. Results suggested that obese men only showed a significantly increased GMV in the left putamen. Further analysis suggested that the GMV of left putamen could predict the BMI and insulin level.

Using functional MRI, Chen et al. measured brain activity of undergraduate young females when they performing a food rating task. They rated various kinds of food on their taste, healthy, and willingness to eat. Behavioral results showed a positive correlation between taste rating and willingness to eat, a negative correlation between healthy rating and emotional eating, as well as a positive correlation between taste rating and external eating. MRI data suggested that activity in DLPFC were positively correlated with successful self-control; and activity in midcingulate cortex was positively correlated with failed self-control.

Lehner et al. investigated the group difference of eye movement during Pavlovian conditioning to measure the incentive salience amongst normal-weight, overweight, and obese individuals (Lehner et al.). Results showed that the goal-directed behavior of overweight individuals was more strongly influenced by food-predicting cues than that of normal-weight and obese individuals. The fixation style also exhibited a complex interaction with the weight category.

Li et al. proposed an intelligent recommendation techniques for consumers' food choices in restaurants (Li et al.). Results suggested that this artificial intelligence based technique can provide effective dish recommendation for customers. This system could be used to aid food choices for obese individuals.

The study by Lyu et al. hypothesized that women with binge eating would show greater deficits in response inhibition than control group tested by flanker task (Lyu et al.). Results suggested that they responded slower for incongruent trials than congruent trials, while no difference were detected for controls.

Similarly, Yan et al. investigated the associations between decision-coping patterns, monetary decision-making, and binge-eating behavior in a large sample of college students (Yan et al.). Results suggested that, compared with the non-binge-eating group, the binge-eating group displayed elevated scores on maladaptive decision-making patterns.

Lastly, study by Vicario and Felmingham investigated the time perception in adolescent with anorexia nervosa (Vicario and Felmingham). Results suggested patients with anorexia nervosa displayed lower timing accuracy than controls.

The wealth of theories, protocol, and original researches covered by the authors in this research topic uncovered the basic underlying mechanism for overeating and decision making vulnerabilities. We hope to provide some insights for weight management, treatment of obesity and related disorders through this window.

AUTHOR CONTRIBUTIONS

QH and XG wrote the first draft. YL and HC made critical revision. QH, XG, YL, and HC approved the final version of the manuscript.

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HYPOTHESIS AND THEORY
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Decision Making Deficits in Relation to Food Cues Influence Obesity: A Triadic Neural Model of Problematic Eating

Rui Chen[1†], *Danni P. Li*[2,3,4*†], *Ofir Turel*[5,6], *Thomas A. Sørensen*[4,7], *Antoine Bechara*[6], *Yonghui Li*[3,8] *and Qinghua He*[1,6,9*]

[1] Faculty of Psychology, Southwest University, Chongqing, China, [2] Sino-Danish Center for Education and Research, Beijing, China, [3] Department of Psychology, University of Chinese Academy of Sciences, Beijing, China, [4] Center of Functionally Integrative Neuroscience, Institute for Clinical Medicine, Aarhus University, Aarhus, Denmark, [5] College of Business and Economics, California State University, Fullerton, Fullerton, CA, United States, [6] Department of Psychology, University of Southern California, Los Angeles, CA, United States, [7] Department of Communication and Psychology, Centre for Cognitive Neuroscience, Aalborg University, Aalborg, Denmark, [8] Institute of Psychology, Chinese Academy of Sciences, Beijing, China, [9] Chongqing Collaborative Innovation Center for Brain Science, Chongqing, China

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Edited by:
Roumen Kirov,
Institute of Neurobiology (BAS),
Bulgaria

Reviewed by:
Susana Jiménez-Murcia,
Hospital Universitario de Bellvitge,
Spain
Eva M. Conceição,
University of Minho, Portugal

***Correspondence:**
Danni P. Li
dpengli92@gmail.com
Qinghua He
heqinghua@gmail.com

† These authors have contributed equally to this work.

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In this review article we propose a model of the brain systems, the deficiency of which may underlie problematic eating. This integrative model is based on studies that have focused on discrete brain components involved in problematic eating, combined with insights from studies on the neurocognitive basis of other addictive and problematic behaviors. The model includes: (a) a hyper-functioning reward anticipation and processing system (amygdala-striatum dependent) in response to food-related cues; (b) a hypo-functioning reflective and inhibitory control system (prefrontal cortex dependent), that fails to anticipate and properly weigh future outcomes; and (c) an altered interoceptive awareness system (insular cortex dependent) that translates homeostatic violation signals into a strong consumption desire that hijacks the inhibitory system and excites the reward system. We posit that when the abovementioned systems are imbalanced in such a way that the dopamine axis is hyperactive in relation to food cues and the inhibitory system is weak, and this is further aggravated by an altered interoceptive awareness system, people may experience loss of control or inability to resist tempting/rewarding foods. This loss of control over food consumption can explain, at least in part, the development of excess weight and contribute to the obesity epidemic.

Keywords: obesity, impulsive system, reflective system, interoceptive system, tripartite model of addictive behaviors, prefrontal cortex, insular cortex, amygdala-striatum system

INTRODUCTION

Obesity ($BMI = kg \cdot m^{-2} > 30$) is one of the most serious health issues in the developed world; it affects approximately 500 million people (1). In high-income English-speaking countries, 70% of the population were overweight ($BMI > 25$) or obese in 2014. In China, the absolute number of obese individuals has now surpassed the number in the United States, making China the most obese country in the world (2). Obesity and overweight are major risk factors for developing multiple lifestyle diseases such as hypertension, type II diabetes mellitus, metabolic syndrome, and cardiovascular diseases (3). They therefore have major financial implications for people and nations (1).

Obesity can be viewed as a chronical lifestyle disorder caused by overconsumption of calories relative to calorie expenditure. It is a multifactorial problem affected by environment, culture, socio-economic status, and genetics (4). Recent research has indicated that obesity may be, at least partially, rooted in decision-making deficits in relation to food; and that such deficits resemble those observed in other addictive and problematic behaviors. That is, a strong "wanting" of food, combined with poor inhibition and foresight abilities, can explain why some people overconsume food. The terms "food addiction" and/or "eating addiction" encapsulate this perspective and imply that the rewarding and reinforcing properties of foods combined with the way humans decide on food consumption, make excessive food consumption similar to the consumption of rewarding substances, or to the enactment of other addictive behaviors (5–10).

In support of this perspective, animal studies have demonstrated that there are similarities between the neural mechanisms that underlie substance addiction and excess food consumption. For example, Johnson and Kenny (11) showed that highly palatable and processed foods may trigger biological changes in the mesolimbic pathways (part of the reward system) of obese rats. Striatal dopamine D2-receptors were downregulated in obese rats compared to in their lean counterparts, thereby triggering compulsive eating behavior and addiction-like neuro-adaptive responses.

Neuroimaging studies in humans have also provided evidence for similarities between substance and behavioral addictions and excess food consumption. Volkow et al. (12) reviewed the overlapping neural circuits in addiction and obesity; they showed that both drugs and palatable food can act on reward, motivation, learning, and inhibitory control systems. In further support of this view, a meta-analysis by Garcíagarcía et al. (13) included 87 studies and mapped the blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) response to reward in participants with obesity, substance addiction and non-substance addiction, including pathological gambling and Internet gaming. They observed various overlaps between obesity and substance addictions in BOLD activations, but fewer commonalities between non-substance related addictions and obesity were found. These results indicate that it is likely that at least some obese individuals can share similar neurological and physiological impairments in the reward circuitry of their brains with substance addicts.

Due to the possible similarities between substance and behavioral addictions and excess food consumption, we propose a triadic neurocognitive model of excess food consumption and the resultant obesity. This model is based on research from the substance addiction domain combined with anecdotal evidence regarding brain systems that can underlie excess food intake and obesity.

THE TRIADIC NEUROCOGNITIVE SYSTEM

Individuals suffering from addictive disorders are characterized by compulsive drug- or behavior-seeking conduct, despite facing negative consequences such as financial and emotional problems when they continue with substance-consumption or addictive-behavior enactment. These addictive behaviors are often viewed as rooted in impaired behavioral learning processes, strong and uncontrollable impulsions, weak self-regulation, and impaired decision-making abilities (14–18). These impairments reflect a simplistic dual system view of addictions, which portrays the imbalance between a hyperactive bottom-up impulsive reward system and a hypoactive top-down reflective control system as the decision-making deficit that subserves over consumption of substances and enactment of behaviors (19). However, recently a more refined hypothesis has been proposed, that addictions are also subserved by a disrupted insula-mediated interoceptive awareness system (20, 21). The impulsive and reflective systems together reflect a dual-process view, in which one (the impulsive system) is faster, autonomic, and subconscious, and the other (the reflective system) is slower, deliberative, and conscious (22, 23). Adding the interoceptive awareness system creates a triadic model. This interoceptive awareness system integrates homeostatic signals, thereby regulating processes of the dual-process system (24) and subserving behaviors through the subjective feelings of urges /cravings that it mediates (25). Evidence has been accumulating regarding the viability of the triadic system perspective for explaining excessive behaviors (26, 27), as well as regarding the role of the interoceptive awareness system in decisional deficits (28)

If indeed food overconsumption can be viewed as a decision making deficit that is similar to substance addictions in that it is rooted in an imbalance between the abovementioned three systems, then a tripartite model of decision making in relation to food cues can explain the loss of control or inability to resist tempting/rewarding foods (and the resultant obesity). Based on this perspective, food-related stimuli can trigger bottom-up involuntary habitual desire mediated by the amygdala-striatal system, the goal-driven reflective system can fail to anticipate future outcomes of food overconsumption and/or fail to inhibit excess food intake, and this imbalance can be exacerbated by an altered interoceptive awareness system that hijacks inhibition/reflection resources and excites the impulsive system.

The aim of this mini-review is to provide initial support for this perspective. To do so, we integrate evidence regarding an impaired triadic system in individuals with problematic or disordered eating. Our proposed neurocognitive model of problematic eating is depicted in **Figure 1**. We suggest that the portrayed imbalance can provide one reasonable explanation for excess food intake.

The Impulsive System

The development and maintenance of addictions can be explained via the incentive salience theory, which couples classical Pavlovian conditioning principles (29, 30) with associative learning mechanisms by automatically

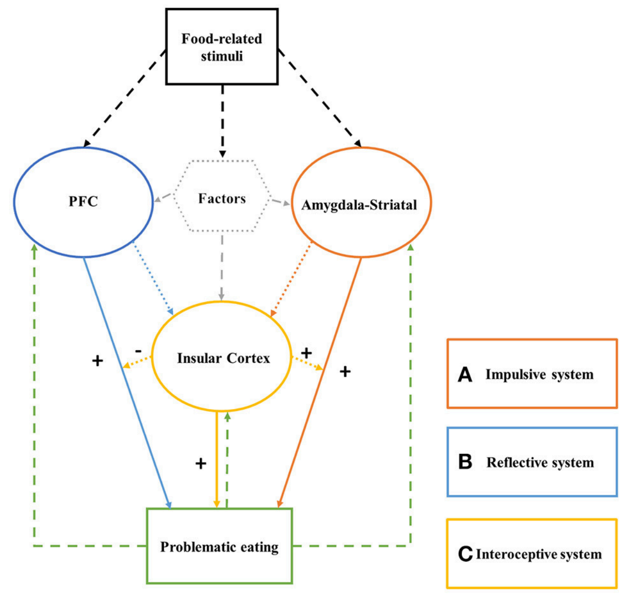

FIGURE 1 | The Triadic System of problematic eating consists of: (a) a hyper-functioning impulsive system; (b) a hypo-functioning reflective/inhibition system; and (c) an altered interoceptive awareness system. After exposure to food-related stimuli, the impulsive system generates fast, automatic, unconscious, motivation to consume the food. The reflective system, if intact, considers future outcomes of this act, and inhibits it as needed. The interoceptive awareness system acts as a modulator of the impulsive and reflective system effects; its activation excites the impulsive system and "hijacks" the cognitive resources the reflective system requires for reflecting on and inhibiting food consumption.

generating drug- or gambling-related action and craving (19). Environmental cues that trigger such responses are mediated by subcortical structures of the basal ganglia and its cortical inputs. Specifically, the dopamine-dependent striatum-amygdala neural circuit promotes habitual, incentive-motivational and salient behaviors in response to non-natural rewards [e.g., psychoactive drugs; see (31)], natural rewards (e.g., food, and sexual intercourse) (32) and behavioral cues (33–36).

Addictive substances, including highly palatable foods, can sensitize vulnerable reward systems to food stimuli and lead to hyper–activation. Eating can lead to the release of dopamine in the ventral tegmental area (VTA) and its transmission to the nucleus accumbens (NAcc; a part of the ventral striatum), which in turn, translates it into release of opioid peptides that make people feel good. Learning to expect and subconsciously anticipate such rewards from food consumption induces in some people strong motivational states for food intake, which, if remains unchecked or uninhibited, can drive excess eating (37).

Indeed, increased activation in the amygdala-striatal area has been reported in many fMRI studies that used food-related stimuli. For example, obese individuals had greater activation in brain areas associated with reward processing when exposed to visual food cues compared to lean individuals, but without food stimulation this activation was decreased (38–40). Morris and Dolan (41) reported a PET study according to which the activation of the left amygdala and the right anterior orbitofrontal cortex (OFC) correlated positively with recognition memory for food items and the activation of the right OFC was negatively correlated with recognition memory for non-food items. Ng et al. (42) found that compared to lean people, obese people show higher activity in somatosensory (Rolandic operculum), gustatory (frontal operculum), and reward valuation (amygdala) regions, and in the ventromedial prefrontal cortex (vmPFC) in response to intake and anticipated intake of a milkshake vs. a plain drink. Similarly, He et al. (43) used a food-specific go/nogo task to measure the inhibitory control ability of high BMI participants. Results indicated that high BMI participants responded faster in go trials related to high-calorie food images, compared to the go trials related to low-calorie food images. In nogo trial, these participants expressed stronger difficulty to inhibit their responses. In addition, fMRI results showed that the right striatum was more active in go trials focusing on high-calorie food images, and that the PFC was more active in nogo trials; PFC activation negatively correlated with subjects' BMI. Contrerasrodríguez et al. (44) examined potential abnormal functional connectivity in obese people. They found that overweight participants displayed increased functional connection between the ventral striatum and the medial prefrontal and parietal cortices; and between the dorsal striatum and the somatosensory cortex. Moreover, these participants' connectivity of the dorsal striatum was associated with food craving and can predict BMI increases. These results support the view that a hyper-responsivity of the impulsive system (and a deficit in the reflective system) may promote excess, impulsive eating behaviors.

Likewise, Coveleskie et al. (45) have examined the structural/anatomical differences between obese women and lean controls. Voxel-Based Morphometry (VBM) analysis revealed significantly greater gray matter volume (GMV) in the NAcc in the high BMI-group compared to the control group. This suggests that brain structures, and specifically increased GMV in the areas associated with the impulsive reward system, may be a marker for obesity and essentially food "addiction."

Collectively, such studies indicate that the impulsive system likely plays an important role in processes that automatically gauge the value of food-related stimuli and generates motivational consumption states. This motivational state, if not assessed and inhibited properly, may result in problematic eating.

The Reflective System

The impulsive system is indeed a key mediator of the "wanting" component during reward anticipation and processing; it creates strong incentive-motivation to act. However, it does not account for controlling the "wanting" and acting upon it. These are regulated by the reflective system, which includes vmPFC, anterior cingulate cortex, dlPFC, and lateral orbitofrontal/inferior frontal gyrus (32). The PFC is involved in decision-making, executive functions, forecasting flexible future outcomes, and controlling the action drives mediated via the impulsive system (46). Indeed, damage to this area impairs decision-making abilities; it results in reckless decisions without sufficient consideration of the consequences of the behavior (47).

The reflective system is based on the integration of two functions that are mediated via two neural sub-systems; "cool" executive functions and "hot" executive functions (48). "Cool" executive functions are mediated via the dorsolateral prefrontal cortex (dlPFC) and anterior cingulate cortex (ACC), and involve inhibitory control, basic working memory, analytical thinking, cognitive flexibility, and the maintenance and updating of new relevant information (49). This view is in congruence with theories of economic decision-making, according to which humans are rational, reflective, and goal-directed decision-makers. In contrast, "Hot" executive functions integrate emotions into decision making, and are mediated by the ventromedial PFC (vmPFC) and the OFC. These structures are involved in eliciting somatic states from memories and knowledge, which in return initiate emotional and affective responses (50), and consequently are based on one's "gut-feeling," intuition, and heuristics (51). Adequate decision-making often involves an integration of the "cool" cognitive and "hot" emotion-involved systems; it relies on one's ability to more optimally evaluate probable outcomes of an action by weighing short-term gains against long-term, often more uncertain, losses (52, 53).

A growing body of fMRI studies has examined the abnormal function of the reflective system in obese people. Le et al. (54) compared the activation of the left dlPFC in lean and obese people following a meal. They discovered lower activity in obese people. A meta-analysis conducted by (55) examined the most common functional differences between normal-weight and obese people responding to food stimuli. The results indicated that obese participants had increased activation in the left dorsomedial prefrontal cortex, right parahippocampal gyrus, right precentral gyrus, and right anterior cingulate cortex, as well as reduced activation in the left dlPFC and left insular cortex. This decreased activation may be indicative of the notion that obese people have weaker inhibitory control and interoceptive awareness when exposed to food-related stimuli, compared to people in the normal weight range. Combining such inhibitory deficits with high sensitivity to food stimuli, often presented by obese people, can provide a neurocognitive account for problematic eating and consequent obesity.

An fMRI study investigating unhealthy food choices (43) found that increased activity in the PFC and reduced activity of the insula were positively correlated with high consumption of vegetables. In contrast, consumption of high calorie foods correlated with reduced activity of the PFC and elevated activity of the insula. These results indicated that in order to make healthy food choices, people have to spend more cognitive resources encapsulated in the reflective system. Moreover, Verdejo-Román et al. (56) found less effective functional connectivity between frontal areas responsible for cognitive control and striatal areas involved in reward anticipation and processing in obese individuals who performed a food-based reward task. This suggests that the reward circuitry of obese people is incongruent with the cognitive control areas, thus making obese individuals' self-regulation ability poor when trying to control consumption of palatable foods.

Structural imaging studies using VBM also support this perspective (57, 58). Specifically, a longitudinal study (59) examined a total of 292 obese and normal weight subjects over two time-points, 5 years apart. Obese subjects had significantly smaller total brain volumes (with no difference in white matter; or cerebrospinal fluid). The most robust finding in their study was the reduced GMV in dlPFC in obese people, which can be indicative of poor foresight and risk assessment, and is common in other addictions (60).

Taken together, these studies indicate that obese individuals may have a hypo-functioning reflective system, which can manifest structurally through decreased GMV in key regions of the reflective system. This again points to possible similarities between problematic eating and other addictive behaviors.

The Interoceptive-Awareness System

The third and final component in the tripartite model is an interoceptive awareness system, which is primarily insular cortex dependent. This system is reciprocally connected to several limbic regions including the vmPFC, the amygdala, and the ventral striatum (61). Besides being the primary taste area in the brain (4), it has recently been argued that the insular cortex may contribute to the onset and maintenance of addiction by integrating and translating interoceptive, somatic signals into subjective experiences like the feeling of anticipation, desires, urges, or cravings (53). These interoceptive manifestations can potentiate the activity of the impulsive system, and simultaneously weaken the goal-driven cognitive functions mediated by the reflective system. In other words, interoceptive signals can "hijack" the cognitive resources of the reflective system that are required for executing inhibitory control over tempting behaviors, such as eating high-calorie dense foods.

This view is supported by fMRI studies showing increased insular activity in response to food-related stimuli. According to Simmons et al. (62) and Frank et al. (63), when presented with high calorie pictures of food, subjects show increased activity in the insular cortex and the OFC. In a recent review article (64), neural responses to visual food cues according to weight status were analyzed. Findings indicated that both the insula and OFC have increased activity in obese subjects in a majority of the sixty fMRI studies they reviewed. In addition, increased brain response to appetitive tastes in both the insula and the amygdala have been demonstrated in satiated obese compared with satiated healthy weight children (65). Deficient emotion regulation can also be associated with obesity. Steward et al. (66) asked participants to modulate their negative emotions induced by negative pictures. Overweight participants continuously displayed high activation in the right insula. Functional connectivity between the right insula and right dorsal lateral PFC and dorsal medial PFC was less effective in overweigh participants compared to normal-weight participants.

Studies of adolescent obesity indicated that the activation of the insula was positively correlated with interoceptive sensitivity in obese adolescents, but negatively correlated with interoceptive sensitivity in healthy-weight adolescents. While in healthy weight adolescents insular activation negatively correlated with external eating, it positively correlated with external eating in obese adolescents (67). Although the insula activated in both healthy and overweight adolescents, it reflected different mechanisms in these groups. The interoceptive insensitivity in obese people may explain increased food consumption; this consumption serves as a means to achieve equal satiation to this experienced by normal weight individuals.

VBM studies also support the hypothesis that obese or individuals with disordered eating have similar structural differences in the GMV and white matter in the insular cortex as substance addicts. Both Shott et al. (68) and Jauchchara et al. (69) studied gray and white matter densities in obese cases vs. lean controls. They both found that areas associated with the impulsive system (striatum and putamen) and the interoceptive awareness system (the insula) had reduced GMV [and associated white matter in (68)] in obese subjects. Smucny et al. (70) however, have shown that the reduction in insular GMV also can be seen in lower ranges of BMI. After controlling for age, sex, and total GMV, the results showed that obesity-prone people had reduced GMV in the OFC and insula compared to obesity-resistant subjects. They also found that GM volume in the insula was inversely correlated with reported ratings of hunger after a meal and inversely correlated with plasma leptin concentration. These findings illuminate the importance of and associations between GMV, homeostatic and hormonal responses, as related to food intake.

Other than obesity, studies also showed that the following factors can be associated with differences in the activity of the insula; and indirectly influence impulsive and reflective system functions.

An Eating Disorders Factor

Brain imaging studies showed that abnormal activity of the insula exists in different eating disorders. When presented with food stimuli, the OFC, ACC and insula exhibited increased activation in all participants. However, eating disorder patients showed stronger medial OFC activity, whereas bulimic patients presented greater activation of both the ACC and the insula (71). Furthermore, Kim et al. (72) measured the functional connectivity of the anterior insula in both anorexia nervosa (AN) and bulimia nervosa (BN) and reported that the left anterior insula was significantly connected with the right insula and right inferior frontal gyrus in the AN group. Nevertheless, in the BN group, the left anterior insula showed significant connection with the medial OFC.

VBM studies examining recovered AN and BN patients (who had to be symptom-free for a minimum of 2 years) (73) found that recovered patients had increased insular GMV volume compared to women without any history of eating disorders. However, a study investigating WM in actual BN patients found decreased fractional anisotropy in the bilateral corona radiata extending into the posterior limb of the internal capsule, corpus callosum, and right sub-insula (74). These results collectively underline the differences within the spectrum of disordered eating; and more importantly emphasize the possible association between diet and eating behavior's and the GMV in the insula and insula-associated areas.

Satiation and Deprivation Factors

The distinction between different somatic states, specifically hunger vs. fullness, also seem to be an important factor for insular activity. A meta-analysis including ten fMRI studies examining the non-fasted neural response to food stimuli in obese vs. lean subjects found significant evidence for reduced activation in the left dlPFC and the left insular cortex (55). However, it has also been suggested that food cue presentation can significantly increase activation in superior temporal, anterior insula, and orbitofrontal cortices during a fasting state (75), and that increased activation of OFC was positively correlated with ratings of hunger. Moreover, Uher et al. (76) found that the response to taste stimuli in the left anterior insula was significantly stronger during a fasting state compared to in the satiated state in healthy normal weight individuals. Similarly, healthy satiated females demonstrated increased activity in both lateral and medial OFC, PCC, caudate, putamen, fusiform gyrus, and the insula when responding to low calorie food cues. In contrast, activation during a deprivation state was related to reward processing areas increases following the presentation of high calorie food cues (77).

Thus, it may be especially important to acknowledge differences in insular activity during deprivation vs. satiation, regardless of the type of the deficient decision-making context (e.g., drugs, food, addictive behaviors). In line with these findings, recent result indicated that the reflective system (Specifically dlPFC and ACC) was engaged when participants tried to control food-related responses in an fMRI food-specific go/nogo task (He et al., under review). It was also found that the vmPFC was activated in inhibitory control attempts executed when the participants were satiated. In addition, these results revealed that the insular cortex was significantly more active during deprivation vs. during satiation states. Importantly, these changes were more pronounced in participants with higher BMI compared to their lean counterparts. Hence obese individuals may be hypersensitive to interoceptive/somatic signals of hunger, following an increased positive alliesthesia (the affective part of sensation), incentive-salience and craving for food cues, as well as being insensitive to interoceptive/somatic signals of satiation (78). Collectively these studies indicate that deprivation vs. satiation can modulate insular activity in all people, but especially among obese individuals.

CONCLUSION AND FUTURE DIRECTIONS

The proposed triadic neurocognitive model of problematic eating includes three systems. First, the impulsive system contains the amygdala-striatal circuits. It processes reward expectations and production in response to food-related cues and/or food consumption. Second, the reflective system includes the PFC and its sub-regions. It mediates planning, anticipation of future outcomes and behavior inhibition processes. Lastly, the interoceptive awareness system includes the insula. This system translates homeostatic and interoceptive signals into self-awareness regarding desires/urges/cravings; presumably also in relation to food cues and satiation/hunger states.

As individuals develop social expectations and norms, as well as the ability to set long-term goals, the reflective system can inhibit the action motivation generated via the impulsive system if this action is deemed as sub-optimal. When the systems are balanced, there are no major decision making deficits beyond typical biases [e.g., social desirability bias, framing bias, sunk cost bias, etc.; see Uher et al. (79)]. However, when the impulsive system is hyperactive and the reflective system is hypoactive, the behavior, in our case food consumption, becomes impulsive, unplanned, disadvantageous, disordered, and problematic. The interoceptive awareness system extends this view, because it can occupy the reflective system and suppress the inhibitory control function, and simultaneously further excite the impulsive system. Under such circumstance, the existing imbalance or gap between the strength of the impulsive and reflective systems widens, and the behavior patterns becomes much more impulse-driven (26). Together, these decision making deficits can influence over-consumption of food and ultimately obesity.

Although in this article we portray a triadic model of problematic eating, which may influence obesity based on addiction research, it is critical to consider the fact that individuals with problematic eating can be neurologically different from individuals with substance addiction. Moreover, in comparison to drug cues, cues associated with food are multimodal and less salient in terms of their interoceptive effects. Palatable foods may begin as relatively strong reinforcers compared to drugs, but cocaine and other drugs create implicit associations that last longer than associations between stimuli paired with natural reinforcers such as food (80, 81). Hence, despite the many similarities between substance and food consumption, more research is needed to shed light also on possible differences between neural deficits that may subserve excessive food and substances intake.

This need for more research is exacerbated by the fact that the intersection between neural mechanisms of the proposed triadic model and excess food consumption is relatively new, yet has the potential to produce strong theoretical and practical implications. For example, understanding the neural systems sub-serving excess eating can lead to pharmacological- or cognitive-behavioral therapies that may help excess eaters to overcome their food indulgence. Moreover, such future research is also of social importance, because it would potentially help society to understand how and why some individuals are more vulnerable to environmental food related cues, not simply from a conventional dietary perspective, but also from a decision-making standpoint. We hence call for more research on obesity from a neurocognitive decision making perspective. Last, the proposed neurocognitive model still requires empirical support and possible fine-tuning, because physiological aspects can also play an important part of weight management, and hormones can impact interoception of satiety and hunger. Such aspects should be included in extension of the model proposed here; and we call for future research to account for such extensions.

AUTHOR CONTRIBUTIONS

OT, TS, AB, YL, and QH conceived the model and study structure. RC and DL wrote the first draft. OT, TS, AB, YL, and QH made critical revisions. All authors approved the final version of this manuscript.

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To What Extent Memory Could Contribute to Impaired Food Valuation and Choices in Obesity?

Zhihao Zhang[1,2]* and Géraldine Coppin[3,4,5]*

[1] Haas School of Business, University of California, Berkeley, Berkeley, CA, United States, [2] Department of Neurology, University of California, San Francisco, San Francisco, CA, United States, [3] Swiss Center for Affective Sciences, University of Geneva, Geneva, Switzerland, [4] Laboratory for the Study of Emotion Elicitation and Expression, Department of Psychology, University of Geneva, Geneva, Switzerland, [5] Department of Psychology, Distance Learning University Switzerland (Unidistance), Brig, Switzerland

Obesity is associated with a diverse array of cognitive and affective deficits, among which impairments in food valuation and choices have received increasing attention. The neural underpinnings of such impairments, however, remain poorly understood, partly because a complete understanding of these processes under normal conditions has yet to be achieved. A rapidly growing literature on the interaction between memory and decision-making has begun to highlight the integral role of memory in decision making especially in the real world, as well as the role of the hippocampus in supporting flexible decision making. Perhaps not coincidentally, altered memory performances in obesity have been well documented, and the underlying neurobiological bases of these memory alterations have also started to be better described, involving pathologies at the biochemical, cellular, and circuit levels. Despite such correspondence, the link between memory impairments and food valuation/choice deficits in obesity has received little attention. In this article, we first summarize the growing empirical support for the relevance of memory for decision making, focusing on flexible value-based decisions. We then describe converging evidence on different forms of memory impairments accompanying obesity. Building on these findings, we formulate a general neuropsychological framework and discuss how dysfunctions in the formation and retrieval of memory may interfere with adaptive decision making for food. Finally, we stress the important practical implications of this framework, arguing that memory deficits are likely a significant contributor to suboptimal food purchase and eating behavior exhibited by obese individuals.

Keywords: obesity, memory, value-based decision making, food, hippocampus, episodic memory, semantic memory

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Xiao Gao,
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Institute of Psychology (CAS), China
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Correspondence:
Zhihao Zhang
zhihao.zhang@haas.berkeley.edu
Géraldine Coppin
geraldine.coppin@unige.ch

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INTRODUCTION

Obesity, characterized by excessive accumulation of body fat as a result of disrupted energy intake and expenditure, shows worldwide epidemic that threatens the health and well-beings of many individuals – life expectancy is decreased by 7 years at the age of 40 (Peeters et al., 2003) and in the United States only, between 280,000 and 325,000 deaths could be attributed to obesity annually (Allison et al., 1999). Rates of obesity worldwide are still rising, and nowadays, there are more overweight than underweight individuals (NCD Risk Factor Collaboration [NCD-RisC], 2016), and the economic cost of obesity for the United States alone is estimated to exceed $275 billion annually (Spieker and Pyzocha, 2016).

Apart from dysfunctions in metabolism, obesity is associated with several cognitive and affective deficits (Elias et al., 2003; Rochette et al., 2016), which have become increasingly well documented. These deficits include those in associative learning (Coppin et al., 2014; Zhang et al., 2014), memory (Gunstad et al., 2006), attention (Cserjesi et al., 2007; Mobbs et al., 2011), and executive functions (Gunstad et al., 2007; Smith et al., 2011). Such deficits have important ramifications as they might exacerbate obesity through their impact on behavior. Out of these diverse behavioral deficits, decision making impairments appear to be robust and consistent across many studies (Davis et al., 2004; Alonso-Alonso and Pascual-Leone, 2007; Jarmolowicz et al., 2014; Amlung et al., 2016), although a large amount of heterogeneity exists under the umbrella of decision-making. Importantly, despite a growing volume of data [see (Wu et al., 2016) for a recent meta-analysis], it remains unclear what the underlying behavioral or neural drivers of such impairments in decision making are.

Among the decision making deficits in obesity in various types of tasks and paradigms, of particular interest are choices regarding food because of their impact on the energy intake. Increasing evidence shows that the consumption of food is driven not only by basic metabolic needs, but also to a large extent by hedonic aspects (Kenny, 2011), highlighting the importance of understanding food-related decision making from a cognitive perspective. In a general sense, decision making can be defined as the cognitive processes that lead to a choice between alternative options or courses of action. A common theoretical framework widely used for modeling and analyzing decision-making assumes that the choice between available options is "on *the basis of a subjective value that [the agent] places on them*" (Rangel et al., 2008), namely a process of *value-based* decision making. The success of such framework lies in its close link to existing theories in economics and psychology (Samuelson, 1948; Tversky and Kahneman, 1981) and its applicability to a remarkably wide range of choice situations in both the laboratory and real life. Furthermore, converging evidence in decision neuroscience also points to the existence of a 'valuation system' in the human brain (and probably in brains of other animals as well) including the ventromedial prefrontal cortex (vmPFC) and the ventral striatum (Bartra et al., 2013; Clithero and Rangel, 2014). The activities in these regions apparently encode subjective value signals that seem to be independent with the exact identity or category of the option (Zhang et al., 2017), providing further support for the notion of value-based decision-making.

This framework offers promise in uncovering the mechanisms of suboptimal decision-making with food in obesity. Using neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), a well-established literature has shown altered brain reward value responses and dopaminergic activities in obesity (Stice et al., 2008; Volkow et al., 2011; Frank et al., 2012; Babbs et al., 2013; Eisenstein et al., 2013; Guo et al., 2014). These alterations may further be coupled with structural and connectivity changes in the valuation system (Marques-Iturria et al., 2015; Shott et al., 2015). However, rather than an ultimate mechanistic answer to why obese individuals sometimes make suboptimal decisions, these findings should be more appropriately viewed as a step forward, which raises deeper and more challenging questions: If value for certain food items goes awry in obese individuals, why are they not able to get it right in the first place? What goes wrong in the construction and maintenance of value?

In this article, we argue that disruptions in memory mechanisms are likely a key contributor to suboptimal food-related decision making in obesity. To support this claim, the rest of the article is organized as follows. We will first briefly summarize empirical evidence of changes in the valuation system in obesity and point out why this is insufficient for fully understanding both the cause and the scope of changes in decision making in obesity. We will then review the growing literature investigating how memory and hippocampal processes support value-based decision making. This will be followed by a survey of the existing evidence that demonstrates memory impairments in obesity and the accompanying dysfunctions in the hippocampus and related neural circuits. Building on these two lines of research, we will propose a general neuropsychological framework and discuss how dysfunctions in the formation and retrieval of memory may interfere with adaptive decision-making. Finally, we explore the real-world applications of this framework and discuss the possibility that memory deficits contribute to suboptimal food purchase and eating behavior exhibited by obese individuals.

SUBOPTIMAL FOOD CHOICES IN OBESITY: THE NEED FOR GOING BEYOND THE VALUATION SYSTEM

A great deal of effort has been devoted to investigating how the reward value of food might be processed differently in obesity. Compared with healthy-weight controls, obese individuals show heightened activation of value-related brain regions in response to food-associated cues (Gautier et al., 2000; Rothemund et al., 2007; Stice et al., 2008; Stoeckel et al., 2008; Dimitropoulos et al., 2012; Rapuano et al., 2016), consistent with the notion that over-valuation of food, especially palatable food, may be a key neurocognitive component of obesity. Meanwhile, a large body of literature reports blunted neural responses during food reward receipt in overweight and obese individuals (Stice et al., 2008; Green et al., 2011; Babbs et al., 2013). In addition, disturbances in value processing is also observed in obesity at the network level, in the form of altered functional connectivity in prefrontal and striatal areas (Stoeckel et al., 2009; Nummenmaa et al., 2012; Garcia-Garcia et al., 2013; Carnell et al., 2014), and such change is not necessarily limited to the processing of food-related stimuli (Verdejo-Roman et al., 2017), potentially reflecting a more general deficit in value-based decision-making. Although most of these studies are cross-sectional and correlational by nature, two recent streams of research provide new evidence of a potential causal link. First, reward responses to food cues in valuation areas such as the striatum, the orbitofrontal cortex (OFC), and the amygdala were found to be predictive of future weight gain by prospective imaging studies (Stice et al., 2010; Demos et al., 2012; Yokum et al., 2014; Sun et al., 2015; Stice and Yokum, 2016). Second, such reward responses were at least partially normalized in patients who underwent bariatric surgery treatment (Shin and Berthoud, 2011; Miras et al., 2012; Faulconbridge et al., 2016).

These advances clearly show the promise of a cognitive approach to obesity, offering a unique perspective complementary to, but distinct from, the traditional approach focusing on metabolism and its related biological factors. It is necessary to consider, however, the gaps that remain to be filled between what we already know and what is needed for the ultimate goal of effective prevention and treatment of obesity. We argue that there are two important avenues for taking this area of research to a new height:

First, it remains poorly understood what the sources of the obesity-related changes in reward responses are. This is by itself a question of great scientific interest. From a biological standpoint, neuroinflammation has recently been proposed to be partially responsible for the cognitive impairments (Miller and Spencer, 2014). In a complementary, cognitive perspective, changes in valuation and its neural correlates are likely the product of changes in a variety of upstream cognitive processes that are coupled to obesity, and the exact identities of these processes remain elusive. For food, knowledge about nutrient qualities as well as past experiences with the food item of interest are likely to be key inputs for value construction. Furthermore, this question also bears significant translational implications for obesity and overeating. Given that options for direct manipulation of the valuation system in the human brain remain extremely limited, behavioral and physiological interventions on the sources of input for valuation may be a more feasible strategy for reliable and consistent changes in food-related choices.

Second, the paradigms used in laboratory studies of decision making with food could be improved to better incorporate the richness of everyday food choices. Typically, many existing studies employ relatively simple, stripped-down choice scenarios, where participants are presented with a fairly small number of options that vary on a limited number of dimensions. While being a useful research strategy, such approach inevitably produces choices that are devoid of many common and important elements in consumer decisions about food in the real world, such as brand knowledge, marketing campaigns, or environmental and contextual influences. Without these factors, how much existing results could generalize to everyday food purchase and eating decisions, which ultimately have the greatest impact on the long-term health and well-being of obese individuals, remain uncertain.

Memory is one attractive point of convergence for these two avenues for future investigations (although of course not the only one). It is likely a critical source of input for the computation and construction of value, and also a key process mediating diverse contextual impacts on decisions in the real world. To lay the foundation for our later discussion on how memory may contribute to impaired food valuation and choices in obesity, we will introduce recent theoretical and empirical advances on the role of memory in decision making in the next section.

CONTRIBUTIONS OF MEMORY TO VALUE-BASED DECISION MAKING AND THEIR NEURAL BASES

Memory and decision making have long been prominent fields of study in psychology and neuroscience (Eichenbaum, 2017; O'Doherty et al., 2017). Despite the significant progress made in both fields, the interactions between memory and decision-making have received little attention until very recently (Weilbacher and Gluth, 2016). In this section, we summarize the emerging evidence showing the crucial roles of memory in supporting value-based decision making. Our discussion will be focused on both new findings and older but potentially overlooked literature that have particular relevance to value-based decisions on food purchase and consumption. We emphasize that memory, which has multiple forms with distinct neural substrates (Squire and Wixted, 2011), could provide important input to different stages of the computations involved in value-based decision making with food.

Retrieval and Assignment of Value With Memory Mechanisms

In essence, value-based decision making depends critically on the agent being able to construct or retrieve value, the key decision variable, based on the information it has available. A large body of literature on both animals and humans has established that value can be acquired through incremental learning, supported by dopaminergic mechanisms in striatum (Rangel et al., 2008). Note that such process requires repeated experience with the same stimulus and is thus slow and relatively rigid. In contrast, memory mechanisms in the hippocampus provide a complementary implementation of value encoding and retrieval that is faster and more flexible. Such mechanisms may possess better ecological validity, as most decisions outside of a laboratory setting need to be made without the guidance from many past experiences.

In the simplest case, the value of a stimulus is readily available in memory, and can be retrieved to guide decisions directly. In a recent behavioral study (Murty et al., 2016), human participants made decisions about house or face stimuli, each of which representing a certain monetary outcome that they had only a single encounter prior to the decisions. They were able to make optimal decisions based on the value of the stimuli (i.e., choosing the higher value stimulus), but only when they had intact associative memory of the item and the monetary outcome coupled with it. Importantly, such decisions cannot be supported by incremental mechanisms because participants had only experienced the stimulus-reward coupling once and therefore had to rely on the episodic memory of the specific one-shot experiences with the stimuli.

Apart from providing the direct link between value and stimulus identity, memory can also assign value to stimuli with no previously learned value via associative mechanisms. In an influential study by Wimmer and Shohamy (2012), participants first learned to associate pairs of neutral stimuli (S_1 and S_2) by their co-occurrence. They then learned the values of one half of these stimuli (S_2) by experiencing their associations with different amounts of money through classical conditioning. Afterwards, when they were asked to choose between pairs of stimuli drawn from the other half (S_1) that were never paired with reward and thus had no associated value, they exhibited a robust bias toward those stimuli that were associated with high-value S_2 stimuli. Again, incremental learning could not be the underlying mechanism for such bias, as participants had not experienced any S_1-reward association. In support of the involvement of memory mechanisms, hippocampal activation correlates with this decision bias during the S_2+reward phase, implicating the hippocampus in generalizing the value to the S_1 stimuli that were otherwise neutral. Decision bias was also related to the functional connectivity between hippocampus and striatum, suggestive of an interaction between memory and valuation. These findings were nicely corroborated by a later animal study reporting the impairment of value generalization through similar higher-order conditioning by hippocampal lesions (Gilboa et al., 2014).

These hippocampal memory mechanisms may not necessarily be mutually exclusive with striatum-based incremental learning; they can influence and interact with each other in a more subtle and nuanced manner. A common strategy to study such interactions is to superimpose a classic incremental learning paradigm with incidental, trial-unique images (Wimmer et al., 2014; Wimmer and Buchel, 2016; Bornstein et al., 2017) or context cues spreading a block of trials (Bornstein and Norman, 2017), so that the influences on value by incremental learning and by episodic memory can be separately modeled and analyzed at both behavioral and neural levels. Collectively, these studies show that episodic memory of past experiences or contexts have a significant impact on the value of available options and, in turn, on choice behavior, which is not captured by incremental learning models (Wimmer et al., 2014; Wimmer and Buchel, 2016; Bornstein and Norman, 2017; Bornstein et al., 2017). Such impact is mediated by neural signatures of memory retrieval, including activities in hippocampus (Wimmer et al., 2014) and in surrounding regions (Bornstein and Norman, 2017), as well as re-activations of value-related neural patterns corresponding to the recalled memory traces (Wimmer and Shohamy, 2012; Wimmer and Buchel, 2016).

Construction of Value With Memory Mechanisms

So far, we have discussed how memory mechanisms are utilized in retrieving and assigning values to choice options, as well as how they interact with other value learning mechanisms. A common theme in these studies is that value (encoded in and retrieved from memory) is simple and well defined, most often in the form of some fixed amount of monetary reward. In the real world, however, many decisions are more complicated. For instance, one may encounter unfamiliar or novel options in a decision problem, for which there is no pre-experienced or pre-computed value readily available to be retrieved from memory. Under such circumstances, value needs to be constructed on the fly based on certain links that could be drawn between the novel option and past experiences in memory.

A typical way one novel option arises is by combining two or more familiar goods, a key feature of an elegant fMRI study by Barron et al. (2013). Participants were asked to choose between pairs of novel food items, each of which was formed by the combination of two familiar component food types. Critically, such combination had not been tasted together previously, for example tea-jelly and pea-mousse. As a result, participants had to first retrieve the sensory and hedonic experiences of consuming the individual components, imagine the likely experiences of their combinations, and in turn perform online construction of values to guide their choices. Using the technique of repetition suppression (also known as fMRI adaptation), which enables inference of neural representations at the sub-voxel level, Barron et al. (2016) interrogated where and how value was constructed from separate memory traces. Most interestingly, they found indications of simultaneous activations of multiple memories in both the anterior hippocampus and the vmPFC, while the latter region also encoded the chosen value constructed from memories of individual food components during decisions about the novel goods. These results extended previous findings on value encoding in the vmPFC, showing that value signals in this region could also result from the integration of memories retrieved in the hippocampus. Furthermore, this study bears particular practical relevance to everyday food choices in a modern world, where numerous food manufacturers, retailers, and restaurants constantly bombard consumers with opportunities of novel eating experiences that stem from more familiar components.

One important question that remains open is the nature of those memories being integrated to construct value in light of the framework of multiple memory systems (Squire, 2004; Squire and Wixted, 2011). On one hand, one could draw information from episodic/autobiographical memory and therefore focus on the more experiential and contextual aspects, for example "When was the last time I had a mousse and how did I feel about its taste and texture?" In this case, associative mechanisms similar to those summarized in the previous section are likely to be employed, with hippocampus and vmPFC serving a central role in retrieval and integration (Benoit et al., 2014; Madore et al., 2016; Gershman and Daw, 2017). On the other hand, one may rely on the abstract conceptual knowledge about the options and its components, which falls under the system of semantic memory, for example "How much sugar and fat does this ice cream cone contain and is it good for my health?" This kind of semantic knowledge is a powerful tool for efficient generalization by utilizing commonalities between novel and known stimuli (Shea et al., 2008; Kumaran et al., 2009), without the need for first-hand experiences of everything. For many real world decisions with numerous dimensions, it is a very attractive strategy for making such complex decisions tractable by reducing them to the evaluation and integration of a few core attributes that one possesses relevant knowledge about. For food-related decisions, both caloric density (Tang et al., 2014; Suzuki et al., 2017) and macro-nutriments (Suzuki et al., 2017;

DiFeliceantonio et al., 2018) are key determinants of value. It has recently been shown that conceptual beliefs about elemental nutritive attributes of food, including carbohydrates, protein, fat, and vitamin content, are represented and integrated in the orbitofrontal cortex (OFC), an area adjacent to the vmPFC, to compute the overall value of a food item (Suzuki et al., 2017). But caloric density is also associated with responses in the vmPFC, even though participants cannot correctly estimate the food items' caloric content (Tang et al., 2014; Suzuki et al., 2017). Interestingly, this effect may vary with different macro-nutriments: DiFeliceantonio et al. (2018) recently showed that participants are better at estimating caloric density of fat foods compared to carbohydrate or fat + carbohydrate foods, with such effects associated with the functional connectivity between the vmPFC and the fusiform gyrus.

More broadly, value computation for many realistic decisions, whether they are about familiar or novel items, may need the input from both episodic and semantic memory. A general theoretical model that could be applied to such cognitive processes mandates that the sequential sampling of evidence from memory serves as the basis of value construction (Shadlen and Shohamy, 2016). Viewed from this perspective, value is not instantaneously constructed from all relevant pieces of information. Instead, value is updated by the incorporation of every new piece of evidence generated from a sequential process of memory sampling/retrieval. Analogous to the drift diffusion model widely used in studies on perceptual decision-making (Gold and Shadlen, 2007), once this sequentially updated value reaches a certain threshold, a decision will be committed. One recent fMRI study provided initial empirical support to this model by showing that hippocampal activation was related to the time it took the participants to make a choice between two familiar food items, presumably reflecting the amount of information sampled from memory (Bakkour et al., 2018). Similarly, hippocampal lesion patients also showed deficits making binary choices between familiar food items, but had performance comparable to healthy controls on a number-comparison control task, again highlighting the role of hippocampus in value construction from memory (Enkavi et al., 2017).

Generating the Choice Set With Memory Mechanisms

Previously, we have discussed how memory can contribute to value-based decision making when the available options are clearly specified. This constraint is readily fulfilled by most laboratory studies on decision making, but often does not hold in choices made in the real world. Imagine that, after being seated at a table in a restaurant, you are asked by the waitress, "Can I get you something to drink?" In this case, what you can choose from (i.e., the "menu" for this choice) is not explicitly communicated. Despite such apparent ambiguity, most people have no difficulty making a choice, without having to refer to the actual beverage menu or asking the waitress what are available.

More formally, this decision can be modeled as a two-stage process: constructing the choice set from memory, followed by a decision over the items in the set (Shocker et al., 1991). Examples alike are abundant in daily life, ranging from picking a vacation destination to deciding on what grocery products to buy before arriving at the store. A critical feature of such decisions is that memory places a constraint on choices: an option can only be chosen if it is successfully recalled. In this case, the effect of memory on choice is different from the assignment and construction of values. Indeed, a series of behavioral studies demonstrated that changes in the ease of retrieval of certain options have a significant effect on such open-ended choices, while the preferences remain unchanged (Nedungadi, 1990; Posavac et al., 1997; Shapiro et al., 1997; Posavac et al., 2001).

This type of decisions is largely neglected by studies of cognitive neuroscience so far, but has been a popular research topic in consumer behavior (Alba et al., 1991), because of its close link to advertising and marketing (Krishnan, 1996). However, the source of the memory necessary to generate the choice set can be much more diverse than marketing campaigns, such as word of mouth, general knowledge learned from formal schooling, facts and ideas acquired from news media, and even cultural and religious beliefs. One common type of decisions with self-generated choice sets involve choosing an alternative from a given category (e.g., different kinds of fruit, brands of smartphones, etc.), for which semantic memory provides the most suitable input for the choice set. In addition to semantic memory, episodic memory of past experiences (e.g., "What kinds of fruit were available in the farmers market last week?") or choices (e.g., "Which restaurant did we go to when John visited?") may also contribute to the generation of choice sets, albeit likely in a more context-dependent manner. Yet, the arbitration of what information to retrieve from semantic and episodic memory, as well as the neural mechanism supporting the integration of memory and value, still need to be clarified.

Lastly, it is worth noting that memory-based constraints on choice sets may still apply even when all relevant information is physically present (e.g., standing in front of a shelf full of different breakfast cereal brands), as most decision makers may not have the motivation or the cognitive resources to process it (Park et al., 1989), leading their attention and/or search effort to be largely guided by memory (Hutchinson and Turk-Browne, 2012). In a related setting, Gluth et al. (2015) showed that options for which the spatial locations were remembered were more likely to be chosen. In parallel, this bias was linked to the effective connectivity between hippocampus and vmPFC, a key valuation area in the brain. Hence, the constraint on the choice set by memory is likely to have a far-reaching effect on many real world decisions than just the ones that require an internal choice set to be generated completely from memory.

MEMORY IMPAIRMENTS IN OBESITY

We now move on to discuss empirical evidence showing memory impairments in obesity, as well as their neural signatures. Although the study of memory has a remarkably long history, the investigation on memory impairments in obesity is still a burgeoning field involving exciting research efforts with both human and animal studies. Notably, while the two streams of research serve the common goal of unraveling the complex interactions between eating behavior, energy dysregulation, and memory functions, they have largely employed different methodologies due to practical constraints. Unlike animal studies where manipulations of energy intake, diet, and even neural activities are possible, human studies on this topic often involve cross-sectional comparisons between obese individuals and healthy controls. As a result, causal inference is usually not possible. Despite such limitations, a common thread has emerged from accumulating data, indicative of an association between obesity, suboptimal memory performances, and functional disruptions in neural circuits supporting important aspects of memory in humans.

Episodic Memory Impairments in Obesity

Episodic memory is defined as the memory for specific events or episodes in one's past experience (Tulving, 1972). Following traditions dating back to Ebbinghaus (2013), a widely used way to probe episodic memory is through learning and recalling items on a pre-defined word list, which have also been employed by a majority of publications on obesity and episodic memory. In one of the earliest studies, Cournot and colleagues reported higher body mass index (BMI) was significantly associated with lower score at the delayed memory recall test, after adjusting for demographic variables (age, sex, education level, and region of residence) and physical activity (Cournot et al., 2006). Similarly, Gunstad and colleagues also found an association between poorer performance in the verbal list-learning task and higher BMI (Gunstad et al., 2006). Using a sample with a wide age range (21–82 years), they also tested the possible interaction between BMI and age on memory performance and found no evidence of such interaction. This finding shows that lower memory performance in obese individuals are not likely an artifact of higher age, and that age-related and obesity-related memory decline may have separable etiologies. Extending the results from these two studies, Dore et al. (2008) replicated the inverse association between memory and body weight status (measured by waist circumference and waist/hip ratio, WHR, rather than BMI, in their study), and also showed that such association was attenuated with adjustment of physical activity levels. Importantly, these studies all used relatively large samples, ranging from several hundreds (Gunstad et al., 2006; Dore et al., 2008) to more than two thousand (Cournot et al., 2006), which lends strong statistical support for their findings.

Building on these groundbreaking findings, a recent series of research sought to examine if such negative associations could be reversed following interventions that reduce body-weight, such as diet and bariatric surgery [for a recent review and meta-analysis, see (Veronese et al., 2017)]. Across multiple studies, beneficial effects of bariatric surgery on memory performance on the same verbal list-learning task were found, accompanying post-operative weight losses (Gunstad et al., 2011; Miller et al., 2013; Alosco et al., 2014a; Spitznagel et al., 2014). These studies also replicated memory impairments in obese individuals before the surgery. Along the same line, another group of studies also demonstrated a moderately positive effect of dietary interventions on memory in obese/overweight individuals (Siervo et al., 2011; Boraxbekk et al., 2015). Overall, such prospective or experimental studies took an important step forward from cross-sectional studies comparing memory performances between groups of participants with different body weight status, and substantially strengthened the link between episodic memory functions and obesity.

As a probe to episodic memory, the verbal list-learning task is a paradigm easy to implement and analyze. However, such simplicity also makes it challenging to connect this paradigm to the much more complicated contents of episodic memory in real life that may be related to food choice and consumption. As a result, there have been attempts to take advantage of novel paradigms for episodic memory that capture richer dimensionalities to test and validate memory deficits in obesity. In a pair of behavioral and neuroimaging studies (Cheke et al., 2016, 2017), Cheke and colleagues employed a so-called "Treasure-Hunt task" that directly tests the three key elements of episodic memory – object recognition, location, and temporal order ("what-where-when") – as originally defined by Tulving (1972). In a group of young adults, performance in all individual elements of this task was negatively associated in BMI (but see Cole and Pauly-Takacs, 2017). In the follow-up fMRI study, when compared with healthy controls, obese participants showed reduced neural activities in medial temporal regions including hippocampus and parahippocampal gyrus, as well as the angular gyrus and parts of the prefrontal cortex, a network implicated in memory retrieval. Being the first studies investigating memory deficits in obesity that broke away from the tradition of verbal list-learning tasks, these results were still exploratory and should be interpreted with caveat (e.g., the behavioral differences were not fully replicated in the neuroimaging study despite the significant between-group differences in neural activities). Still, the work by Cheke and colleagues highlighted the utility of aiming for better ecological validity while still maintaining experimenter control over what participants learn and retrieve.

In a similar vein, autobiographical memory tasks that ask participants to retrieve information about past experiences in their daily lives also enable researchers to test episodic memory abilities (Cabeza and St Jacques, 2007). This subtype of episodic memory may also exert a considerable impact on eating behavior (see Section 2.2). This may also be true for false memories, i.e., memories of events that never occurred (Bernstein and Loftus, 2009; Chen et al., 2017; Howe et al., 2017). However, to our knowledge there has been no behavioral or neuroimaging study that examines autobiographical memory performances in obesity. Furthermore, recent evidence implies that list-learning tasks and autobiographical memory tasks recruit different neural substrates, challenging the degree to which episodic memory is a unified construct (Chen et al., 2017). Therefore, future studies are needed to address potential impairments of autobiographical memory in obesity and how well they correspond to known deficits in verbal list-learning tasks.

More generally, for most if not all of the episodic memory tests in existing studies, the content of information that participant needed to encode into and retrieve from episodic memory had little relationship with food and eating behavior. Because of the centrality of energy intake and eating behavior in obesity and related disorders, the question of domain specificity of any associated cognitive deficits is an important one and bears crucial implications for how such deficits affect behavioral output. This gap in literature should be filled by future studies.

Semantic Memory Impairments in Obesity

Contrary to episodic memory, semantic memory is defined as memory for facts, concepts, beliefs not attached to specific events or episodes, or more broadly as one's world knowledge (Tulving, 1972). Semantic memory is believed to be one of the cognitive processes that are uniquely human, and it guides a large variety of our everyday activities (Binder and Desai, 2011). As previously mentioned, clinical assessments of semantic memory capabilities usually involve tasks like semantic fluency and categorization. Generally, semantic memory in obesity have so far received less attention than episodic memory, and only a small number of studies included semantic memory assessments as part of a bigger battery of cognitive tests. With limited data, evidence regarding the existence of semantic memory impairments in obesity is inconclusive. Several studies reported significant differences between obese and control participants, pointing to a decline in semantic memory retrieval accompanying obesity. For instance, a mostly obese sample of patients with metabolic syndrome showed lower scores in an animal-naming semantic fluency task (Segura et al., 2009). Similarly, a large cohort study reported significant lower verbal fluency (a composite measure of semantic and phonemic fluency) in obese and overweight participants, and in metabolically abnormal participants (Singh-Manoux et al., 2012), although information about semantic fluency itself was not made available. On the other hand, a couple other studies reported no significant difference in semantic fluency (using animal naming tasks as well) between obese and controls (Boeka and Lokken, 2008; Alosco et al., 2014a).

We argue that studies on semantic memory in obese individuals are still inadequate, and that extant results should not be interpreted as weak or even no association between obesity and semantic memory. First, similar to episodic memory tests conducted on obesity-related studies so far, the category chosen for semantic fluency tasks is usually limited to animal, which may have limited generalizability and also has little to do with food and eating behavior. It is of great scientific interest to specifically test the semantic memory about food-related items and categories in obese and overweight individuals, as well as comparing it with knowledge with other common categories and domains. Second, while analysis of performances in the semantic fluency tasks has almost always focused exclusively on the number of correct items generated within the time limit, there is much richer information that remains unexplored. Semantic memory is thought to be organized in complex tree- or network-like structures (Jones et al., 2015), and retrieval processes in the semantic fluency task can be modeled as a random walk on such underlying structures (Abbott et al., 2015). Mere comparison of the number of items generated may fail to uncover important changes in semantic memory structure associated with obesity. Third, most extant studies had relatively small sample sizes and were unable to sufficiently control for heterogeneities in comorbidity conditions, adding to the difficulty of identifying potentially subtle but impactful differences.

Neural Correlates of Memory Impairments in Obesity

As summarized above, although both the extent and the nature of memory dysfunctions in obesity have yet to be fully determined, suboptimal memory performances in obese individuals have been reported in a variety of tasks. In parallel with these behavioral findings, a growing literature has also documented alterations or abnormalities in the anatomy and/or physiology of brain regions known to underlie memory functions, lending further support and mechanistic understandings to deficits shown in behavior.

The earliest evidence for such alterations came from three large-scale neuroanatomical studies. Obesity, as measure by BMI or WHR, was reported to be associated with smaller global brain volume (Ward et al., 2005), temporal lobe atrophy (Gustafson et al., 2004) or decrease in hippocampal volumes (Jagust et al., 2005), with the latter two focusing on aging samples. The same association was later confirmed on young adults as well (Mueller et al., 2012). Other studies further explored other age or specific gender groups (Walther et al., 2010), the use of different measures of adiposity and metrics of anatomy (e.g., voxel-based morphometry, or VBM), as well as potential anatomical changes in brain regions outside of the temporal lobe [for a review, see (Willette and Kapogiannis, 2015)]. Of interest to our discussion here are reports showing that higher BMI also predicted less gray matter volume in a limbic lobe ROI that included hippocampus and surrounding areas in children and adolescents (Alosco et al., 2014b), further confirming that such association was not specific to an aging population. A recent longitudinal study also showed that change in BMI over a 5-year period was specifically associated with change in hippocampal volume but not with any other ROIs (Bobb et al., 2014), highlighting the centrality of structural changes in hippocampus in obesity. In addition, several studies pointed to a negative association between BMI or fat mass and less gray matter volume in parts of the prefrontal cortex, (Pannacciulli et al., 2006; Ho et al., 2010; Kurth et al., 2013), especially its medial wall, known to be important in memory retrieval and integration.

Findings using other imaging modalities have further expanded these results. With diffusion-weight imaging that provides information about local movement of water molecules, Alkan et al. (2008) showed altered fluid distribution in a range of brain regions in obese individuals, including hippocampus and middle temporal cortex. Volkow et al. (2009) demonstrated an inverse association between BMI and prefrontal metabolic activity using positron emission tomography (PET). Geha et al. (2017) found that functional connectivity between different brain regions was reorganized in obesity, involving parts of prefrontal cortex and anterior hippocampus.

In summary, there is converging evidence supporting the notion that obesity is associated with changes in a core brain network that is crucial for memory functions. It should be noted that memory impairments and brain changes in obesity have largely been studied separately so far. The issue is alleviated to some degree by the fact that the neural circuits mediating episodic memory and semantic memory have been reasonably well delineated (Binder and Desai, 2011; Moscovitch et al., 2016; Ralph et al., 2017). Still, the link between these two levels of analysis needs to be more firmly established in future studies that directly test their correspondence.

AN INTEGRATIVE FRAMEWORK FOR CONTRIBUTIONS OF MEMORY MECHANISMS IN SUBOPTIMAL FOOD CHOICE IN OBESITY

All cognitive processes serve the ultimate goal of more adaptive behavior, and memory is no exception. Identification of memory impairments in obesity is an important research topic, but its actual impact on obese individuals can only be understood if we know how such impairments translate to behavior. In this section, we seek to provide a synthesis that combines (1) how information retrieved from memory can act as the essential input for different stages of value-based decision making and (2) the empirical evidence for memory impairments and accompanying neural changes in obesity. To achieve this goal, we propose a unified neuropsychological framework capable of explaining and predicting how memory impairments in obesity map onto altered decision making, in particular the ones involving food valuation and choice. Such framework will be beneficial for organizing existing findings under a common theme of understanding maladaptive choice behavior, as well as for identifying gaps and holes that future studies can be planned to fill. More importantly, this framework will also be valuable for guiding the discovery of more effective interventions and public policies addressing overeating and associated decision making vulnerabilities.

Effects of Memory on Eating Behavior

Connecting memory and eating behavior is an important step toward better understanding of how cognitive deficits in obesity lead to problematic behavior. A series of pioneering studies from Higgs and colleagues have beautifully illustrated the utility of such approach. In this line of research, Higgs (2002) focused on how memory for recent eating experiences influences subsequent intake of food. Prompting female participants to recall what they had eaten for lunch today caused them to eat less in an experimental session, compared to participants who received no cues or a cue for the lunch yesterday (Higgs, 2002). Distraction during lunch by television watching increased the intake of afternoon snacks in female participants, which was caused by interfering with formation of memory for the eating experience during lunch (Higgs and Woodward, 2009). Similarly, a different manipulation on attentiveness during lunch (i.e., focusing on food vs. a newspaper article about food) lowered snack intake afterwards, while the amount of snack intake was negatively associated with rated vividness of lunch memory (Higgs and Donohoe, 2011). The effect of (episodic) memory for a meal and interference of memory encoding by a distractor task on subsequent food intake was further replicated in other contexts and with different manipulations (Oldham-Cooper et al., 2010; Mittal et al., 2011) [for a review and meta-analysis, see (Robinson et al., 2013)]. Furthermore, these behavioral studies were nicely complemented by the findings that amnesiac patients with hippocampal damage were not able to form and retrieve memory for recent eating and, as a result, showed excessive food intake when offered multiple meals (Rozin et al., 1998), despite intact sensory specific satiety (Higgs et al., 2008).

So far, this fruitful line of studies has largely focused on episodic memory about a particular event of eating and how it affects the amount of food intake shortly after. In fact, as we discussed in section "Contributions of Memory to Value-based Decision Making and Their Neural Bases" of this review, there are many more channels through which memory (not necessarily limited to memory about an earlier meal) could play an important role in choices regarding food intake. In addition, despite the abundance of behavioral data from healthy participants and lesion patients, it remains unclear through what computational and neural mechanisms that memory changes subsequent food intake. Incorporating these findings and extending them through the framework of value-based decision making will take advantage of the well-understood neural circuitries supporting valuation and choice.

Memory Impairments and Suboptimal Food Choices in Obesity

To establish a general neuropsychological framework for suboptimal food choices in obesity that is driven by memory impairments, we propose the following taxonomy based on our previous discussion and raise a series of research questions that are worth pursuing in future studies (**Figure 1**). First, in the simplest situation where value can be directly retrieved from episodic memory based on one-shot experience (see section "Retrieval and Assignment of Value With Memory Mechanisms"), suboptimal valuation of certain food items could result from either a bias or an increased level of noise around the true value. Qualitatively, this is similar to impairment in recalling specific items from a previous learned word list. It would be helpful to test the encoding and retrieval of value in episodic memory (Murty et al., 2016) by obese participants and compare their performance with that of healthy controls as well as the generalizability of such impairment (i.e., whether it is restricted to the value of particular types of food). Alternatively, it is also possible that, while the value can be faithfully retrieved from episodic memory, the valuation area is unable to process it correctly. A neuroimaging experiment based on existing insights would be able to tease these apart: given that increased coupling was shown between hippocampus and valuation areas during such choices (Wimmer and Shohamy, 2012), it would be of great interest to test if such connectivity is weakened in obese individuals, causing the deficits in valuation and subsequent choices.

Second, when value of a food item needs to be constructed from memory, a number of different scenarios could give rise to valuation deviating from what it should be. One possibility

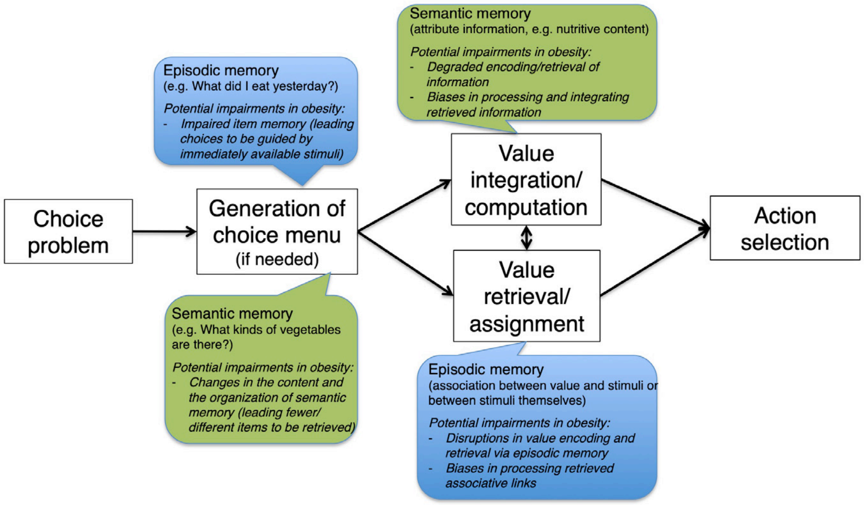

FIGURE 1 | A schematic presentation of the proposed general neuropsychological framework for how memory impairments could lead to suboptimal food-related decision in obesity.

is that the integration of multiple memory traces mediated by hippocampus (Barron et al., 2013) becomes problematic, such that certain traces receive disproportionately higher weights than others. If the choice needs to be guided more by semantic memory about a number of attributes of the item in consideration, dysfunctional communications between valuation areas like the vmPFC, OFC, and striatum and semantic memory areas including the inferior frontal gyrus and the temporal lobe could be a key driver of suboptimal choices. For food-related decisions in obese individuals, it is of particular interest to investigate if abnormalities exist in the representation of major nutrient contents of food (Suzuki et al., 2017). Again, existing experimental paradigms that have proved successful in uncovering the cognitive and neurocomputational mechanisms in healthy individuals would be a useful reference and baseline for investigations on obese participants and the like.

Third, for food-related decisions where the choice set needs to be assembled on one's own (e.g., picking a nearby restaurant to go to from memory) or be pruned for efficiency (e.g., choosing from an overload of breakfast cereal brands), semantic memory of specific categories and exemplars is a vulnerable point where suboptimal choices can originate from. In particular, if the organization of such memory (including the identity of the concept nodes, the structure of the network, and the strength of links between nodes) is altered (Abbott et al., 2015), it is conceivable that the composition of the internal choice could deviate from what a healthy individual would construct. An example would be someone who always thinks of soda and energy drink instead of more healthy beverages like water or tea when thirsty. In addition, there could also be differences in the sensitivity to information from the external environment, such as marketing campaigns and advertisements, between obese and healthy individuals, such that certain information is preferentially absorbed into semantic memory, which further influences memory-driven choices later.

Such framework helps us better able to leverage the wealth of knowledge garnered from multiple decades of basic science research on memory and decision making. We believe that this integrative framework will not only prove beneficial for relevant research, it also has the potential to shed new light on evaluating and improving behavioral interventions addressing obesity. In particular, it calls for the identification of causes of a known behavioral problem (suboptimal food valuation and choices) at a more up-stream level by examining one of its key inputs (memory). Rather than targeting valuation and choices itself, creating an informational environment that protects vulnerable individuals from pitfalls created by memory could be a more effective strategy.

CONCLUSION AND FINAL REMARKS

In this article, based on recent advances in decision neuroscience and in the study of memory impairments in obesity, we propose an integrative framework on how much memory impairments could contribute to suboptimal food valuation and choices in obesity. We argue that, by placing obese individuals back into the rich, dynamic environment constantly shaping and changing their memory, we can obtain a better insight on their eating behavior by considering how memory affects their everyday decisions with food. We hope that the proposed framework can spark new interest in the intersection between memory, valuation, and obesity.

Finally, it should be noted that we by no means claim that the proposed framework explains all, or even a majority of, decisions with food. For example, we do not discuss the heavily debated topic of food addiction (Gearhardt et al., 2011; Hebebrand et al., 2014; Volkow et al., 2017), nor do we attempt to address the effect of lifestyle, genetics, personality traits (e.g., impulsivity and self control capabilities), and environmental factors (e.g., stress) on eating (Nederkoorn et al., 2006; Hare et al., 2009). Moreover, we do not mean to imply that attentional bias does not play an important role. On the contrary, we believe it is likely that attentional bias may exert further impact on memory processing above and beyond impairments in memory itself, which could exacerbate suboptimal food decisions [for this topic, see (Higgs and Spetter, 2018)]. Rather, we argue that our framework can potentially explain a non-trivial proportion of suboptimal food-related decision making in obesity that other models may have difficulty accounting for. Given the pervasiveness of the obesity epidemic and the lack of effective interventions, even a small step toward a more complete picture of the mechanistic underpinnings of the impairment can be beneficial.

AUTHOR CONTRIBUTIONS

ZZ and GC conceived the project. ZZ wrote the manuscript with GC's input.

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Implementation Intention for Initiating Intuitive Eating and Active Embodiment in Obese Patients Using a Smartphone Application

Damien Brevers[1,2], Anne Rogiers[1], Alexis Defontaine[2], Guy Cheron[3], Anne-Marie Clarinval[3], Jennifer Foucart[2], Anne Bouchez[1], Véronique Bolly[1], Laura Tsartsafloudakis[1], Pénélope Jottrand[1], Pierre Minner[1], Antoine Bechara[4], Charles Kornreich[1] and Paul Verbanck[1,2]*

[1] Laboratory of Psychological Medicine and Addictology, Faculty of Medicine, Université Libre de Bruxelles, Brussels, Belgium, [2] Research in Psychology Applied to Motor Learning, Faculty of Motor Sciences, Université Libre de Bruxelles, Brussels, Belgium, [3] Laboratory of Neurophysiology and Movement Biomechanics, Faculty of Motor Sciences, Université Libre de Bruxelles, Brussels, Belgium, [4] Department of Psychology, Brain and Creativity Institute, University of Southern California, Los Angeles, CA, United States

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****Correspondence:***
Damien Brevers
dbrevers@ulb.ac.be

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This article describes a study protocol, which aims to explore and describe the feasibility of a mobile-phone application for initiating intuitive eating and intuitive exercising in patients who are following an ambulatory treatment for obesity. Intuitive eating refers to one's ability to make food choices based on one's awareness of his/her body's response. Intuitive exercising encourages people in finding enjoyable ways of being physically active. These two components will be trained using an implementation intention procedure, that is, behavioral plans that aim at creating a strong link between a specified situation and a response. We aim to recruit up to 80 overweight and obese patients over a period of 2 years. The smartphone application will be assessed on the basis of (i) data obtained through a 4-week use period, (ii) self-report measures taken before and after the use of the mobile application, and (iii) feedbacks from participants after the use of the mobile application. This pilot study will allow us to better understand the applicability of the use of mobile application within ambulatory treatment settings, and to adapt the design of the app necessary for building cross-sectional studies investigating its efficacy.

Keywords: smartphone application, obesity, health at every size, intuitive eating, intuitive exercise, implementation intention

INTRODUCTION

Since the early 2000s, the Health at Every Size approach [HAES (1)] has challenged traditional public health views stating that obesity and overweight are unilaterally linked to major negative health consequences (2), and that the effective means to assist obese and overweight individuals is to combine a reduction in caloric intake with an increased physical activity to reduce their weight and their risk for chronic illness [e.g., Ref. (3, 4)]. The HAES approach contrasts with this view by encouraging embodiment-like physical activity and healthy nutrition, while respecting individual's own rhythm, regardless of weight status.

Specifically, the HAES approach supports "intuitive eating" and "intuitive exercise." Intuitive eating (also known in the literature as "attuned eating" or "mindful eating") encourages the awareness of body's response to food and the learning on how to make food choices that reflect one's own "body knowledge" (5). This process allows people to make connections between what they eat and how they feel [e.g., mood, satiety, ease of bowel movements, and comfort eating (5–11)]. Intuitive exercise [also referred to as "active embodiment" (5)] encourages people to find enjoyable ways of being physically active, independent of weight loss and of explicit guidelines for frequency and intensity of exercise (5).

As a whole, HAES-based interventions have been shown to improve or maintain behavioral, psychological, physiological, and clinical outcomes, including weight loss (1, 5, 12–14). Importantly, even in the case of weight regain, maintained behavioral practices, such as those produced in HAES interventions, have sustained health benefits [e.g., better blood pressure and lipids, higher energy expenditure, less susceptibility to hunger, higher self-esteem, lower depression, and better self-perception of body image (1, 13, 15–19)]. One explanation for these observed outcomes in case of weight regain is that, by not using weight changes as a marker for health, individuals may be less discouraged by weight stabilization or gain (20, 21).

There is considerable evidence that intuitive eating can be learned [e.g., Ref. (1, 13, 22–26)]. Nevertheless, coming to eat intuitively is a challenging and gradual process, which requires replacing old food habits by new ones (5). Accordingly, HAES-based interventions are usually offered by professionals from health services and include psychoeducation and behavioral therapy sessions [e.g., Ref. (17, 23)].

In the present research project, we advance that the implementation of intention interventions in health behavior change could be used as a promising and complementary established approach for stimulating intuitive eating and active embodiment by bridging the gap between intentions to perform a particular behavior and the actual behavioral change (27–30). Implementation intentions are behavioral strategies that follow an "if–then" structure, which aims to create a strong link between a specific situation and a response. Implementation intentions will allow people to select the appropriate response when confronted to a specified situation [e.g., Ref. (31, 32)]. These "if–then" strategies will enhance health behavior by linking a critical situation (e.g., "IF I am taking the stairs instead of the elevator") with an appropriate response (e.g., "… THEN I will enjoy the feeling of having my body active"). Overall, implementation intention interventions have been shown to be effective in promoting behavior changes, including physical activity, eating habits, smoking, alcohol consumption, rehabilitation from injury, sun-screen use, cancer screening behaviors, contraception use, and dental health behaviors [for a review see Hagger and Luszczynska (29)].

This study protocol will thus examine the impact of implementation intentions (i.e., an established intervention procedure) as an initial intervention for initiating intuitive eating and active embodiment (i.e., an established intervention approach) in overweight and obese patients. A couple of studies have already examined the effect of implementation intention and goal planning intervention in obesity (33–36). It has been shown that the development of implementation intentions to adhere to a weight-loss program (e.g., "I will try to lose 1 kg by consuming 3–4 portions of fruit") can achieve greater weight reduction (34, 35). Two ongoing studies are currently examining the impact of implementation intention on physical exercise, energy/calorie intake, and eating strategies (33, 36). Nevertheless, while weight loss could trigger positive (short-term) outcomes, it is usually followed by weight regain [e.g., Ref. (37–40); see also Ref. (41)], which could be detrimental on both the physical [e.g., the weight regained does not replace bone mass or lean mass lost during weight loss (42, 43)] and the mental health of the individual [stress, depression, dissatisfaction toward weight loss, and stigmatization (20, 44–47)]. These considerations highlight the need for more evidence on the usefulness of implementation intentions in obesity, such as using interventions that focus primarily on intuitive eating/exercise rather than weight loss.

Another innovative aspect of this study is that the implementation intention intervention will be undertaken through the use of a mobile-phone application. A main advantage of using mobile devices is its ease of use, as compared with paper tools (48–51): mobile-phone applications have repeatedly been found to improve the completeness and accuracy of patient documentation. Hence, because it allows the direct coding of behavior observations, the use of a mobile app device could provide accurate [e.g., diminished memory bias (52)] and detailed information in the enactment of specific strategies of implementation intention [e.g., frequency, time, subjective experience of efficiency, difficulty, or satisfaction (53)]. Therefore, we reasoned that a mobile-phone application could be used as a promising new tool for enhancing the efficiency of an implementation intention intervention that aims at initiating intuitive eating and active embodiment in individuals who seek help regarding overweight or obesity problems.

MATERIALS AND EQUIPMENTS

Participants

Participants will be recruited at the Interdisciplinary Clinic for Obesity (CITO) of the Brugmann University Hospital (Université Libre de Bruxelles, Brussels, Belgium). The CITO unit proposes group therapy sessions in a day clinic setting for patients suffering from to individuals who seek help regarding overweight or obesity problems. The program consists of a twice-monthly stay in the day clinic of the hospital every 2 weeks over 12 sessions during 6 months (6 months in total). A morning session is dedicated to active embodiment (e.g., stretching and hiking), cooking classes and guidance on nutritional habits, provided by mental health professionals (psychologists, nurses, and occupational therapists). The afternoon is dedicated to therapeutic group sessions where patients reflect on how they experienced their last 15 days with regards to their eating and physical activity habits. These discussions are moderated by two certified psychotherapists of the CITO unit within the theoretical framework of mindful eating and intuitive exercise.

We aim to recruit up to 80 participants throughout a 2-year period. This number will allow obtaining a representative sample of patients for this pilot study. Participation will be voluntary and participants will be provided with a study information sheet and consent form. Participants should be at least 18 years old and must own an Android or IOS phone with Internet access.

Design of the "IF → THEN" Mobile Application

Sample screen shots of the "IF → THEN" mobile app are demonstrated in **Figure 1**. The building of the design and structure of the "IF → THEN" mobile app took place between July 2016 and May 2017. It was the result of several multidisciplinary meetings of scientific researchers (Université Libre de Bruxelles) and clinical practitioners (CITO unit). The aim was to create a mobile tool and to select implementation intention strategies that should have the greatest impact and adherence rate in obese patients with regard to mindful eating and embodiment-like physical activity. The "IF → THEN" mobile app includes two main categories of implementation intention strategies: "EATING," which focuses on mindful eating; and "MOVING," which focuses on intuitive exercise (i.e., embodiment-like physical activity). Each category includes 5 strategies of implementation intention (i.e., 10 strategies in total; see **Table 1** for a listing of the strategy). We decided to use five implementation strategies, as it has been shown that this number leads to the greatest behavior engagement into implementation intention interventions (54).

The EATING category includes an optional step of observation, namely: the recognition of (i) the intensity of hunger, (ii) inner body sensation, and (iii) affective state (see **Figure 1A**). Participants will be invited to undertaken these steps before eating. Specifically, participant will be first requested to self-report the level of their hunger (on a 10-point scale). Thereafter, they will have to (i) select the bodily regions in which they feel increasing or decreasing (divided in 13 regions-of-interest; see also Figure S1 in Supplementary Material) based on a topographical self-report method (55) and (ii) identify their affective state based on the State-Anxiety Inventory (56): calm, secure, tense, strained, at ease, upset, satisfied, frightened, comfortable, self-confident, nervous, jittery, indecisive, relaxed, content, worried, confused, steady, and pleasant. The goal of this procedure is to reinforce the intuitive eating approach, which encourages the individual to identify the intensity of hunger while recognizing the inner body sensations emerging from affective feelings (5, 20).

After these aforementioned (non-mandatory) steps of observation (i.e., the intensity of hunger, inner body sensation, and affective state), participants will have the possibility to report on the use of an EATING strategy. Participants will also be able to report directly after they used a strategy without going through the first steps of observation (see **Figure 1A**). Participants will report on each strategy use, by indicating (i) the level of difficulty associated with the enactment of the strategy (on a 10-point scale); and (ii) the level of satisfaction associated with the enactment of the strategy (on a 10-point scale). Participant will be instructed to report on the strategy after finishing eating, not to interfere with its enactment and with the action of eating. Participants will be able to use multiple strategies simultaneously or consecutively: e.g., when the participant is intermittently focusing on the taste of the food and on the size of the serving, he/she should report on the use of each strategy and on the associated levels of difficulty and satisfaction.

In the MOVING category, the participants will be simply requested to "push" on the implementation intention strategy that they just have been undertaken (see **Figure 1B**). Thereafter, the participants will be asked (i) to rate the level of difficulty associated with the enactment of the strategy (on a 10-point scale); (ii) to rate the level of satisfaction associated with the enactment of the strategy (on a 10-point scale); and (iii) to validate their observation. Participants will be instructed to report on the strategy after their physical exercise not to interfere with the activity. Similarly as in the EATING category, participants will be able to use multiple strategies simultaneously or consecutively (e.g., when a participant has intermittently focused on bodily sensation and on his/her environment during his/her exercise), he/she will have to report on the use of each strategy and on the associated levels of difficulty and satisfaction.

For both the EATING and MOVING categories, participants will have access to numerical information related to their observations (see **Figures 1A,B**). Specifically, participants will be able to see for each strategy the frequency (i.e., the number of time that a strategy is used), the average level of difficulty (i.e., calculated across each strategy use), and the average level of satisfaction (i.e., calculated across each strategy use). Participants will also have the opportunity to view these numbers according to a specific time interval (i.e., last week, total). Through the function "MY BODY," they will view the level of hunger associated with each type of affective state, and the topographical observation on body activation/deactivation for each type of affective state (see **Figure 1C**).

STEPWISE PROCEDURES

Presentation of the "IF → THEN" Mobile App to the Participants

The study protocol will be explained in detail to the patients during the first day of the CITO therapy. Patients will receive information on (i) implementation intention strategies on the MOVING and EATING categories and (ii) how to use the app in his/her daily life. Patients who accept to participate to the study will be asked to sign the informed consent. All patients will receive the standard of care of the psychotherapeutic CITO program. Patients accepting to participate will have the possibility to use the app additionally to the standard care. The use of the app will not be discussed during the therapeutic sessions.

Individualized Tutorial on the IF → THEN App

This individualized tutorial session will be organized after 2 weeks after the presentation of the app. During this session, a member of our research group will give detailed instructions to the participant on how to use the app in his/her daily life. To closely approximate real-world conditions, there will be no specific instructions given for frequency of use of the app other than to report each use of an implementation intention strategy.

Then, participant's subjective motivation to use the mobile application will be assessed by asking the following question: "Are you motivated to use this app for 4 weeks?" (on a 7-points scale, ranging from "non-motivated" to "highly motivated"). Next, participant will complete the French version of the Intuitive Eating Scale-2 (57) and the Intuitive Exercise Scale (58). The Intuitive Eating scale is a 18-items self-reported questionnaire (5-point Likert scale; ranging from "Strongly Disagree" to "Strongly Agree") that includes three dimensions: (i) eating for physical rather than emotional reasons (eight items; e.g., "I find other ways to cope with stress and anxiety than by eating"); (ii) reliance on hunger and satiety cues (six items; e.g., "I trust my body to tell me when to eat"), and (iii) unconditional permission to eat (four items; e.g., "I do not follow eating rules or dieting plans that dictate what,

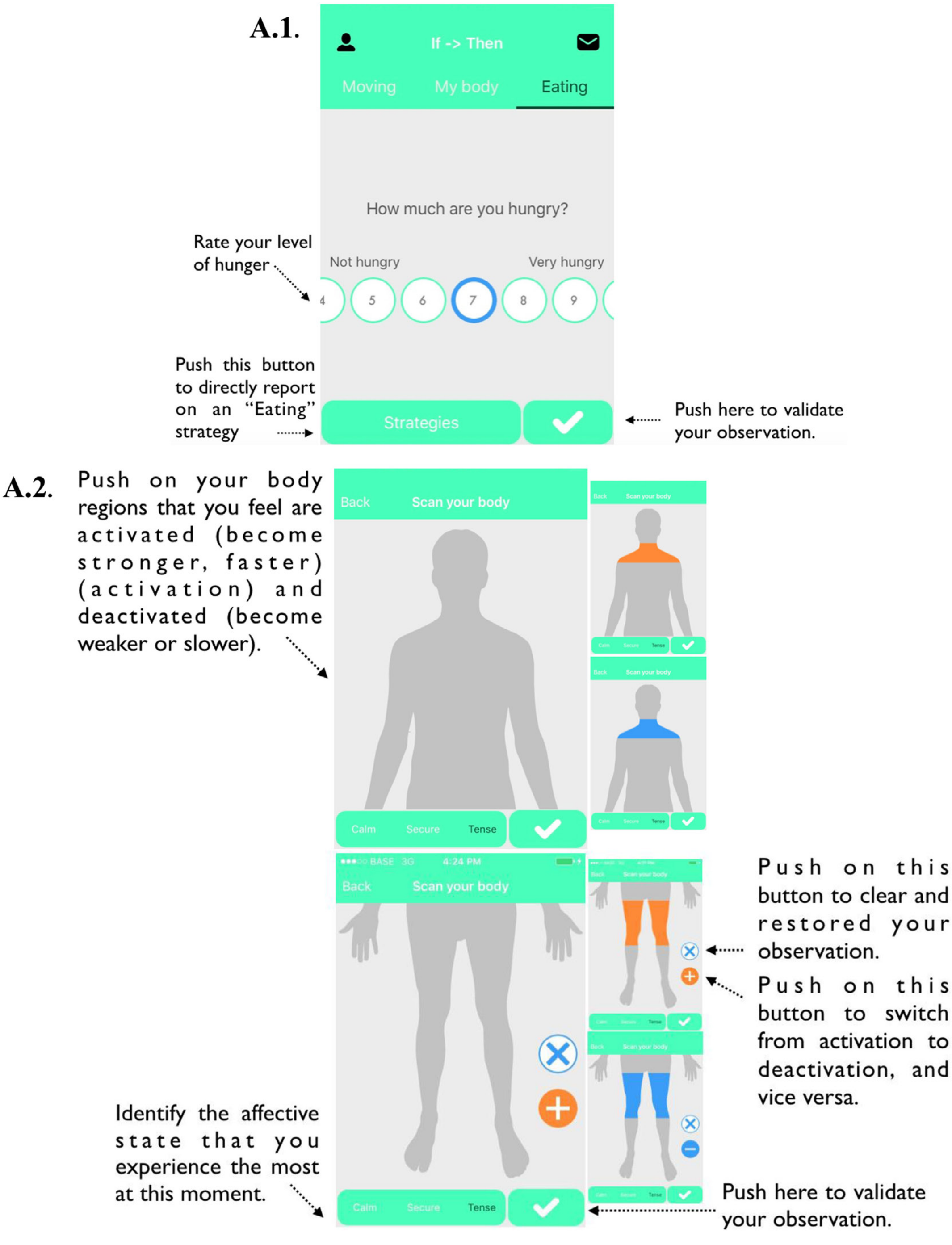

FIGURE 1 | Continued

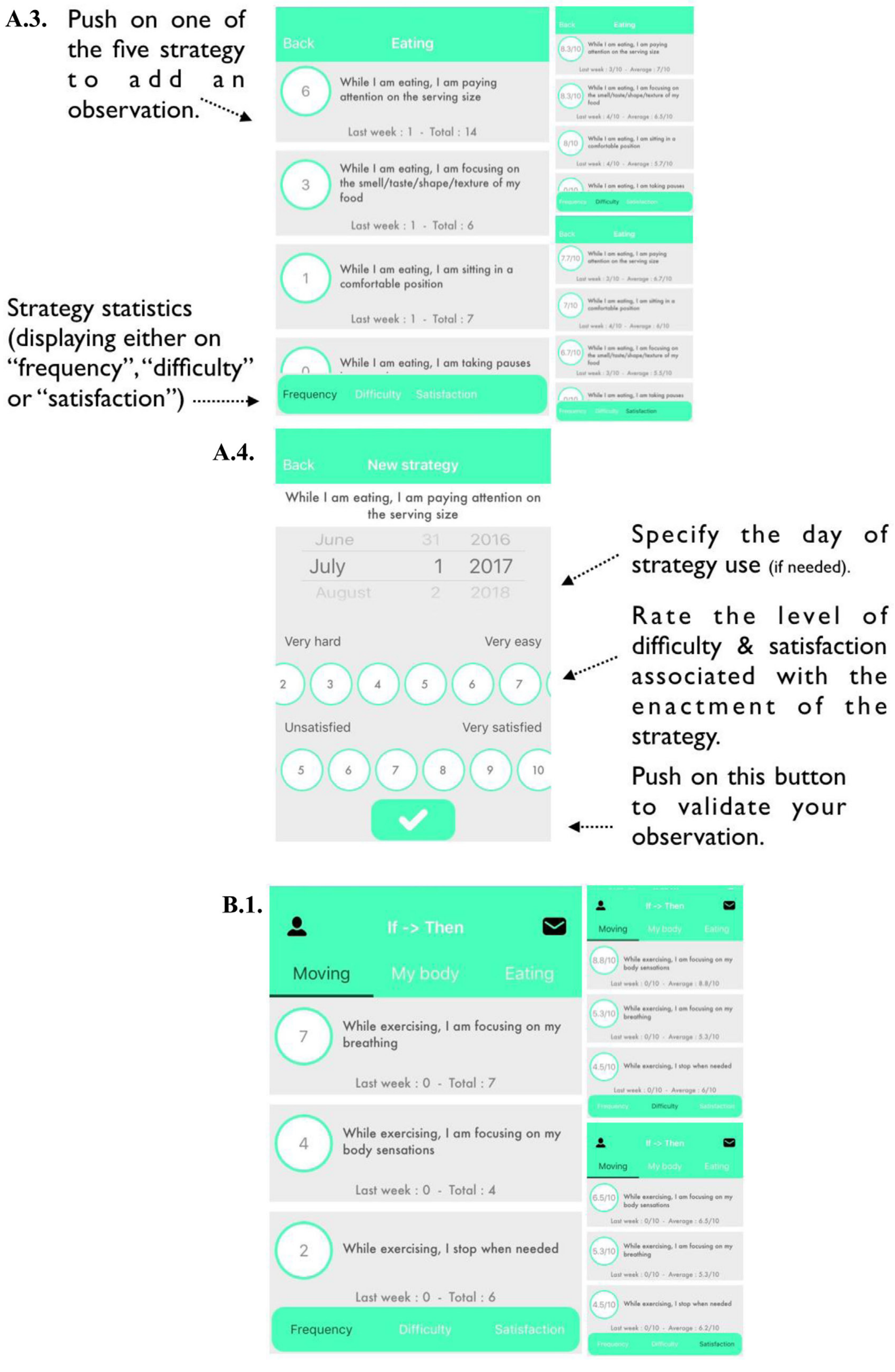

FIGURE 1 | Continued

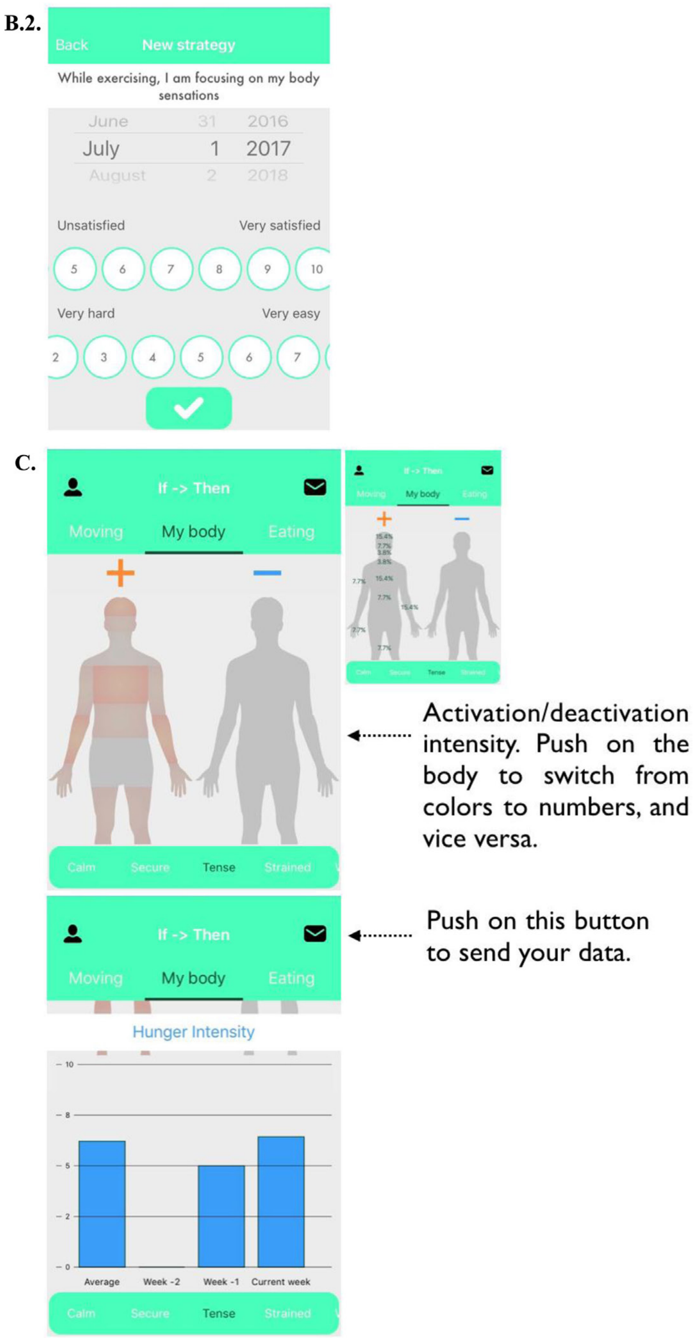

FIGURE 1 | An illustration of the "IF → THEN" smartphone application. **(A1)** After having pushed on "Eating," participant can either rate the degree of hunger or have a direct access to the implementation intention strategies; **(A2)** after having rated the degree of hunger, the "Scan your body" screen appears; **(A3)** next, the implementation intention strategies appear; **(A4)** after having pushed on a specific strategy, participant has to rate the difficulty and satisfaction associated with the enactment of this strategy; **(B1)** after having pushed on "Moving," the implementation intention strategies appear; **(B2)** after having pushed on a specific strategy, participant has to rate the difficulty and satisfaction associated with the enactment of this strategy; **(C)** after having pushed on "My body," participants can have access to descriptive statistics linking the level of hunger associated with each type of affective state, and the topographical observation on body activation/deactivation for each type of affective state.

when, and/or how much to eat."). The Intuitive Exercise Scale is a 14-items self-reported questionnaire (5-point Likert scale; ranging from "Strongly Disagree" to "Strongly Agree") that includes four dimensions: emotional exercise (5 items; e.g., "I use exercise to help soothe my negative emotion"), body trust (3 items; "I trust my body to tell me how much exercise to do"), exercise rigidity (3 items; "I engage in a variety of different types of exercise"), and mindful exercise (3 items; "When my body feels tired, I stop

TABLE 1 | Implementation intention strategies that will be proposed to the patient.

	"IF"	"THEN"
EATING	While I am eating	I am sitting in a comfortable position I am paying attention on the serving size I am focusing on the smell/taste/shape/texture of my food I am taking pauses between bites I am assessing my degree of fullness before I decide to take another portion of food
MOVING	While exercising	I am enjoying the surroundings I am focusing on conscious breathing I am focusing on my body sensations I am feeling proud of myself I stop when needed

exercising"). The Intuitive Exercise Scale will be translated into French by using back translation. Participants will also complete the French version of the 13-item Brief Self-Control Scale [BSCS (59, 60)], a widely used measure of trait self-control. Items (e.g., "I am good at resisting temptation") are endorsed on a 5-point scale, where 1 = *not at all like me* and 5 = *very much like me*. This measure was added to the protocol on the basis of previous studies which have shown that high trait self-control predicts both positive health behaviors and success in weight loss [e.g., Ref. (61)].

After having completed these self-report measures, participants will be asked to use the app for 4 weeks and a feedback session will be scheduled.

Data Collection and Mobile App Rating

This session will occur 4 weeks after the individualized tutorial session. First, the participant will be asked to send the data from the "IF → THEN" app by pushing on the "send" icon (see **Figure 1C**). This procedure will allow to save the data (under.xls file format) to a secure server. To protect against loss of confidentiality, all data will be identified by a unique numeric ID code. The list linking the participants' ID codes with their names will be stored in a password-protected file on an internal server, accessible only to the experimenters and selected project staff. Secondly, the participant will complete the Intuitive Eating Scale-2 and the Intuitive Exercise Scale. Finally, the participant will be invited to fill in an anonymous feedback form on the level of (dis)satisfaction with their overall app user experience and with regard to the MOVING, EATING, and MYBODY sections.

Follow-up

After completion of the CITO program (i.e., 6 months after the tutorial session), participants will be invited to fill-in the Intuitive Eating Scale-2 and the Intuitive Exercise Scale.

Ethics Approval and Current Status of Project

The study protocol has been approved by the CHU-Brugmann University Hospital Institutional Review Board (REF: B077201732743/I/U). The IF → THEN mobile application is available (on both Android and IOS smartphone) under request to dbrevers@ulb.ac.be. Data collection is planned to start in October 2017 until October 2019.

ANTICIPATED RESULTS

Main Goals

The aim of this study is to explore and to describe the use of a mobile-phone application, using "IF → THEN" strategies to initiate intuitive eating and intuitive exercise in overweight and obese patients. In other words, this exploratory study is to gain some insight on the mechanisms attached to an implementation intention intervention, targeting intuitive eating and embodiment-like activity that are proposed through a mobile app. Therefore, we expect that the information gained from this study will help to collect useful information for improving intuitive eating and intuitive exercise with a mobile application in clinical settings and, ultimately, conducting cross-sectional studies for testing the efficacy of such type of intervention.

Specific Research Questions and Applicable Data Analyses

Is There a Difference in Frequency, Difficulty, and Satisfaction between the Five Strategies of Implementation Intention?

McNemar tests (corrected for multiple comparisons using Bonferroni–Holms) will be used to examine differences in the frequency of use between each five strategies. Repeated measures analyses of variances (ANOVA) will be undertaken with the five types of strategies as within-subject factor, and with scores of difficulty or satisfaction as dependent variables. These analyses will be undertaken separately for the EATING and MOVING categories.

Do Frequency, Difficulty, and Satisfaction Attached to Implementation Intention Strategies Differ over Time?

Scores of frequency, difficulty, and satisfaction will be averaged across the five strategies of implementation intention, separately for each week of use (weeks 1, 2, 3, and 4). Reliability for these indices (i.e., frequency, difficulty, and satisfaction) will be estimated with Cronbach's alpha coefficients. Third, repeated measures ANOVA will be undertaken with weeks (1, 2, 3, and 4) as within-subject factor, with either frequency, mean score of difficulty or mean score of satisfaction as dependent variables.

Does Motivation to Use the IF → THEN App and Trait Self-Control Are Associated with Self-Reported Improvements of Intuitive Eating and Intuitive Exercise?

First, scores on the Intuitive Eating Scale-2 and the Intuitive Exercise Scale obtained in step 2 and step 3 will subtracted from the one obtained in step 4 (i.e., step 4 minus step 2; step 4 minus step 3), respectively. Second, Pearson correlation analyses (corrected for multiple comparisons using Bonferroni–Holms) will be undertaken between scores of app motivation use (obtained in step 1), BSCS scores, and the two computed scores of intuitive eating (step 4 minus step 2; step 4 minus step 3) and intuitive exercise (step 4 minus step 2; step 4 minus step 3).

Data Obtained from Bodily Sensation Maps and Affective States

Data recorded through the "MY BODY" tool will be examined through frequency and descriptive levels of analyses on bodily sensation maps and affective states.

Pitfalls, Artifacts, and Troubleshooting

The smartphone application will be assessed during 4 weeks, which is a limited assessment time. However, this length is common for implementation intention interventions (29). This short-time period has also been chosen to minimize missing data and respondent's time burden, which could have been increased by a prolonged assessment period. The stepwise procedure has also been designed in order for the participants to perceive the app use as an inherent part of their treatment. Indeed, the mobile app focuses on two components (intuitive eating and active embodiment) that are being learned during their group therapy sessions at the CITO unit. Moreover, participants will receive step-by-step information of the participation process. In addition, the mobile app "IF → THEN" was designed in an attractive, and intuitive navigable way, which might further increase participant's level of engagement. Finally, participant's motivation to use the app will be assessed in the beginning of the intervention. This should inform us on how intuitive eating and intuitive exercise improved among participants with different levels of engagement toward mobile app use, and further shed light in potential feasibility drawbacks.

ETHICS STATEMENT

The study protocol has been approved by the CHU-Brugmann University Hospital Institutional Review Board (REF: B077201732743/I/U).

AUTHOR CONTRIBUTIONS

DB, AR, AD, A-MC, ABouchez, VB, JF, ABechara, CK, LT, PJ, GC, PM, and PV designed the study and wrote the protocol. DB and AR wrote the first draft of the manuscript, and all authors contributed to and have approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/article/10.3389/fpsyt.2017.00243/full#supplementary-material.

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Altered Regional Gray Matter Volume in Obese Men: A Structural MRI Study

Bin Zhang[1]*†, Xiao Tian[2]†, Derun Tian[3]*, Jinhong Wang[4], Qiming Wang[3], Chunshui Yu[5], Chunbo Li[1] and Jijun Wang[1]

[1] Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [2] Key Laboratory of Cancer Immunology and Biotherapy, Biotherapy Center, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center of Cancer, Tianjin, China, [3] Department of Anatomy, Tianjin Medical University, Tianjin, China, [4] Department of Medical Imaging, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [5] Department of Radiology, Tianjin Medical University General Hospital, Tianjin, China

Obesity is associated with a number of health problems, especial insulin resistance and Type 2 diabetes. Our previous study showed that obese males had decreased neural activity in the orbital frontal cortex (OFC) and increased activity in the left putamen (Zhang et al., 2015b), which could indicate altered eating behaviors in obesity related to a hyper-functioning striatum and hypo-functioning inhibitory control. Accordingly, our goal of the current study was to determine whether there are alterations in the brain structures within these two neural systems in obese individuals. Twenty obese men (age: 20–28 years) and 20 age-matched lean male subjects were involved in the current study. Plasma glucose and insulin were tested during hunger state, and homeostasis model assessment of insulin resistance (HOMA-IR) was based on the blood samples. In the study, we used structural MRI and a voxel-based morphometry (VBM) method to investigate regional structures in obese subjects and find out whether there are correlations between the insulin and the brain structures. We found that obese men only showed a significantly increased gray matter volume (GMV) in the left putamen and that the GMV of the left putamen was positively correlated with body mass index, plasma insulin and HOMA-IR. The putamen is a core region participating in insulin signal regulation, and our results showed an abnormal GMV of the putamen is a core alternation in aberrant insulin. Furthermore, the GMV of the OFC was negatively correlated with hunger rating, despite there being no significant difference between the two groups in the OFC. In conclusion, the altered structure and function of the putamen could play important roles in obesity and aberrant insulin.

Keywords: obesity, functional MRI, gray matter volume, hunger rating, insulin, putamen

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Qinghua He,
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Reviewed by:
Timo Partonen,
National Institute for Health and Welfare, Finland
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Chengdu University, China

****Correspondence:***
Derun Tian
tiandr@tijmu.edu.cn
Bin Zhang
zhang.bin845@foxmail.com

† These authors are first author.

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INTRODUCTION

Obesity is a public health challenge worldwide, and a number of health problems are related to it (Flegal et al., 2007; Renehan et al., 2008). In particular, obesity is linked to insulin resistance, which is the major factor leading to Type 2 diabetes (Prince et al., 2014). The factors causing obesity are multiple, and its etiology is not well understood. However, excessive weight gain is largely due to energy imbalances in calories consumed over calories expended (Janssen et al., 2005; Stice et al., 2006), so abnormal eating behavior has become a core factor in clarifying the obesity epidemic. The hypothesis of altered eating behaviors in obesity is related to three neural systems: a hyper-functioning striatum, hypo-functioning inhibitory control and altered insula (He et al., 2014a,b). However, there is no study investigating whether the structure of these systems altered in obese individuals.

Functional imaging techniques have been applied to investigate behaviors in obesity, and the functional MRI studies have found that dysregulation of eating behaviors serves as a pivotal pathophysiologic feature in obesity (Passamonti et al., 2009; Kullmann et al., 2013b; He et al., 2014a,b; Tuulari et al., 2015). Tuulari et al. (2015) found that obese subjects had lower responses in the medial prefrontal cortex (PFC), a core region of inhibitory control, viewing the stimuli passively or imagining eating the foods. Passamonti et al. (2009) found that the viewing of appetizing foods compared with bland foods produced changes in the appetitive network, suggesting that the findings might determine an individual's risk of obesity. In our previous study, we used resting state functional MRI method to observe spontaneous neural activity during hunger state in obese individuals and found that obese males had decreased activity in the orbital frontal cortex (OFC) and increased activity in the left putamen (Zhang et al., 2015b), which is consistent with the altered eating behaviors hypothesis (He et al., 2014a,b).

Previous MRI studies have also shown that regional structures are altered in obese individuals (Pannacciulli et al., 2006; Brooks et al., 2013; Lou et al., 2014; He et al., 2015). One study showed that gray matter atrophy in obese subjects occurred in the left PFC, bilateral cingulate cortex and bilateral putamen (Lou et al., 2014). Another study found that gray matter volumes (GMVs) in obese participants were smaller in the bilateral supplementary motor area, left inferior frontal gyrus and left postcentral gyrus (Brooks et al., 2013). However, Sharkey et al. (2015) did not find any significant association between cortical thickness and body mass index (BMI) in children. Due to the inconsistent findings of previous studies, in the current study, we used voxel-based morphometry (VBM) methods to investigate whether there are altered regional structures in obese subjects, especially in striatum and impulse control systems.

Insulin plays an important role in regulation of food intake (Zhao and Alkon, 2001). Previous studies have shown that insulin signals could modify the neural circuitry and regulate whole body energy homeostasis (Figlewicz and Sipols, 2010). Kullmann et al. (2013a) found that intranasal insulin application induced increased activation in hypothalamus. Furthermore, our previous functional MRI study showed that the negative correlation between plasma insulin and the regional brain activity (Zhang et al., 2015a). However, there is no study investigating the relationship between the GMV of the region related to obesity and plasma insulin.

In the present study, we used VBM methods to investigate whether there are altered regional structures in obese subjects. The purpose of the study was to find out the altered structures in obese subjects and the relationship between the GMV of the altered brain region and plasma insulin level. The investigation was motivated by two hypotheses: (1) regional structures of the striatum and impulse control systems are altered in obese individuals, and (2) there is the positive correlation of the altered regional GMV with plasma insulin.

MATERIALS AND METHODS

Subjects

Twenty obese men (age: 20–28 years) and 20 age-matched lean male subjects (age: 20–28 years) were recruited via print poster advertisement in university campuses of Tianjin. Lean subjects were required to have a BMI from 18.5 to 23.9 kg/m^2, and obese subjects were required to have a BMI $>$ 28 kg/m^2 using the adjusted Chinese guideline, which is an equivalent of WHO class I obesity (He et al., 2007). None of the subjects had a history of illicit drug dependence or alcohol abuse, and they were not currently dieting to lose weight. Exclusion criteria also included psychiatric medical illnesses, history of seizures, and pregnancy. This study was performed in accordance with the guidelines of the International Committee of Medical Journal Editors. This study was approved by the institutional review board of Tianjin Medical University General Hospital. All of the participants provided written informed consent in accordance with the Helsinki declaration.

Procedure

All of the subjects completed the paradigm between 5:30 PM and 8:00 PM. On the day of the scan, the subjects fasted for 6–8 h prior to scanning. After lunch, the subjects were asked not to ingest anything except for water until the beginning of the experiment. We assessed the hunger rating using visual analog scales, in which the subjects were asked to rate their sensations of hunger from 0 ('not at all hungry') to 100 ('very hungry') at the moment. Each subject should mark somewhere suited their sensations of hunger on the visual analog scale. At the beginning of the study, first seven subjects were not taken this test. Then we calculated the score according to their markers. After the assessment of sensations of hunger, all subjects immediately went to the scanning room to do the MRI test.

Blood Samples Acquisition

Blood samples were obtained from the cubital vein before the scan session. Plasma glucose concentrations were determined by an automated clinical chemistry analyzer (Medical Cooperation, USA), and plasma insulin concentrations were determined by chemiluminescence immunoassay (Siemens Diagnostics, USA). Based on the blood samples, homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as $\text{HOMA-IR} = \text{glucose}\left(\text{mmol}/\text{L}\right) \times \text{insulin}\,(\text{mU/L})\,/22.5$. HOMA-IR is a method used to quantify insulin resistance, the higher value of HOMA-IR, higher level of insulin resistance (Matthews et al., 1985).

Image Data Acquisition

Brain imaging data were acquired with a 3T MR imaging system (Signa-HDx, General Electric, USA). The subjects' heads were fixed using foam pads to minimize head motion, and earplugs were used to reduce the scanning noise. Structural images were acquired using a 3D magnetization-prepared rapid-acquisition gradient echo sequence with the following parameters: repetition time = 2000 ms, echo time = 2.6 ms, inversion time = 900 ms, flip angle = 9°, matrix = 256 × 224, field of view = 256 mm × 224 mm, and 176 continuous sagittal slices with a 1 mm thickness. The structural scan time is 352 s.

Voxel-Based Morphometry Procedure

Structural images were processed using Statistical Parametric Mapping software (SPM8[1]). Images were transformed using Voxel Based Morphometry Toolbox (VBM8), which includes segmentation, bias correction, and normalization using diffeomorphic anatomical registration and the exponentiated lie algebra technique (Ashburner, 2007) with a pre-defined tissue probability map registered to the Montreal Neurological Institute space. Modulation was performed to compensate for the effects of non-linear transformations. Finally, a Gaussian filter of 8 mm full width at half maximum was applied to increase the signal-to-noise ratio.

Statistical Analyses

We used the independent samples t-test to compare group differences in plasma glucose, plasma insulin, HOMA-IR and hunger rating (in subjects with obesity and lean male subjects).

The differences between obese subjects and healthy controls (HCs) were examined with the independent samples t-tests between the two groups to create a group difference map. Threshold correction was undertaken by family-wise error (FWE) using SPM with the threshold at a voxel p value of $p < 0.05$.

For OFC as a core region of hypo-functioning inhibitory control in obese individuals with *a priori* hypothesis (Zhang et al., 2015b), the search for GMV changes within the OFC was confined accordingly by performing a small volume correction based on the results of our previous study (Zhang et al., 2015b), extracting the OFC (one different activity region between two groups) as a mask. To account for multiple comparisons within this considerably smaller volume of interest, we applied FWE.

For insula as a core region regulating in eating behaviors (He et al., 2014a,b), the search for GMV changes within bilateral insula was confined by performing a small volume correction, extracting the bilateral insula as a mask using WFU PickAtlas[2]. To account for multiple comparisons within this considerably smaller volume of interest, we applied FWE.

We then selected regions of interest from the VBM results (left putamen) and our previous study (OFC). Then, we entered the GMV of the left putamen into correlation analyses with BMI, HOMA-IR and plasma insulin, and we entered the GMV of the OFC into correlation analyses with subjective hunger ratings.

[1] www.fil.ion.ucl.ac.uk/spm
[2] http://fmri.wfubmc.edu/

TABLE 1 | Characteristics of the study population.

	Lean (n = 20)	Obese (n = 20)	Group effect P value
Age (y)	20∼28	20∼28	
Body weight (kg)	63.52 ± 5.66	100.51 ± 13.32	0.015
BMI (kg/m^2)	21.48 ± 1.43 (range: 18.5–23.9)	33.56 ± 3.53 (range: 28.0–41.5)	0.004
Glucose (mmol/L)	4.46 ± 0.44	4.12 ± 0.72	0.142
Insulin (uU/mL)	4.84 ± 5.30	14.81 ± 11.32	0.001
Hunger Ratings (mm)	71.56 ± 9.61	72.92 ± 13.24	0.330
HOMA-IR	0.80 ± 0.47	2.87 ± 2.96	0.006

RESULTS

Plasma glucose levels were similar between the lean and obese subjects ($p > 0.05$). The plasma insulin concentrations and HOMA-IR of obese individuals were significantly higher ($p < 0.05$) than those of lean subjects. However, there were no differences in hunger ratings between the groups ($p > 0.05$; **Table 1**).

On the whole brain level, VBM analysis revealed that obese men showed a significantly increased GMV in the left putamen ($x = -33$, $y = 63$, $z = -9$, $k = 331$, $T = 7.43$, $p < 0.05$, FWE correction; **Figure 1**). No other brain regions showed significant GMV changes.

Within the OFC, the small volume correction results did not reveal any regions with significant differences in GMV between controls and obese men.

The GMV of the left putamen was positively correlated with BMI ($r = 0.7$, $p < 0.001$; **Figure 2A**, **Table 2**), plasma insulin ($r = 0.514$, $p = 0.001$; **Figure 2B**, **Table 2**), and HOMA-IR ($r = 0.445$, $p = 0.004$; **Figure 2C**, **Table 2**), and the GMV of the OFC was negatively correlated with hunger rating ($r = -0.302$, $p = 0.047$; **Figure 2D**, **Table 2**).

DISCUSSION

Previous studies showed that altered eating behaviors in obesity is related to the hyper-functioning striatum and hypo-functioning inhibitory (He et al., 2014a,b). In the present study, we would like to investigate whether the structure of these systems altered in obese individuals and the relationship of the regional GMV with plasma insulin. We found obese men showed a significantly increased GMV in the left putamen, which was positively correlated with plasma insulin. But, we did not find the significant differences of GMV in OFC. However, the GMV of the OFC was negatively correlated with hunger rating. Our findings contribute to the existing literature by reporting

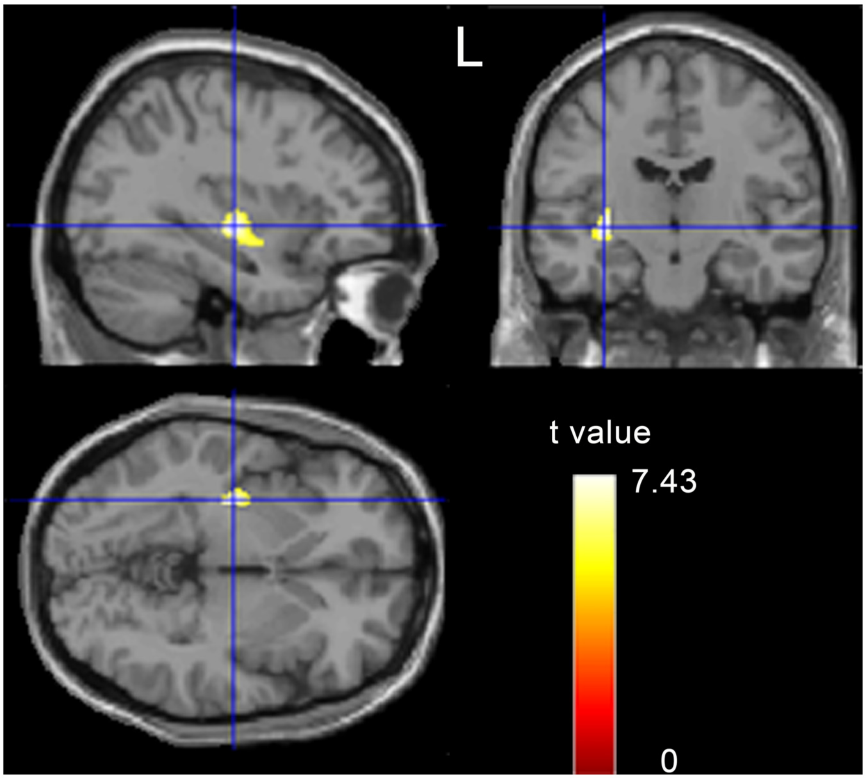

FIGURE 1 | A t-statistic map showed the gray matter volume (GMV) differences between obese subjects and controls (p < 0.05, corrected).

regional deviation, altered structure of striatum system in obese individuals.

The current study found that obese subjects showed significantly increased GMV in the left putamen. Previous studies have shown that the putamen is a core region of the impulsive system (Bechara, 2005; Noel et al., 2013), and it plays an important role in goal-directed control of behavior in motivational contexts (Jimura et al., 2010). The study of Rothemund et al. (2007) showed that BMI could predict activation of the putamen during high caloric food viewing. Furthermore, our previous study showed that obese men had increased activity in the left putamen during hunger state (Zhang et al., 2015b). In all, our functional MRI findings and previous research supported that a hyper-functioning striatum exists in obesity; additionally, the current study showed an abnormal structure of the putamen, which may be the reason for excess food intake in obese individuals.

In the current study, there was no difference in plasma glucose between the two groups. However, the levels of plasma insulin and HOMA-IR in obese men were greater than in HCs; in particular, the mean value of HOMA-IR in the obese group was three times more than that in the HCs, which indicated that the islet function of obese subjects in our study was altered, namely due to insulin resistance (Wallace et al., 2004; Chiu et al., 2007). Our findings were consistent with previous studies showing that insulin resistance was associated with obesity (Boden et al., 2005; Isganaitis and Lustig, 2005) and that the pathological condition would progress to Type 2 diabetes. Meanwhile, the GMV of the left putamen was positively correlated with BMI and HOMA-IR, which indicated that the altered GMV of the left putamen may be an important biomarker of the insulin resistance. And, the current study showed that the GMV of the left putamen was positively correlated with plasma insulin, which might clarify that the putamen is a core region participating in insulin signal regulation. However, it is still unclear how the putamen regulates the insulin signal, which need the future research to investigate.

The prefrontal region plays an important role in decision-making and inhibitory control, and several researchers have shown that the PFC regulates the cognitive control of food intake (Grabenhorst et al., 2008; Davis et al., 2010). Previous studies have found increased activation of the OFC in response to high calorie food images (Killgore and Yurgelun-Todd, 2005; He et al., 2014a), and obese individuals showed less activation of the PFC when attempting to inhibit responses to food images, compared to lean subjects (Batterink et al., 2010). Furthermore, our previous study showed that the obese male individuals had significantly decreased neural activity in the OFC during hunger state (Zhang et al., 2015b). Abnormal eating behavior in obesity is related to hypo-functioning inhibitory control, and the OFC is the key region of the inhibitory system (He et al., 2014a,b). In the current study, we did not find a significant difference between obese and healthy subjects in the GMV of the OFC;

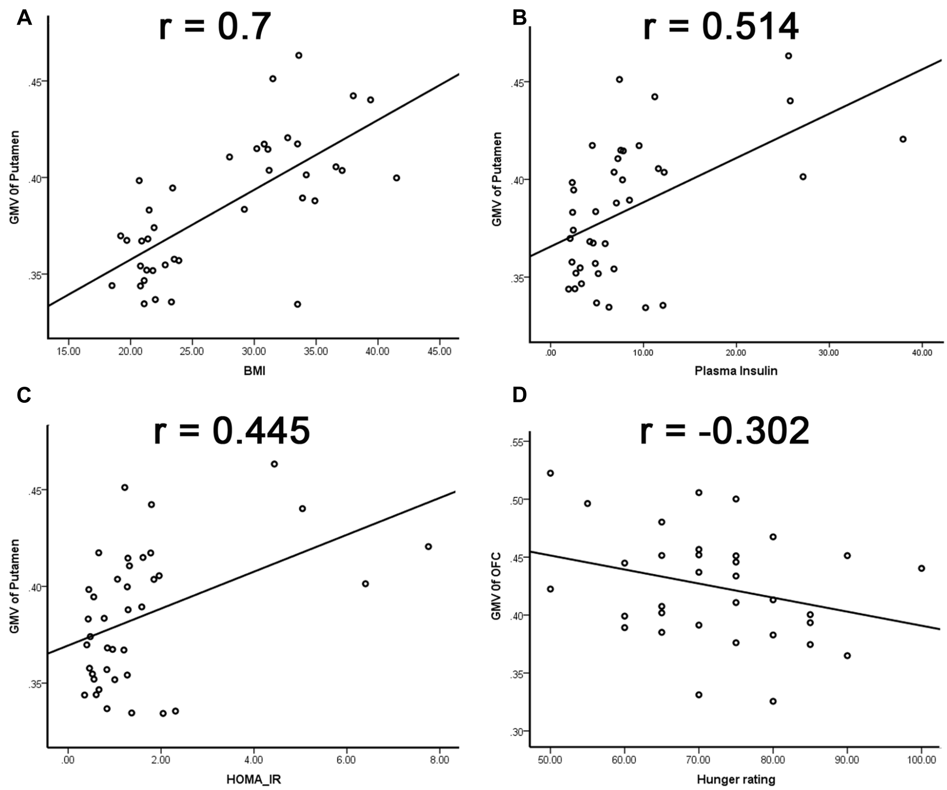

FIGURE 2 | Relationship between region GMV and physiological factors. (A) Positive correlation between GMV of the left putamen and BMI; **(B)** positive correlation between GMV of the left putamen and plasma insulin; **(C)** positive correlation between GMV of the left putamen and HOMA-IR; **(D)** negative correlation between the GMV of OFC and hunger rating.

TABLE 2 | Correlation coefficients among all the study variables.

	GMV of left putamen		GMV of OFC	
	r	*P*	*r*	*p*
Plasma Insulin	**0.541**	**0.001**	0.242	0.069
HOMA_IR	**0.445**	**0.004**	0.255	0.059
BMI	**0.7**	**0.000**	0.112	0.248
Hunger Rating	−0.161	0.185	**−0.302**	**0.047**

Bolded values mean significant correlation.

however, the GMV of the OFC was negatively corrected with hunger rating. Accordingly, the GMV of the OFC could be related more directly to increased subjective motivation toward increased eating behavior.

The current study had several limitations to be addressed in the future. First, we only enrolled male subjects in the current study. Previous studies have shown that obesity in males and females follows different routes, which can affect insulin resistance (Aldhoon-Hainerova et al., 2014; Bosch et al., 2015). With the moderate sample size, it would have become problematic to investigate potential interactions. We will enlarge the sample size and involve subjects of both genders in a future study. Second, we did not assess cognitive and affective status, which are important factors associated with obesity. In the future, we will perform some psychological testing and diagnostic interviews for mental disorders.

CONCLUSION

Our study showed an abnormal GMV of the left putamen, which was positively correlated with BMI, plasma insula and HOMA-IR, so the putamen could be a core region participating in insulin signal regulation, and an abnormal structure and function of the putamen could play important roles in obesity and aberrant insulin. Additionally, the current study showed that the GMV of the OFC was negatively corrected with the hunger rating, which indicated that the OFC could be related more directly to increased subjective motivation toward increased eating behavior. The putamen and OFC are two key regions associated with obesity and eating behavior, and structural abnormalities of the two regions might contribute to causing obesity.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of International Committee of Medical

Journal Editors with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the institutional review board of Tianjin Medical University General Hospital.

AUTHOR CONTRIBUTIONS

BZ, CY, and DT designed the work. BZ, XT, CY, QW, JHW, and DT did acquisition and analysis. BZ, XT, CL, and JJW interpreted of data. BZ, XT, CY, JHW, DT, and CL wrote the draft. BZ, XT, CY, JJW, JHW, CL, QW, and DT approved the final version. All authors reviewed the manuscript.

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Increased BOLD Signals in dlPFC Is Associated With Stronger Self-Control in Food-Related Decision-Making

Fuguo Chen[1,2], Qinghua He[1,2], Yan Han[1], Yunfan Zhang[1] and Xiao Gao[1,2,3]*

[1] Key Laboratory of Cognition and Personality (Ministry of Education), Southwest University, Chongqing, China, [2] Faculty of Psychology, Southwest University, Chongqing, China, [3] CAS Key Laboratory of Mental Health, Institute of Psychology, Beijing, China

Self-control is the ability to comply with a request, to postpone acting upon a desire object or goal, and to generate socially approved behavior in the absence of external monitors. Overeating is actually the failure in self-control while feeding. However, little is known about the brain function that allows individuals to consciously control their behavior in the context of food choice. To address this issue, we used functional MRI to measure brain activity among undergraduate young females. Forty-one undergraduate female students participated in the current study. Subjects underwent the food rating task, during which they rated each food item according to their subjective perception of its taste (from Dislike it very much to Like it very much), its long term effect on health (from very unhealthy to very healthy) and decision strength to eat it (from Strong no to Strong yes). Behavioral results indicate the positive correlation between taste rating and its corresponding decision strength to eat, no matter the food is high caloric or low. Moreover, health ratings of high caloric food was negatively correlated with DEBQ-emotional eating, and taste ratings of high caloric food was positively correlated with DEBQ-external eating. Whole brain analysis of fMRI data indicates that BOLD responses in dlPFC were positively correlated with successful self-control; BOLD responses in midcingulate cortex were positively correlated with failed self-control. This study provided direct evidence that dlPFC was involved in self-control in food-related choice.

Keywords: self-control, food choice, fMRI, dlPFC, decision-making

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Roumen Kirov,
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Hospital Universitario de Bellvitge, Spain
Jin Li,
Chinese Academy of Sciences, China

***Correspondence:**
Xiao Gao
gaoxiaox@swu.edu.cn

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INTRODUCTION

We are living in an environment which promotes over-consumption of palatably high-energy food, and the obesity epidemic shows no signs of abating (1). Individual differences in food reward sensitivity is responsible for overeating (2, 3). Sensitivity to food reward, insensitivity to internal state, and/or defects in impulsive control were found to predict overeating and a preference for foods high in fat and sugar. Moreover, the above these factors would, in turn, predict higher body mass index (BMI). Sensitivity to food reward works as the hot system which drives a person to food intake; impulsive control, on the contrary, works as the cool system which could restrains feed behavior. Numerous studies have focused on the hot system (2, 4, 5), whereas studies referring to cool mechanism in the brain is relatively scarce.

Self-control has been variously defined as the ability to comply with a request, to initiate and cease activities according to situational demands, to modulate the intensity, frequency, and duration of verbal and motor acts in social and educational settings, to postpone acting upon a desire object or goal, and to generate socially approved behavior in the absence of external monitors (6). Self-control is also defined as an umbrella construct that bridges concepts and measurements from different disciplines, such as impulsivity, conscientiousness, self-regulation, delay of gratification, inattention-hyperactivity, executive function, will power and inter temporal choice (7). Some scholars take self-control and self-regulation as the same concept. In general, self-regulation is the broader term, encompassing both conscious and unconscious processes and sometimes referring to all behavior guided by goals or standards, whereas self-control refers more narrowly to conscious efforts to alter behavior, especially restraining impulses and resisting temptations (8).

Overeating is actually the failure in self-control while feeding. High-sugar/high-fat food induce appetite-food reward, which drives food intake. Food reward is so strong that defect in self-control will, apparently, lead to overeating. Neuroimaging studies, using positron emission tomography (PET) and magnetic resonance imaging (MRI), which focused on food intake, yield valuable insights into the neurobiology underlying variation in regulation of food intake in human (9). Regulation of food intake is based on two major interacting systems: homeostatic needs affect the behavior mediated by gastrointestinal hormones and hypothalamic integration (integration of gastrointestinal hormone and hypothalamus function); the pleasure from food intake can provide reinforcement beyond homeostatic value and lead to overindulgence in high-caloric food (10). The hedonic component of feeding behavior is suggested to be mediated by reward-related cortical and sub-cortical systems, that is, the ventral striatum, the ventral tegmental area and the orbitfrontal cortex (OFC). However, little is known about the brain function that allows individuals to consciously control their behavior in the context of food choice.

Neuroimaging studies focusing on self-control found that cognitive control is the highest level of cognitive activity, and prefrontal lobe plays as the central role in cognitive control system (11–13). Difference sub-region of PFC perform its own functions: the ventromedial prefrontal cortex (vmPFC) is responsible for reward assessment and goal orientation; the dorsolateral prefrontal cortex (DLPFC) is in charge of process of self-control; the medial orbitofrontal cortex (mOFC), via the lateral prefrontal cortex (lPFC), dedicates to represent subjective reward values at the time of choice (14–16). Other brain areas like insula and its relying operculum also participate in self-regulation of cognitive control function s (17).

Contrary to the activity of self-control system, the brain reward system, containing vmPFC, lPFC, OFC, striatum, insula, anterior cingulum gyrus cortex, hippocampus, amygdale, and midbrain structures, encodes the subjective value of rewards and the subsequent impulse system, and it consistent with a role for this neuronal network in general hedonic representation (18, 19). Reward activity in lPFC and vmPFC represent characteristics and intense of anticipation to reward (11, 20), and striatum is responsible for coding "liking" and "wanting" qualities of food (21). Amygdala, with projections to nucleus accumbens to trigger motivitioanal behaviors, functions as emotional integration, reward process and feeding regulation (22). Hippocampus, the central part of memory, conserve the pleasure feeling and emotional reaction, and then transport these information to dosal stratum and cerebellum, regulating the feeding or avoiding behavior (23).

Along with previous literature, there is, apparently, an antagonistic effect between the self-control system represented by prefrontal area and the impulsive system represented by striatum. In a particular situation, intense activities in the prefrontal system indicate much weaker activities in the stratum system, and vice versa. It can be summarized that the balance between these two brain systems are vital to regulate feed behavior. Overeating and obesity will happen very likely if the balance is broken. We speculate that delicious high-fat food, which is difficult to resist and reject, may disturb the balance between the self-control system and the impulsive system. Previous studies mainly focused on the activities in stratum system while watching food pictures or the anticipating to intake food. Evidence in prefrontal control mechanism of feeding behavior is scarce. Hence, the current study, based on the activities of the prefrontal system while watching various food pictures, aimed to investigate the intrinsic mechanism underlying the self-control function in food-related decision-making. We employed three food rating tasks in the current study. In these tasks, subjects were required to indicate their decision intensity to consume the food items based on balancing the immediate pleasure from their taste and its long-term effect on health. We categorize subjects as high self-control group or low self-control group according to their score in food rating tasks. We hypothesized that: (1) increased dlPFC function would associate with self-control; (2) food picture would activate numbers of related areas, such as somatosensory cortex (postcentral gyrus), visual cortex (superior parietal lobule, cuneus), primary taste cortex (insular), rewarding areas (striatum, OFC); (3) activity differences would be observed between food-acceptation and food-rejection.

METHODS

Subjects

Forty-three subjects participated in the current experiment [all females; mean age = 20.47 years, S.D. = 1.75, age range = 18–25 years; mean BMI = 23.05, S.D. = 4.44, BMI range = 15.56–29.32]. The demographic information of subjects was presented in **Table 1**. Due to excessive head movement during scanning, four subjects (who exceeded a predetermined limit of 2 mm in any direction) were excluded from the sample. Findings from the resulting sample of 41 were reported. All subjects were right-handed nonsmokers, with no reported past/current neurological or psychiatric illness, normal or corrected-to-normal vision and normal color vision as assessed by basic color tests. None of

TABLE 1 | Demographic information of the subjects.

Variables	Whole sample(N = 41)		
	Range	M	SD
Age	18–25	20.56	1.73
BMI	15.56–28.94	22.85	4.43
DEBQ			
DEBQ-R	1.20–4.00	2.88	0.75
DEBQ-EM	1.15–3.77	2.4	0.67
DEBQ-EX	2.30–4.30	3.21	0.49
BEHAVIORAL RATINGS			
Taste ratings	2.32–3.33	2.77	0.21
Taste ratings	2.27–3.15	2.75	0.21
Decision ratings	2.19–3.17	2.71	0.19

DEBQ-R, Restraint subscale; DEBQ-EM, Emotional Eating subscale; DEBQ-EX, External Eating subscale; HC, High caloric food; LC, Low caloric food.

them took medications. We did not impose a BMI upper-limit or lower-limit. Subjects were included as long as they felt comfortable while inserted in the fMRI scanner. All subjects provided the date of their last period to ensure that they were not scanned during menstruation.

Measures

Demographics

Subjects completed a demographics questionnaire, including age, current and historic medications, and phase of menstrual cycle.

Hunger Ratings

Subjects rated current feelings of hunger on a 5-point Likert scale, ranging from 0 ("*not at all hungry*") to 4 ("*very hungry*").

Dutch Eating Behavior Questionnaire [DEBQ; (24)] was used to assess subjects' eating behavior. It consisted of three subscales, including the Emotional Eating subscale (DEBQ-EM; 13 items; e.g., the degree to which eating is prompted by emotional states like tension and worry rather than by hunger), the External Eating subscale (DEBQ-EX; 10 items; e.g., the degree to which one tends to overeat if food looks and smells good), and the Restraint subscale (DEBQ-R; 10 items; e.g., the extent to which the individuals restrain food intake). Impulsivity in eating behaviors could be reflected by the DEBQ-EM and DEBQ-EX. DEBQ has 33 items in total, and each item was measured on a 5-point Likert scale. It has good reliability and validity. The Cronbach's α of each subscale in the current sample was 0.95, 0.81, and 0.95, respectively.

Stimuli

One hundred and seventy different food items with 85 picturing high-caloric (HC) palatable food (e.g., fried chicken, hot dog, ice cream, etc.) and 85 picturing low-caloric (LC) food (e.g., fruits, vegetables, etc.) were used in the current study. All of the stimuli were adopted from Chinese Food Picture Database (25). The food pictures were presented to the subjects using color pictures (72 dpi). Stimulus presentation and response recording was controlled by E-prime 2.0.

Food Rating and Decision-Making Task

The food rating and decision-making task was similar with the task used in previous study (26). The task had three parts. Subjects first rated all 80 high-caloric and 80 low-caloric food items for both their taste and their long term effect on health in two separate blocks (a taste-rating block and a health-rating block). All ratings were made using a four-point scale that was shown on the screen below each item. The taste ratings were made on a 4-Likert scale from 1 = *Dislike it very much*, 2 = *Dislike it*, 3 = *Like it*, to 4 = *Like it very much*. And all health ratings were made on a 4-Likert scale from 1 =*Very unhealthy*, 2 = *Unhealthy*, 3 = *Healthy*, to 4 = *Very healthy*. Subjects were instructed to rate the taste without regard for its healthiness before the taste-rating block. Similarly, before the health-rating block they were instructed to rate the healthiness of each food item without regard for its taste. After the two rating blocks, subjects were presented with another food picture gallery including 10 food items (5 high-caloric and 5 low-caloric items), and they were asked to choose one food item as a reference item, which was relatively neutral on their taste and health perception.

In decision phase, all subjects were presented with the 160 food items again and were instructed that on each trial they would have to choose between eating the food item shown in that trial and the reference food item. Subjects were told to express the strength of their preferences using a four-point scale: 1 = *Strong No* (choose reference food), 2 = *No* (choose reference food), 3 = *Yes* (choose shown food), 4 = *Strong Yes* (choose shown food) (26).

The taste-rating task and decision-making task was done in the fMRI scanner and the health-rating task was done out of the scanner.

Procedure

Following approval from the Human Research Ethics Committee at School of Psychology, Southwest University, subjects were recruited via on-campus advertisements. Subsequently, 43 female undergraduate students engaged in the current study. All of the subjects took part in an intake session and one fMRI scanning session. Two sessions were conducted on separate days. Body weight and height was measured during the intake session. BMI was calculated as weight (in kilograms) divided by the squared height (in meters) of the subject (BMI = kg/m^2). Specifically, after the removal of shoes and coats, height was measured to the nearest millimeter using a stadiometer and weight was assessed to the nearest 0.1 kg using a digital scale. During the intake session, subjects signed the consent inform after reading a general overview of the study. Anthropometric measurements were then taken.

On the day of the fMRI scan, subjects were instructed to refrain from eating or drinking, with the exception of water, within 12 h before their session. Fasting status was confirmed by self-report questionnaires upon their arrival. Then subjects were introduced with the taste and health rating task, as well as the decision-making task. After that, subjects did the health rating task out of the fMRI scanner, and chose the reference food item.

Then, subjects were taken into the scanner bore, and they did the hunger rating right before the structural image acquisition. After the rating, T1-weighted structural scans and the resting state fMRI (rs-fMRI) run was conducted. Then subjects completed the food taste rating runs and decision-making runs in the scanner, sequentially. Only the results from the decision-making task were reported here and the resting state fMRI data were reported in another study (27). Each subject was paid 140 Yuan as compensation for their participating after the fMRI scanning session.

fMRI Data Acquisition

fMRI data were acquired using a 3-T Siemens Trio scanner in the SWU Imaging Center for Brain Research. Foam pads were used to reduce head movements and scanner noise. Scans were performed by an echo-planar imaging (EPI) sequence with the following scan parameters: repetition time = 2,000 ms, echo time = 30 ms, flip angle = 90°, field of view = 192 × 192 mm^2, acquisition matrix= 64 × 64, in-plane resolution = 3 × $3mm^2$, 32 interleaved 3-mm-thick slices, inter-slice skip = 0.99 mm. Two volumes were discarded before the beginning of data collection in each run to allow for equilibration of the magnetic field.

Data Preprocessing

Neuroimaging data were preprocessed using the SPM12 software (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, United Kingdom) on the Matlab platform. For each subject, the first 10 volumes were discarded to account for signal equilibrium and subjects' adaptation to their immediate environment. Then, the fMRI images were corrected for the acquisition delay between slices and for the head motion. Two subjects were excluded because their head motion exceeded 2 mm in translation or 2° in rotation. Then, anatomical and functional images were normalized to the standard MNI template brain implemented in SPM12, resulting in voxel sizes of 1 and 3 mm^3, respectively. Functional time-series data were then detrended.

Statistical Analysis

Behavioral Data

Firstly, descriptive analysis was conducted with the demographic variables, DEBQ and behavioral ratings of the taste, health and decision making. Then, correlation analysis was conducted between decision strength of HC food or LC food, DEBQ-EM, and DEBQ-EX, respectively. We expected that decision strength-HC would positively correlate with DEBQ-EM and DEBQ-EX, while decision strength-LC would show no such correlation with these variables. According to behavior scores in both the food rating task and decision making task, we divided subjects into three groups: success in self-control (SSC), failure in self-control (FSC) and no self-control (NSC). SSC means rejection to like/healthy food and acceptation to dislike/healthy food; FSC means rejection to unlike/healthy food and acceptation to like/unhealthy food; NSC means rejection to unlike/unhealthy food and acceptation to like/healthy food.

fMRI Data

Whole brain analyses

Analysis was performed with SPM12. Individual level whole brain general linear models (GLMs) and SPM12's standard hemodynamic response function was estimated in three steps. Firstly, we estimated the model separately for each individual. Three events were defined: (1) success in self-control (SSC) including choosing healthy-disliked food and rejecting unhealthy-liked food; (2) failure in self-control (FSC) including rejecting healthy-disliked food and choosing unhealthy-liked food; and (3) no self-control (NSC) including trials with healthy-liked food and unhealthy-disliked food. Secondly, we calculated contrast statistics at the individual level. Two main contrasts were specified for subject-level analysis: (1) SSC vs. FSC and (2) FSC vs. SSC. Thirdly, a general linear model was used to generate the statistical parametric maps for the second-level analysis, while BMI was introduced as a covariate variable in the analysis in the original manuscript. We expected that increased dlPFC function would associate with self-control. Main effects were considered significant using a whole-brain family wise error (FWE) of $p < 0.05$ and a minimum cluster size of 5 voxels.

TABLE 2 | Inter-correlation matrix between variables.

Variables	1	2	3	4	5	6	7	8
1 Taste-HC	1							
2 Taste-LC	−0.213							
3 Health-HC	0.390*	−0.056						
4 Health-LC	0.105	0.564**	0.111					
5 Decison-HC	0.748**	−0.119	0.510**	0.135				
6 Decison-LC	−0.262	0.846**	−0.185	0.433**	−0.309*			
7 DEBQ-R	0.032	−0.079	−0.105	0.039	−0.026	0.052		
8 DEBQ-EM	0.029	0.21	−0.322*	0.013	−0.106	0.26	0.089	
9 DEBQ-EX	0.331*	−0.049	−0.141	0.028	0.094	−0.027	0.092	0.525**

HC, High caloric food; LC, Low caloric food; DEBQ-R, Restraint subscale; DEBQ-EM, Emotional Eating subscale; DEBQ-EX, External Eating subscale.
**p < 0.05 two tailed.*
***p < 0.01 two tailed.*

RESULTS

Behavioral Results

The results of descriptive statistical analysis on three rating tasks were shown in **Table 1**, and the inter-correlation between variables of interest was presented in **Table 2**. Results show that taste-likeness for low caloric food negatively correlated with DEBQ-EM ($r = -0.32$, $p = 0.05$); taste-likeness for high caloric food positively correlated with DEBQ-EX ($r = 0.35$, $p = 0.05$); there is positive correlation between food liking and its corresponding eating choice, no matter the food is high caloric or low; health assessment of high caloric food negatively correlated with DEBQ-EM ($r = -0.32$, $p = 0.05$); likeness assessment of high caloric food positively correlated with DEBQ-EX ($r = 0.33$, $p = 0.05$).

Brain Image Results

We estimated a general linear model of brain responses in which activity during the entire evaluation period was modulated by self-control. Whole brain analysis showed that SSC vs. FSC significantly activated BOLD responses in DLPFC, whereas FSC vs. SSC significantly activated BOLD responses in midcingulate cortex (MCC) (**Table 3** and **Figure 1**).

TABLE 3 | Brain regions showing significant correlation between the activity area and self-control.

Brain region	MNI coordinates			*Z*	*p*
	X	*Y*	*Z*		
SSC-FSC					
DLPFC	−48	27	36	3.47	0.026
FSC-SSC					
MCC	−12	−24	45	4.35	0.008

SSC, Successful self-control; FSC, Failed self-control.

Correlation With DEBQ

Correlation analysis was performed with the SSC vs. FSC and FSC vs. SSC maps against individual's scores of three DEBQ subscales. However, no significant finding was obtained.

Then, we divided SSC into two events at individual level: (1) choosing healthy-disliked food (SSC-C) and (2) rejecting unhealthy-liked food (SSC-R). Meanwhile, FSC were divided into two events at individual level: (1) choosing unhealthy-liked food (FSC-C) and (2) rejecting healthy-disliked food (FSC-R). Four main contrasts were specified for subject-level analysis: (1) SSC-R vs. FSC-R, (2) FSC-R vs. SSC-R, (3) SSC-C vs. FSC-C and (4) FSC-C vs. SSC-C. Correlational analysis were performed with the four contrast maps against individual's scores of three DEBQ subscales. Results showed that BOLD responses in bilateral putamen were positively correlated with DEBQ-R on SSC-R vs. FSC-R contrast. Meanwhile, BOLD responses in left MCC were positively correlated with DEBQ-R on FSC-C vs. SSC-C (**Table 4** and **Figure 2**).

TABLE 4 | Brain regions showing significant correlation between the activity area and DEBQ.

Brain region	MNI coordinates			*Z*	*p*
	X	*Y*	*Z*		
SSC-R vs. FSC-R					
putamen R	27	6	−6	4.05	0.014
putamen L	−21	9	3	3.86	0.028
SSC-C vs. FSC-C					
MCC	3	−18	42	4.21	0.015
FSC-C vs. SSC-C					
MCC	−12	−24	45	4.35	0.008

SSC, Successful self-control; FSC, Failed self-control; MCC, Midcingulate cortex.

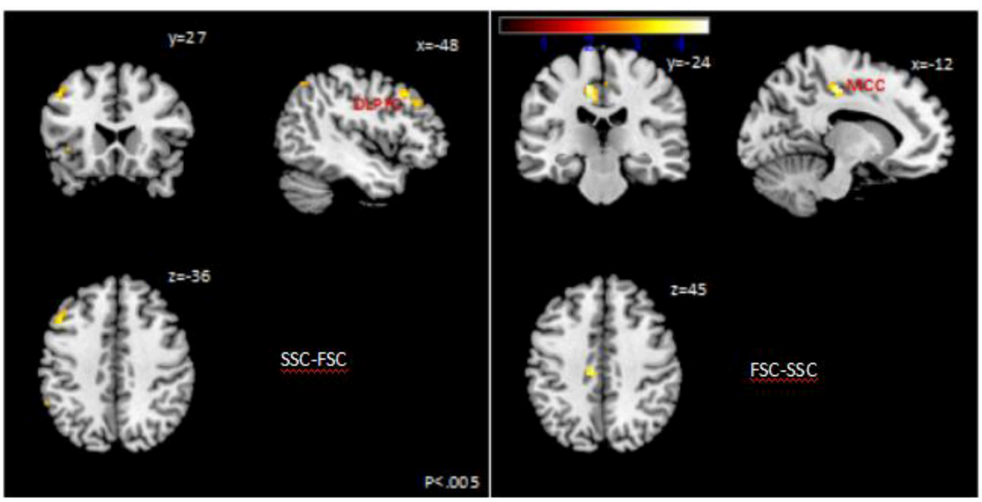

FIGURE 1 | Activation map of Successful self-control (SSC-FSC) vs. Failed self-control (FSC).

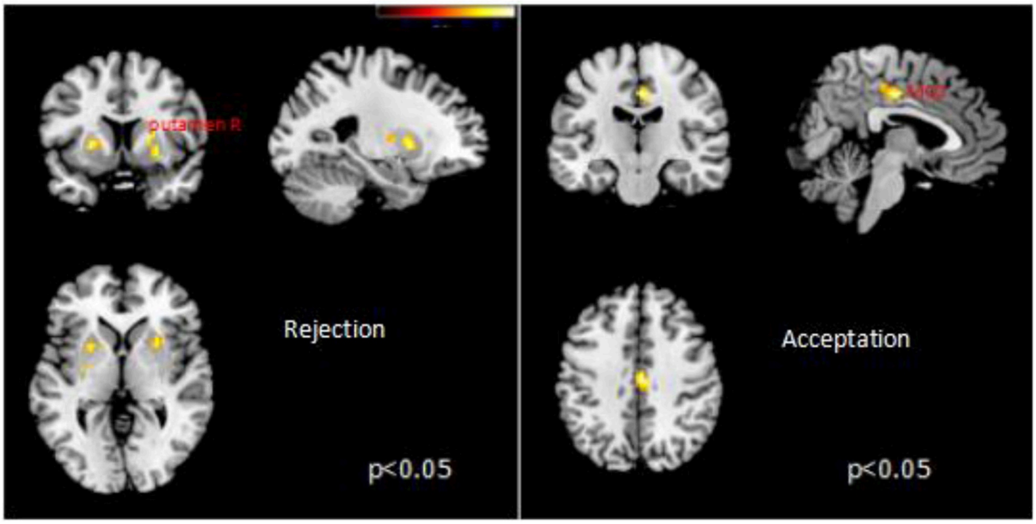

FIGURE 2 | Correlation between SSC-R vs. FSC-R **(left)**, SSC-C vs. FSC-C **(right)** and DEBQ-R.

DISCUSSION

Based on the reinforcement learning hypothesis of self-control and food decision making, this study provides an approach to characterize the association between self-control on food-related choice.

As expected, self-control, which was indexed by the food choice between two food items, was positively correlated with BOLD responses in dlPFC. This is direct evidence showing the importance of dlPFC on self-control. Meanwhile, BOLD responses in MCC were positively correlated with unsuccessful self-control. These findings were in line with previous observations of the positive association between dlPFC with inhibition to energy intake (28), or smokers (29, 30). Dorsal lateral PFC also functions as the translation mechanism, which reinforces self-power, motivating one's goal-directed behavior in the long run (31, 32). DLPFC also projects to other brain areas, promoting or inhibiting various neuro-functions, such as executive control and emotion regulation n (33, 34). Subjects with damaged dlPFC had difficulty in focusing on cognitive task, implying a defect in self-control (35).

Under the "rejection" conditions, BOLD responses in bilateral putamen were positively correlated with DEBQ-R, no matter it's successful or unsuccessful self-control; Under the "acceptation" conditions, responses in MCC, unilaterally, were positively correlated with DEBQ-R, no matter it's successful or unsuccessful self-control. Although activities can be observed under both condition, we speculate there may exist difference between them, which implying different neuromechanisms between "accepting" food and "rejecting" food. Cingulate gyrus is crucial structure functioning in the regulation system (36). Neuroimaging studies referred to food pictures found that cingulate gyrus was stably activated during the attention to food stimulus (28, 37). In our daily life, while choosing food, we have to face the conflict which was caused by flavor of food and its healthy meaning to our bodies, and self-control help to regulate feeding behavior. In the current study, we defined successful self-control as rejection to like/healthy food or acceptation to dislike/healthy food; we defined unsuccessful self-control as rejection to unlike/healthy food or acceptation to like/unhealthy food. Based on the definition, subjects who have weaker self-control may usually choose food with better flavor, ignoring its impact on health. Functional MRI results in the study presented evidence implying that cingulate gyrus had stronger BOLD reaction when subjects focused on the flavor of food.

Interestingly, fMRI results in the current study also confirmed that DEBQ scores had positive correlation with BOLD responses in putamen, bilaterally, no matter self-control is successful or unsuccessful. Studies concerning restrained eating verify that high score of DEBQ reveals stronger cognitive control while in feeding environment, which, consequently, lead to restricted eating behavior (10). Besides putamen, dorsal striatum and caudatum may function to regulate restricted eating (10, 38). Studies concerning the old reveal similar conclusion, that putamen, caudatum and dlPFC collaborate with each, functioning as the self-control system to regulate delay of discounting and delay of gratification (39). Inversely, defect collaboration among these areas may lead to the reduction of resisting food temptation (40). What's more interesting is that, in the successful self-control trails, "acceptation" and "rejection" respectively activated different areas. "Acceptation" decision activated MCC and "rejection" the putamen. This underlies that these two decision-making behaviors may associated with different mechanism, despite they were both "successful" self-control reaction. Successful self-control owes to two ways: one is to resist the current temptation; the other is to think a lot of the future reward. From this perspective, successful self-control equals to the ability to choose health food, which is in accordance with long-term goals and succeeding in losing weight requires both behaviors (41).

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of The Regulations of Ethical Reviews of Biomedical Research Involving Human, Ministry of Health,China. The protocol was approved by the Ethic Committee of Faculty of Psychology, Southwest University. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

FC: wrote this manuscript. YZ and YH: analyzed the data. QH: edited the manuscript and did the proof reading. XG: designed this study and got the funding.

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Food-Predicting Stimuli Differentially Influence Eye Movements and Goal-Directed Behavior in Normal-Weight, Overweight, and Obese Individuals

Rea Lehner[1,2], Joshua H. Balsters[1,3], Alexandra Bürgler[1], Todd A. Hare[2,4] and Nicole Wenderoth[1,2,5]*

[1] Neural Control of Movement Laboratory, Department of Health Science and Technology, ETH Zurich, Zurich, Switzerland, [2] Neuroscience Center Zurich, ETH Zurich, University of Zurich, University and Balgrist Hospital Zurich, Zurich, Switzerland, [3] Department of Psychology, Royal Holloway University of London, Egham, United Kingdom, [4] Laboratory for Social and Neural Systems Research, Department of Economics, University of Zurich, Zurich, Switzerland, [5] Movement Control and Neuroplasticity Research Group, Department of Kinesiology, Biomedical Sciences Group, KU Leuven, Leuven, Belgium

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Hong Chen,
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***Correspondence:**
Rea Lehner
rea.lehner@hest.ethz.ch

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Obese individuals have been shown to exhibit abnormal sensitivity to rewards and reward-predicting cues as for example food-associated cues frequently used in advertisements. It has also been shown that food-associated cues can increase goal-directed behavior but it is currently unknown, whether this effect differs between normal-weight, overweight, and obese individuals. Here, we investigate this question by using a Pavlovian-to-instrumental transfer (PIT) task in normal-weight (N = 20), overweight (N = 17), and obese (N = 17) individuals. Furthermore, we applied eye tracking during Pavlovian conditioning to measure the participants' conditioned response as a proxy of the incentive salience of the predicted reward. Our results show that the goal-directed behavior of overweight individuals was more strongly influenced by food-predicting cues (i.e., stronger PIT effect) than that of normal-weight and obese individuals ($p < 0.001$). The weight groups were matched for age, gender, education, and parental education. Eye movements during Pavlovian conditioning also differed between weight categories ($p < 0.05$) and were used to categorize individuals based on their fixation style into "high eye index" versus "low eye index" as well. Our main finding was that the fixation style exhibited a complex interaction with the weight category. Furthermore, we found that normal-weight individuals of the group "high eye index" had higher body mass index within the healthy range than individuals of the group "low eye index" ($p < 0.001$), but this relationship was not found within in the overweight or obese groups ($p > 0.646$). Our findings are largely consistent with the incentive sensitization theory predicting that overweight individuals are more susceptible to food-related cues than normal-weight controls. However, this hyper-sensitivity might be reduced in obese individuals, possibly due to habitual/compulsive overeating or differences in reward valuation.

Keywords: Pavlovian-to-instrumental transfer, cue-controlled behavior, incentive salience, conditioned response, eye movements, obesity

INTRODUCTION

The worldwide increase of individuals being overweight or obese produces a high medical and psychosocial burden (1–4), particularly since this condition is related to several comorbidities, such as cardiovascular disease, which is known as the global leading cause of death (2, 4).

One factor which has been hypothesized to influence decision-making in the context of ingestive behavior and energy balance (5, 6) is the augmented food marketing (7–10) creating a so-called "obesogenic" environment, i.e., customers are surrounded by a plethora of food-associated sensory cues reminding them constantly of meals or drinks as for example food packaging images at train stations, Coke commercials on TV, or the two arches of the McDonald's sign in front of every store.

Recent studies in humans have shown that food-associated cues influence behavior even when satiated or when rewards are no longer available (11–14). Initial reward-seeking behavior controlled by food cues might lead to habitual and ultimately compulsive overeating as suggested by the incentive sensitization theory of addiction (15–21). The theory implies that in a first phase, motivational value is directed to the reward itself, and in a second phase, to the cues and objects related to the reward, turning them into attention-grabbing incentives (20). In animals, this process can be measured by the Pavlovian conditioned approach/response, i.e., when animals start to sniff, lick, or bite the lever or food tray, which predicted reward delivery (22–24). Such cues can then become motivators and act as reinforcers themselves leading to strong reward-seeking behavior (15, 25, 26). However, it is currently controversially debated whether this model developed in the context of addiction applies also to obesity (6, 19, 20, 27–31). Previous studies have shown an abnormal sensitivity to rewards and reward-predicting cues in obese individuals (32–38) but did not test whether this modulates goal-directed behavior. Here, we address this question and investigate whether food-predicting cues differentially influence goal-directed behavior of normal-weight, overweight, and obese individuals. We employed Pavlovian-to-instrumental transfer (PIT) [for review, see Ref. (26)] to measure the influence of food-related cues on goal-directed behavior. The PIT phenomenon has been widely investigated in both animals [for review, see Ref. (25)] and humans (11–13, 26, 39–57), making this a useful paradigm for translational research.

Furthermore, we applied eye tracking during Pavlovian conditioning as a proxy of the incentive salience of the predicted reward, which might explain potential individual differences. Several studies in rodents have shown that there is considerable individual variation when the extent to which individuals attribute motivation to reward-predicting cues was estimated (22, 23, 58–62). However, it is currently unclear how these findings from animal research translate to humans since the only two available studies (49, 63) substantially differed in how conditioned responses were defined and quantified.

MATERIALS AND METHODS

Participants

In total, 64 volunteers were recruited for this case–control study. The following recruitment strategies were used: announcements of the Swiss Adiposity foundation and advertisements in local clinics, self-help groups, plus-size clothing stores and on the university website. Participants were included when they complied with the following criteria: age 18–65 years, German speakers, normal or corrected-to-normal vision with contact lenses and no food allergies against any ingredient of the four foods used in the experiment (i.e., Maltesers chocolate, Haribo gummy bears, TUC crackers, and Zweifel crisps).

Participants with a diagnosis of any psychological or neurological disease, drug abuse in the past, ocular problems, or intake of psychiatric or neuroleptic drugs during the last 6 months were excluded (i.e., three participants). Five additional participants were excluded because they failed to learn the instrumental and/or the Pavlovian associations. We used the body mass index (BMI) classification according to the World Health Organization (64), to differentiate between normal-weight (BMI < 25 kg/m^2), overweight (25 kg/m^2 $\geq$ BMI < 30 kg/m^2), and obese individuals (BMI ≥ 30 kg/m^2). BMI was calculated by dividing the individual's weight (kilograms) by the square of the individual's height (meters). Weight was measured on a flat scale (Seca 635, Seca, Hamburg, Germany) and height with a mechanical telescopic measuring rod (Seca 222, Seca, Hamburg, Germany). To take into account that a high BMI can arise due to high muscle mass, the participants with a BMI ≥ 25 were asked to estimate if this was due to increased muscle or fat mass. Selecting the muscle mass option led to exclusion (i.e., two participants). The final sample included fifty-four participants (mean age $= 31 \pm 10$ years, mean $\pm$ SD, oldest participant $= 55$ years, 55.6% female). Although the age range of our sample was broad, changes in coping strategies and comorbidities over one's lifetime should not have confounded our results due to group matching. Cases and controls were matched for age, gender, education, and parental education. The final sample characteristics are shown in **Table 1**.

All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the Canton Zurich. Participants were reimbursed with 20 Swiss francs per hour and a snack (i.e., a package of the chosen food and an apple).

Indirect Measures for Body Fat: BMI and Waist Circumference

Overeating high-calorie and palatable foods mainly leads to the accumulation of visceral fat (65), which is reflected in waist circumference measurements (see **Table 1**). Waist circumference was measured on the approximate midline between the top of the pelvis bone and the lower margin of the most caudal palpable rip. It was measured by holding the measuring tape horizontally to the floor (64, 66).

Questionnaires

All participants completed a number of questionnaires in German (see **Table 1**). The following personal details were retrieved: gender, date of birth, education of the participant, as well as parental education. Participants filled in a standard handedness questionnaire (67) to determine the dominant hand for making button presses during the tasks.

TABLE 1 | Descriptive statistics (mean ± SD) for each weight category based on body mass index (BMI).

		Normal-weight (*N* = 20)	Overweight (*N* = 17)	Obese (*N* = 17)	*p*-Value
Age (years)		29 ± 9	30 ± 8	33 ± 12	0.553
Gender	Male	7	11	6	0.127
	Female	13	6	11	
Education		2 ± 0	2 ± 0	2 ± 1	0.363
Parental education		1.5 ± 0.4	1.5 ± 0.5	1.2 ± 0.4	0.170
Barratt Impulsiveness Scale	Non-planning	11 ± 2	10 ± 3	11 ± 3	0.843
	Motor	13 ± 3	13 ± 2	13 ± 3	0.957
	Attentional	11 ± 2	11 ± 3	10 ± 2	0.727
Depression (Beck Depression Inventory)		4 ± 3	7 ± 7	7 ± 6	0.342
Food liking		7.91 ± 1.70	7.51 ± 1.03	7.78 ± 1.36	0.281
Perception of neutral outcome		3.0 ± 2.7	3.2 ± 2.9	1.8 ± 1.8	0.463
Waist circumference (cm)	Male	84.1 ± 6.9	96.5 ± 5.3	109.7 ± 12.9	0.001
	Female	72.9 ± 3.0	91.7 ± 9.9	110.4 ± 15.3	
BMI (kg/m²)		21.9 ± 1.6	27.3 ± 1.5	36.9 ± 5.1	0.001

No significant differences were found in age, gender, education, or parental education (Chi-squared/Kruskal–Wallis test). For education, the higher the value, the higher the education. No significant differences were found in impulsiveness scores, total depression score, food liking and perception of neutral outcome (ANOVA/Kruskal–Wallis test). As expected, waist circumference and BMI differed significantly between weight categories.

We included a measure of self-reported impulsiveness by means of the short 15-item version of the Barratt Impulsiveness Scale [BIS; (68–70)]. The BIS has good internal consistency and test-retest reliability (71). It differentiates between three subscales of impulsiveness: non-planning, motor and attentional impulsiveness.

We measured self-reported depression symptoms by means of the 21-item version of the Beck Depression Inventory [BDI-II; (72–74)]. The BDI-II shows a high internal consistency and test–retest reliability (74).

Furthermore, the preferred snack out of four different options was assessed. Four palatable, high-calorie snacks were used because it was previously shown that the PIT effect was stronger for these food products (14). Our selection included two sweet ones, pieces of chocolate and gummy bears, and two savory ones, crackers, and crisps. In a first step, participants had to rate them according to how much they liked them (1 = I like it best, 4 = I like it least). In a second step, a visual analog scale was used to quantify how much they liked their first choice. A picture of the participant's choice was subsequently utilized as reward/outcome in the PIT experiment.

After the instrumental and Pavlovian conditioning task, participants answered a query to check if they learned the correct associations (i.e., response–outcome in instrumental conditioning, stimulus–outcome in Pavlovian conditioning). At the end of the learning phase, participants rated how they perceived the neutral outcome on a visual analog scale (0 = neutral, 10 = punishment).

There were no significant differences between weight groups for impulsiveness, depression symptoms, food liking and perception of the neutral outcome between the three weight groups (ANOVA/Kruskal–Wallis test, **Table 1**).

Behavioral Experiment

Experimental Setup

The experimental setup consisted of an eye-tracker with the corresponding monitor (Tobii TX300 Eye Tracker, Tobii Technology, Stockholm, Sweden), a custom-made chin rest and a computer (HP EliteDesk 800 G1 Small Form Factor PC, HP Inc., Palo Alto, CA, USA).

We used two gray-scaled fractals as stimuli during the Pavlovian conditioning and PIT task, which were matched for luminance and complexity (75). Furthermore, we used images of Maltesers chocolate, Haribo gummy bears, TUC crackers and Zweifel crisps on a black background as reinforcing food outcomes during instrumental and Pavlovian conditioning (**Figure 1**). Only the participant's favorite food choice was used as a reinforcing outcome in the subsequent tasks. Note that participants were instructed that these images represented real food rewards, which were collected throughout the experiment and received at the end. The corresponding neutral outcome cues had a similar shape and color as the original food item (i.e., yellow oval for crisps) but without the rewarding property. Given that the visual properties of the outcomes were matched, differences in the eye movements can be narrowed down to the rewarding properties of the food outcome.

General Procedure

We used a standard PIT paradigm [for review, see Ref. (26)], consisting of three tasks: an instrumental conditioning task (i.e., response–outcome associations were learned), a Pavlovian conditioning task (i.e., stimulus–outcome associations were learned) and finally, a PIT test. The experiment was programmed in Matlab (version R2013b, The Mathworks Inc., Natick, MA, USA) by means of the Psychtoolbox [version 3; (76)].

Participants were asked to abstain from eating for 4 h before the experiment in order to increase the incentive value of the food and the food-related cue (60). The experiment was performed between 8 a.m. and 7.30 p.m. depending on laboratory, experimenter, and participant availability. A control analysis did not reveal an effect of time of testing on PIT ($r = -0.08$, $p = 0.550$), nor did weight groups differ in the time of testing (ANOVA, $p = 0.208$). Note that we did not control for sleep quantity or quality on the night preceding the experimental day, which can alter the incentive value of food (77) and performance on visual and cognitive tasks (78, 79). Also, we did not collect data on the phase of the menstrual cycle and thus cannot estimate or control for any effects of menstrual phase on our measures of interest. It has been shown that circulating estradiol concentrations have an influence on energy consumption (80) and may reduce food intake by decreasing neural activity to food cues in visual cortical pathways associated with reward (80, 81).

Participants received a general verbal instruction before the experiment. Before each task, three to four example trials were shown by one of two female experimenters to rule out any misunderstandings. During the tasks, the participants had to position their chin on the chin rest. They were instructed to look at the screen during the whole experiment, to maintain a stable position of their head and to blink as little as possible. Importantly, they were told that they would receive all food outcomes collected during the whole PIT experiment after the experiment. Hence,

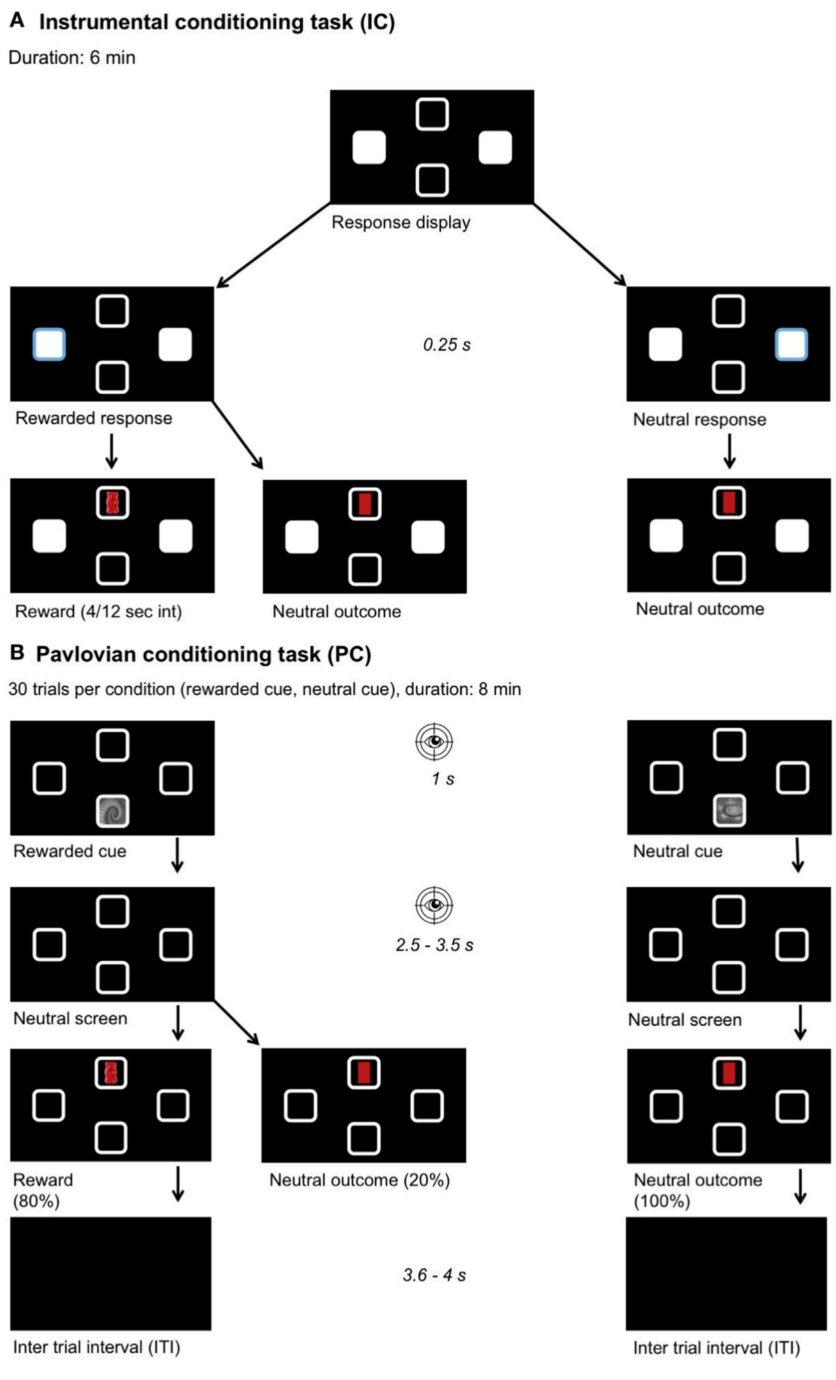

FIGURE 1 | Continued

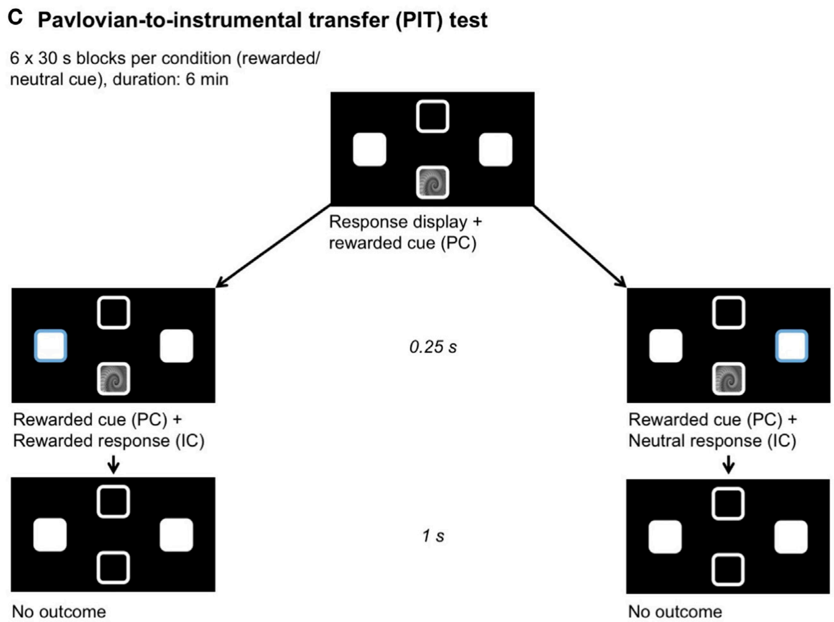

FIGURE 1 | Experimental setup. Participants chose their preferred food out of four options (chocolate, gummy bears, crackers, crisps). A picture of this food was then used as a reward during learning. Participants were instructed they would receive a proportional amount of the collected foods after the experiment. The position of the outcome and stimulus and all learning associations were pseudo-randomized across participants. **(A)** Instrumental conditioning: participants learned the response–outcome associations, one key press yields a reward and the other a neutral outcome. A partial reinforcement schedule was used with a variable time interval between 4 and 12 s. **(B)** Pavlovian conditioning: participants learned the stimulus–outcome associations, one fractal yields a reward and the other a neutral outcome. After stimulus presentation, a neutral screen showing four empty squares appeared. Eye movements were recorded during stimulus and neutral screen presentation to measure the conditioned response toward the rewarded cue. **(C)** Pavlovian-to-instrumental transfer task: we measured the influence of the previously learned associations on the response behavior when the same stimuli as before were presented and under nominal extinction.

participants did not explicitly know how many rewards they collected in the instrumental and Pavlovian task, which reduces a possible satiation effect. The light was switched off during the whole experiment to improve the quality of the eye tracking and keep conditions constant over all three tasks of the PIT experiment.

Instrumental Conditioning Task

The goal of this task was that the participants learned the response–outcome associations (**Figure 1A**). The participant was free to choose between two different response options (left or right) by using their dominant hand to make a left arrow or a right arrow key press. One of these keys was assigned to the food (e.g., crisp), the other to a neutral outcome, which had a similar shape and color as the food (i.e., yellow oval). The response that lead to a reward was called the "rewarded response," the other "neutral response." After the response, the reward or the neutral outcome was shown for 1 s in the top or bottom square depending on the randomization. A partial reinforcement schedule was used with a variable time interval between 4 and 12 s (4/12 s interval). This means that after a rewarded response followed by rewarded outcome, the subsequent rewarded responses for a delay period of 4–12 s led to a neutral outcome. This task lasted 6 min. The participants were asked to collect as many rewards as possible and to memorize, which key was associated with the reward. Participants were told that not every "rewarded response" will lead to a reward (i.e., awareness of the partial reinforcement schedule). Directly after completing the task, the participants were tested on the response–outcome associations. In average, only 20% of all responses were rewarded.

Pavlovian Conditioning Task

The goal of this task was to learn the cue-outcome associations (**Figure 1B**). An optical eye-tracker (Tobii TX300 Eye Tracker, Tobii Technology, Stockholm, Sweden) was used for measuring eye movements. Eye movements were recorded at 60 Hz in order to analyze the amount of time spent within two areas of interest. The areas of interest were defined as the upper and lower square (8.4 cm^2), where the cue and the outcome were presented. Eye movements in these two areas of interest (i.e., upper and lower square) were taken as a measure for the conditioned response that arises in the time course of the Pavlovian conditioning task (49). This conditioned response was later used to categorize the participants into sign- and goal-trackers. Randomly one of the two possible cues was displayed either on the top or bottom square of the screen for 1 s. One cue was associated with the food reward, called the "rewarded cue," and the other was associated with the neutral outcome, called "neutral cue." The cue–outcome associations were counterbalanced across participants. The outcomes were presented in the same square as during instrumental conditioning and the cues were presented in the opposite square.

After stimulus presentation, a neutral screen showing the four empty squares appeared. Eye movements were recorded during cue and neutral screen presentation. This neutral screen was used because otherwise eye movements are naturally biased toward visible cues. The presentation of the neutral screen was jittered between 2.5 and 3.5 s. After the jitter, the reward or the neutral outcome contingent to the presented cue was displayed for 1 s. The rewarded cue was followed by a reward in 80% of the trials and by a neutral outcome in 20% of the trials, whereas the neutral outcome always succeeded the neutral cue (100%). The participant was told to memorize the contingencies. There was an inter-trial-interval (ITI) lasting 3.6–4 s. The ITI (mean = 3.8 s) was deliberately chosen to be longer than the jitter (mean = 3 s), in order to ensure close temporal proximity of the cue to the contingent outcome. Thirty trials per condition were performed and the whole task took about 8 min. In total, 24 rewards were acquired during this task.

PIT Test

The goal of this task was to measure the influence of the previously learned associations on the response behavior (**Figure 1C**). During the PIT test, the response display of the instrumental conditioning task together with cues from the Pavlovian conditioning were presented. In blocks of 30 s, the rewarded and neutral cue were randomly displayed in the square corresponding to the one used during Pavlovian conditioning. Again here, the participants were free to make as many responses with their dominant hand as they wanted to. The test was performed under nominal extinction meaning that their response did not lead to any displayed outcome but the participants were instructed that the rewards were counted in the background. Participants were not explicitly told to collect as many rewards as possible or to pay attention neither to ignore the Pavlovian cues. The task lasted 6 min, each cue was shown for 30 s and six times.

Analysis

Eye-Tracking Data

Eye tracking of the first second of each trial (i.e., during cue presentation) was discarded because all participants fixated the cue. From the remainder, the variable "eye index" was calculated for each participant, each cue (rewarded or neutral) and for six bins of five trials of the Pavlovian conditioning task. We only considered fixation periods greater than 116 ms as suggested by previous literature (49). The eye index was calculated as the time on reward location as a percentage of the total time spent on the reward and cue location (i.e., upper and lower square):

$$\text{eye index} = \frac{\text{time on reward location}}{\text{time on reward location} + \text{time on cue location}} * 100.$$

Even though most participants spent more time on the reward location, there were individual differences in how long participants looked at the cue location. Therefore, a "fixation style" was derived for each participant based on a median split of the eye index based on data from the second half (trials 16–30) of the reward condition. We used the second half of the data because contingency learning has been shown to be stable during the later phases of Pavlovian conditioning experiments (49). Individuals of the group "low eye index" looked relatively longer at the cue location than individuals of the group "high eye index."

Behavioral Data

The "PIT effect" is defined as an interaction between "condition" and "response," i.e., when participants make more rewarded than neutral responses during the presentation of the reward-predicting cue and *vice versa* for the neutral cue. The higher the PIT effect, the stronger is the influence of the Pavlovian cue on goal-directed behavior.

Statistics

The data were analyzed using mixed-effects models in SPSS 23 (IBM Corp., Armonk, NY, USA). Mixed-effects models are more robust to non-normal distributed data and show a better fit for repeated measurements than conventional ANOVAs (82, 83). Depending on the analysis, condition and time or condition and response were modeled as fixed effects and subjects were always modeled as a random effect. We used a compound symmetry covariance structure, which assumes nearly equal variance and covariance across factors and is, therefore, a good fit for repeated measures designs (84). Based on previous literature (49, 52, 85–87), we added impulsiveness and depression as covariates of no interest to our statistical model of PIT. Bonferroni-corrected *post hoc* tests were applied if a significant main effect was detected the linear mixed-effects models. We report Cohen's d as a measure for effect size (small $d = 0.20–0.49$, medium $d = 0.50–0.80$, large $d > 0.80$) (88).

RESULTS

Instrumental Task

Participants ($N = 54$) chose the rewarded response significantly more often than the neutral response indicating that they successfully learned the response–outcome associations (**Figure 2A**; **Table 2**). This learning effect can be considered as strong ($p < 0.001$, $d = 2.9$). Weight category did not significantly influence the number of rewarded and neutral or the total number of responses in instrumental conditioning (**Table 2**). Participants neutral key presses still make up approximately 25% of all responses, which is probably due to the partial reinforcement schedule applied during the instrumental task.

Pavlovian Conditioning Task

Our analysis of eye movements indicated that all participants ($N = 54$) successfully learned the stimulus–outcome associations during Pavlovian conditioning. Specifically, we analyzed the participants eye movements after stimulus onset before the outcome was displayed (i.e., during the neutral screen, see **Figure 1B**).

The eye index was analyzed in bins of five trials to capture learning effects for the rewarded and neutral condition (**Figure 2B**) and each weight category (**Figures 2C–E**; **Table 3**). The rewarded condition showed a significantly higher eye index than the neutral

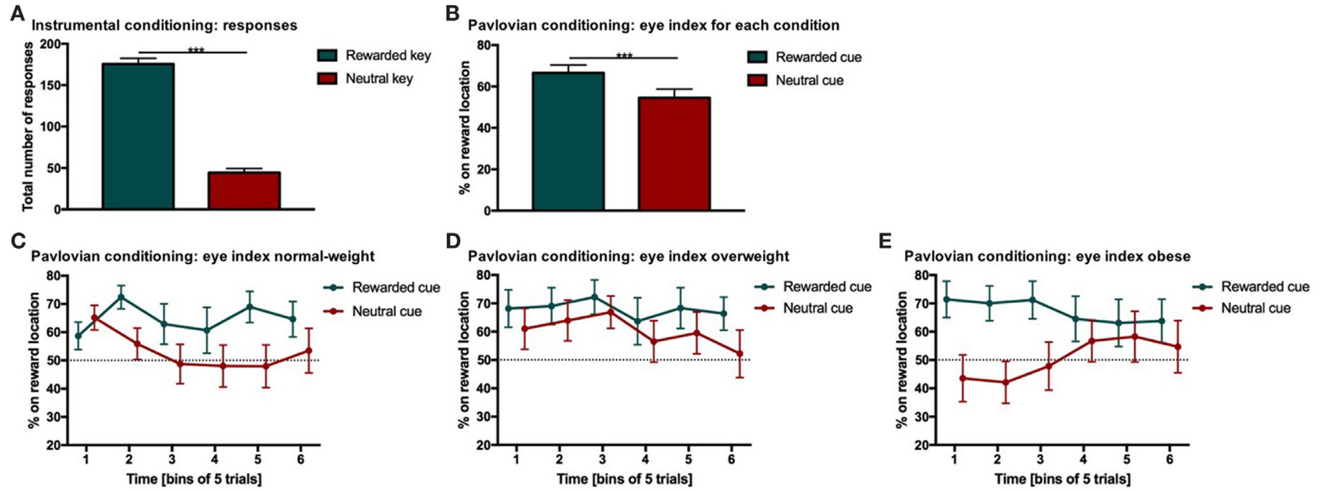

FIGURE 2 | Results from instrumental and Pavlovian conditioning. Error bars indicate SEM. The rewarded key/condition is depicted in green and the neutral key/condition in red. **(A)** Total number of responses for each condition during instrumental conditioning. Participants chose the rewarded response significantly more often than the neutral response (***$p_{\text{RESPONSE TYPE}} < 0.001$, $d = 2.9$). **(B)** Percentage of time on reward location during Pavlovian conditioning. The eye index indicates if more time was spent on the reward location or on the cue location of the screen. The eye index was analyzed in bins of five trials for the rewarded and neutral condition and each weight category. The percentage of time on the reward location differed significantly between rewarded and neutral trials (***$p_{\text{CONDITION}} < 0.001$, $d = 0.41$). **(C–E)** Percentage of time on reward location during Pavlovian conditioning for each weight category. The eye index differed significantly between conditions over time and weight categories (normal-weight $N = 20$, overweight $N = 17$, obese $N = 17$, $p_{\text{CONDITION*TIME*WEIGHT CATEGORY}} < 0.05$).

condition ($p < 0.001$, $d = 0.41$, **Figure 2B**). This finding indicates that for the rewarded condition and throughout the conditioning task, participants spent more time fixating the reward than the cue location. This was different from the neutral condition, in which participants spent relatively more time fixating the cue location.

We found a significant interaction between condition, time and weight category ($p < 0.05$, **Figures 2C–E**; **Table 3**). This effect was driven by patterns of fixation by condition and time in each of the three weight groups. Normal-weight participants consistently fixated on the reward location for rewarded cues and the cue location for neutral cues after the first time-bin. In contrast, overweight participants fixated primarily on the reward location irrespective of whether they saw the rewarded or the neutral cue and this fixation pattern was stable over time. Obese participants showed yet another fixation pattern in that they immediately favored the reward location for the rewarded cues and initially favored the cue location on neutral trials. However, in the second half of the trials the obese subjects shifted to favoring the reward location for neutral cues as well.

In a control analysis, we analyzed the percentage of time participants spent looking at other areas than the defined area of interest (i.e., upper and lower square) for the first and second half of the trials in each condition (**Table 4**). Participants spent slightly more time outside the area of interest after the neutral compared to the rewarded stimulus (reward = 19.13 ± 15.58, neutral = 22.85 ± 15.72, $p < 0.001$, $d = -0.24$). Furthermore, participants spent slightly more time outside the area of interest in the second compared to the first half of the experiment (first = 19.85 ± 15.20, second = 22.13 ± 16.23, $p < 0.05$, $d = -0.15$). In addition, the percentage of time where eye movements could not be tracked for example because of blinks or not focusing the screen (i.e., missing values) changed significantly over time (first = 7.58 ± 11.39, second = 10.79 ± 14.66, $d = -0.24$, $p < 0.001$) and it was slightly higher after the neutral cue (reward = 8.60 ± 12.58, neutral = 9.76 ± 13.82, $p = 0.090$) (**Table 4**). Approximately 9% of the eye-tracking data was discarded from the analysis. Importantly, weight category had no significant influence on the time spent outside of the target areas or on missing values where eye tracking failed.

TABLE 2 | Statistical analysis of the instrumental conditioning.

Effect	df	*F* (nr responses)	*p* (nr responses)
Response type	1, 51	117.6	0.001*
Weight category	2, 51	0.4	0.698
Response type*weight category	2, 51	0.2	0.824

Response type defines if a rewarded or neutral response was made.
Asterisks indicate significant effects.

TABLE 3 | Statistical analysis of eye index during the Pavlovian conditioning.

Effect	df	*F* (eye index)	*p* (eye index)
Condition	1, 561	51.9	0.001*
Time	5, 561	0.5	0.747
Weight category	2, 51	0.3	0.738
Condition*time	5, 561	0.5	0.794
Condition*weight category	2, 561	2.3	0.107
Time*weight category	10, 561	1.0	0.453
Condition*time*weight category	10, 561	1.9	0.042*

Asterisks indicate significant effects.

TABLE 4 | Statistical analysis of the time participants spent outside the targets and missing values during Pavlovian conditioning.

Effect	df	*F* (time outside)	*p* (time outside)	*F* (not tracked)	*p* (not tracked)
Condition	1, 153	13.2	0.000*	2.9	0.090
Time	1, 153	4.7	0.032*	20.2	0.001*
Weight category	2, 51	0.9	0.407	1.2	0.318
Condition*time	1, 153	3.0	0.086	0.1	0.782
Condition*weight category	2, 153	0.1	0.869	0.8	0.439
Time*weight category	2, 153	0.3	0.728	0.3	0.723
Condition*time*weight category	2, 153	1.7	0.185	0.6	0.528

Asterisks indicate significant effects.

TABLE 5 | Statistical analysis of the number of responses during the Pavlovian-to-instrumental transfer including the repeated factors CONDITION, RESPONSE STYLE, and the group variable WEIGHT CATEGORY.

Effect	df	*F* (nr responses)	*p* (nr responses)
Condition	1, 108	1.5	0.229
Response type	1, 108	0.1	0.929
Weight category	2, 36	3.8	0.031*
Condition*response type	1, 108	0.8	0.370
Condition*weight category	2, 108	0.3	0.742
Response type*weight category	2, 108	0.1	0.999
Condition*response type*weight category	2, 108	3.4	0.036*

Asterisks indicate significant effects.

PIT Task

To test for a PIT effect and possible differences between weight categories and fixation style measured during Pavlovian conditioning, we added these factors as between-subject factors to a linear mixed-effects model. Weight categories were formed based on BMI and fixation style based on a median split on the conditioned eye response to the rewarded cue in the second half of the Pavlovian conditioning (see Analysis, for more detail). Furthermore, we added impulsiveness (BIS) and depression (BDI) total scores as covariates of no interest to our statistical model of PIT. This was based on previous literature, which has shown that the PIT effect may be influenced by depression and that the conditioned response is associated with impulsiveness (49, 52, 85–87).

We found a PIT effect such that participants chose the rewarded response more often than the neutral response when the rewarded cue was displayed and vice versa for the neutral cue. The strength of the PIT effect was modulated depending on the participant's weight status as indicated by a significant CONDITION*RESPONSE TYPE*WEIGHT CATEGORY effect ($p < 0.001$, **Tables 5** and **6**; **Figure 3**). This effect reflects that the PIT effect was strongest in overweight individuals (**Figure 3B**, $p_{\text{CONDITION*RESPONSE IN OVERWEIGHT}} < 0.001$), which were highly sensitive to the presence of the rewarded cue (causing a clear preference for selecting the rewarded key). The PIT effect in normal-weight and obese participants was also present but clearly smaller ($p_{\text{CONDITION*RESPONSE IN NORMAL-WEIGHT}} < 0.001$, $p_{\text{CONDITION*RESPONSE IN OBESE}} < 0.025$). Participants pressed the neutral key also during the rewarded cue presentation presumably due to the partial reinforcement schedule used in the instrumental conditioning task.

TABLE 6 | Statistical analysis of the number of responses during the Pavlovian-to-instrumental transfer including the repeated factors CONDITION, RESPONSE STYLE, and the group variables WEIGHT CATEGORY, FIXATION STYLE.

Effect	df	*F* (nr responses)	*p* (nr responses)
Condition	1, 72	0.1	0.934
Response type	1, 72	0.9	0.357
Weight category	2, 24	2.7	0.090
Fixation style	1, 24	1.1	0.309
Condition*response type	1, 72	0.1	0.851
Condition*weight category	2, 72	0.1	1.000
Condition*fixation style	1, 72	0.1	0.955
Response type*weight category	2, 72	0.2	0.786
Response type*fixation style	1, 72	0.1	0.786
Weight category*fixation style	2, 24	0.1	0.869
Condition*response type*weight category	2, 72	8.9	0.001*
Condition*response type*fixation style	1, 72	0.6	0.454
Condition*weight category*fixation style	2, 72	0.2	0.999
Response type*weight category*fixation style	2, 72	0.1	0.872
Condition*response type*weight category*fixation style	2, 72	4.0	0.022*

Asterisks indicate significant effects.

We also reported a significant main effect of WEIGHT CATEGORY ($p_{\text{WEIGHT CATEGORY}} < 0.05$, **Table 5**). However, the differences in the total number of responses between weight categories were in a very small range (normal-weight = 57 ± 38, overweight = 55 ± 41, obese = 54 ± 32). Therefore, we do not believe that this represents a general difference in motivation to do the task.

Next, we tested the association between the conditioned response behavior measured during Pavlovian conditioning (i.e., fixation style) and the PIT effect. Therefore, we identified two groups "low eye index" (i.e., individuals who preferentially fixated the cue location) versus "high eye index" (i.e., individuals who preferentially fixated the reward location) which were similarly distributed across the weight categories (**Figure 4A**). Statistics revealed that the PIT effect is modulated by fixation style but that this modulatory effect depends additionally on weight category (four-way interaction CONDITION*RESPONSE TYPE*WEIGHT CATEGORY*FIXATION STYLE, **Table 6**; **Figures 4B–D**). In both the normal-weight (**Figure 4B**) and obese groups (**Figure 4C**), individuals showing a high eye index exhibited a stronger PIT effect triggered by reward cues than individuals showing a low eye index. By contrast, in overweight participants this dissociation was absent, i.e., we observed a high PIT effect irrespective of whether individuals exhibited low or high eye index tendencies during conditioning. Interestingly, obese individuals with a high eye index (**Figure 4D**) were not only sensitive to the reward cue but also largely *insensitive* to the neutral cue since they chose the congruent versus incongruent key with nearly equal probability for this latter condition.

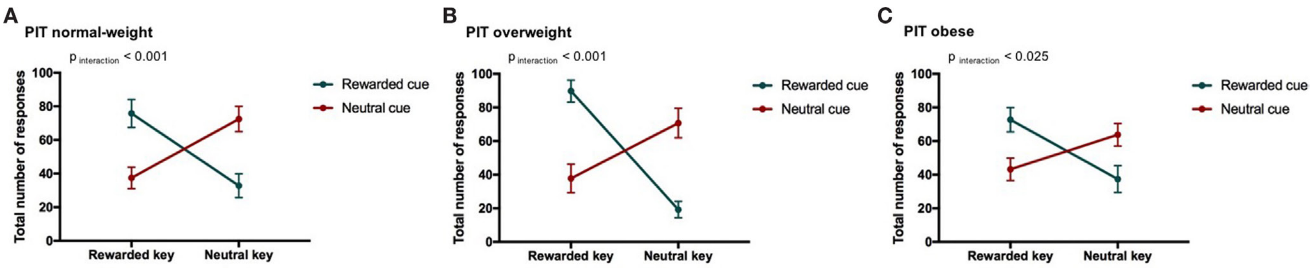

FIGURE 3 | Result from Pavlovian-to-instrumental transfer (PIT) and weight category. Error bars indicate SEM. The rewarded condition is depicted in green and the neutral condition in red. The strength of the PIT effect depends on weight category (normal-weight $N = 20$, overweight $N = 17$, obese $N = 17$, $p_{\text{CONDITION*RESPONSE TYPE*WEIGHT CATEGORY}} < 0.001$). The goal-directed behavior of overweight individuals was most strongly influenced by cues. **(A)** PIT normal-weight, **(B)** PIT overweight, and **(C)** PIT obese.

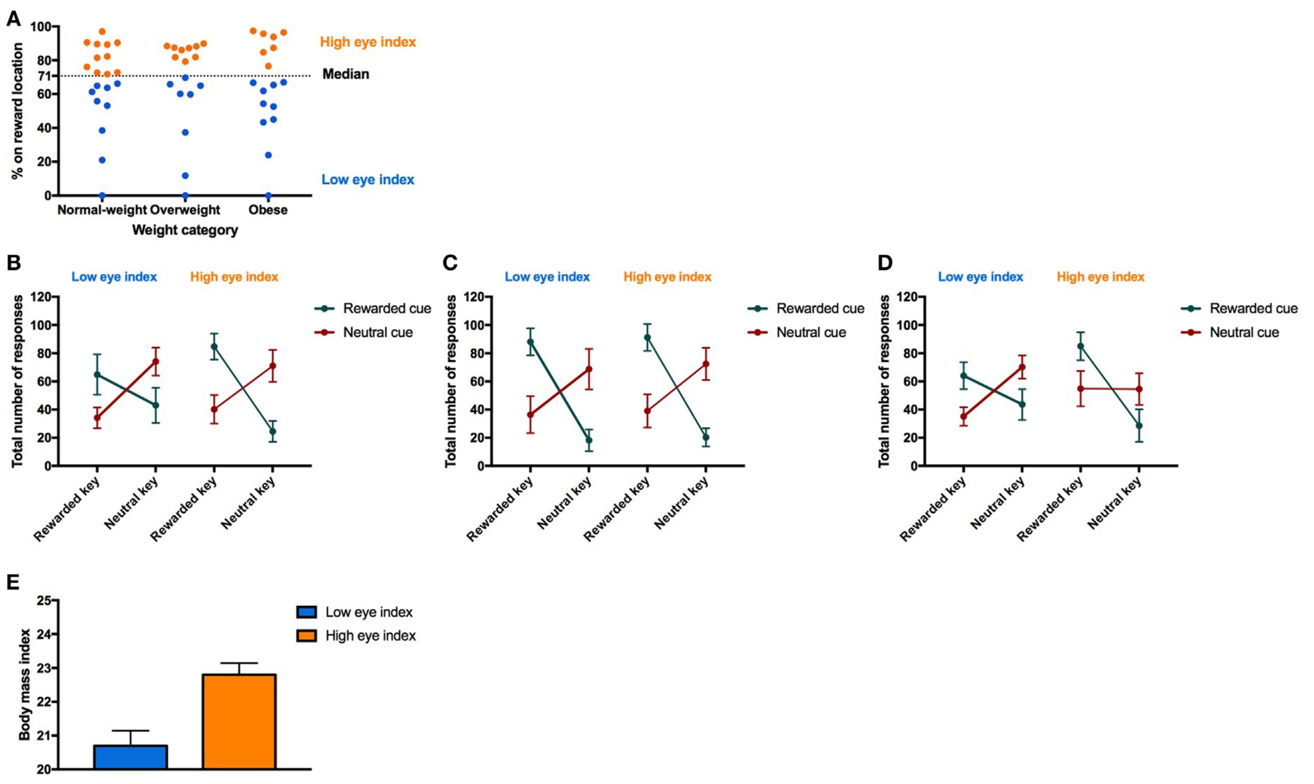

FIGURE 4 | Result from Pavlovian-to-instrumental transfer (PIT) for the "low eye index" and "high eye index" group. Error bars indicate SEM. The rewarded key/condition is depicted in green and the neutral key/condition in red. The "low eye index" group is represented in blue and the "high eye index" group in orange. **(A)** Categorization of fixation style. Fixation style was based on a median split on the conditioned eye response in the second half of all trials after the rewarded cue during Pavlovian conditioning. **(B–D)** PIT effect for different weight categories and fixation styles. Fixation style showed a significant influence on PIT depending on the weight category ($p_{\text{CONDITION*RESPONSE TYPE*WEIGHT CATEGORY*FIXATION STYLE}} < 0.025$). In the normal-weight group, the "low eye index" group consisted of 11 and the "high eye index" of nine individuals. In the overweight group, the "low eye index" group consisted of eight and the "high eye index" of nine individuals. In the obese group, the "low eye index" group consisted of 10 and the "high eye index" of 7 individuals. **(E)** Body mass index (BMI) in normal-weight individuals for each fixation style. The "high eye index" group showed an increased BMI within the healthy range compared to the "low eye index" group ($p < 0.001$, $d = 1.7$).

Finally, we tested whether there is an association between the fixation style observed during Pavlovian conditioning and BMI by running separate mixed-effect models within each of the weight groups. Unexpectedly, we found that normal-weight individuals of the "high eye index" group showed an increased BMI within the healthy range ($d = 1.7$, $p < 0.001$, **Figure 4E**). This effect was surprisingly strong and was not be found in overweight or obese individuals ($p > 0.646$).

DISCUSSION

Here, we tested whether sensitivity to rewards and reward-predicting cues is abnormal in overweight and obese individuals versus normal-weight controls and whether such differences in reward sensitivity modulate goal-directed behavior. We addressed this question with a PIT experiment and investigated whether food-predicting cues differentially influence goal-directed behavior of normal-weight, overweight, and obese individuals. Furthermore, we applied eye tracking during Pavlovian conditioning as a proxy of the incentive salience of the predicted reward. Our findings imply that cue-controlled behavior might be altered in overweight and obese individuals as discussed in further detail below.

Overweight Participants Exhibit a Higher PIT Effect than Normal-Weight or Obese Individuals

Overweight participants showed the strongest PIT effect compared to normal-weight and obese subjects (see PIT Task, **Figures 3A–C**). This finding extends previous observations that overweight and obese adults showed enhanced reactivity to food stimuli during the passive observation of stimuli, a visual dot probe task, different versions of the Stroop task or in questionnaires (37, 87, 89). These studies quantified food cue reactivity by measuring reaction time, eye-tracking duration and direction biases, pupil diameter, electroencephalography, and functional magnetic resonance imaging (37). Eye tracking in particular revealed duration orienting biases toward food cues and decreases in pupil diameter [a marker of noradrenergic increases and higher attentional engagement (90, 91)] to high-calorie foods in overweight and obese subjects (92–94). Our results extend these previous reports by showing that goal-directed behavior in overweight individuals is strongly influenced by cues associated with food rewards, as tested by the PIT paradigm, while the influence of neutral cues was similar to the normal-weight group. Interestingly, no such reward-specific PIT effect was observed for the group of obese individuals. Note that there were no group differences in food liking. Even though this result in obese individuals is puzzling at first, it is in line with a recent study which also found that obese individuals had a PIT effect comparable to normal-weight subjects (57). However, Watson et al. (57) showed an increased PIT effect for high-calorie versus low-calorie foods, which was only found in obese subjects (57). One potential explanation of the finding that the PIT effect is similar in obese and healthy individuals is that habitual intake of energy dense diets may induce a compulsive style of eating that is insensitive to environmental cues (see Physiological Mechanism and Open Questions).

Taken together, our finding that motivation induced by reward-related cues is increased in overweight individuals is in line with the incentive sensitization theory of addiction (15–21). The incentive sensitization theory of addiction predicts an attentional bias toward reward-related cues, which is in line with our eye movement results during Pavlovian conditioning, and a pathological motivation for rewards and reward-related cues (i.e., compulsive "wanting") (17, 20). The pathological motivation for food and food-predicting cues was in the present study displayed by the increased PIT effect in overweight individuals. Some studies in humans investigating the influence of Pavlovian cues on instrumental responding in substance dependence also showed an increased PIT effect in addicts compared to controls (48, 57, 95). There is nevertheless some evidence for no association between PIT and substance dependence in other studies (11, 42, 43, 50, 56, 96).

However, our data further indicate that once the obese status is reached, incentive sensitization might return to normal levels. It is tempting to speculate that hypersensitivity might be reduced in obese individuals due to habitual/compulsive overeating (97, 98), but this was not directly tested in the present study. It is also possible that obese individuals may direct less attention toward small food rewards (as used here) and/or their preference may be shifted to stimuli with a larger subjective value (e.g., more palatable and calorie rich rewards), which has been shown to significantly influence PIT (53). We did not collect data on the subjective reward value in the present study. Therefore, possible differences in reward valuation between weight groups might offer an alternative explanation for the reduced PIT effect observed in obese individuals.

Eye Movements during Pavlovian Conditioning Differ between Normal-Weight, Overweight, and Obese Individuals

We employed eye tracking to measure behavioral changes during Pavlovian conditioning. Eye tracking has been used previously to measure reactivity to passively observed food stimuli (34, 37) and to investigate individual differences in the extent to which individuals attribute incentive salience to reward-predicting cues versus the reward itself (49). Here, we performed eye tracking in the period between seeing the cue and receiving a reward, i.e., while participants saw only a neutral screen but no visual stimuli. We chose to modify previous paradigms (49) because gaze is automatically attracted to visual cues unless these eye movements are actively inhibited.

In our study, the conditioned eye response toward the rewarded and neutral cue location during Pavlovian conditioning was differently modulated depending on the participant's weight status (see Pavlovian Conditioning Task, **Figures 2C–E**). More specifically, we found during Pavlovian conditioning that overweight individuals exhibited a general orientation bias toward the reward location irrespective of whether they performed a reward cue trial or a neutral cue trial. This lack of a clear dissociation between reward and neutral trials remained relatively stable across conditions and is broadly consistent with the observation that overweight adults showed enhanced reactivity to food stimuli during the passive observation of stimuli, a visual dot probe task, different versions of the Stroop task or in questionnaires (37, 87, 89). Specifically, we confirmed and extend these studies by showing that overweight individuals exhibit a general duration orientation bias toward the reward location, suggesting larger sensitivity to the anticipated reward, an interpretation that is consistent with a larger PIT effect for cues that have been associated with food rewards. Also, obese individuals differed from normal-weight controls but mainly during the initial half of Pavlovian conditioning, where they exhibited a clear distinction between conditioned responses to reward cues (which caused long fixation durations on the reward location) and the neutral cues (which resulted in longer fixation durations of the cue location). However, this strong initial differentiation was clearly reduced at the end of the Pavlovian conditioning.

Individual Differences in Conditioned Responses Differentially Influence PIT Effects in Normal-Weight, Overweight, and Obese Individuals

We used the eye movement behavior to detect individual differences and categorize the participants into a group of individuals with a "low eye index," i.e., they fixated predominantly the cue location or "high eye index," i.e., they fixated predominantly the reward location. Our experiment revealed that normal-weight individuals of the group "high eye index" showed a stronger PIT effect for the reward cue than individuals of the group "low eye index" (**Figures 4B,E**). There is only one group of researchers that performed a similar experiment to investigate the influence of the individual fixation style on PIT (49). Contrary to our results, they found that a stronger conditioned eye movement response toward the cue led to an increased modulation of goal-directed behavior. However, they quantified eye movements while the cue was still on the screen proposing that the eye movement behavior was a proxy of cue approach behavior observed in animals, also known as "sign-tracking" (22, 23, 58, 99, 100). By contrast, we tested the conditioned eye response during a neutral screen suggesting that the eye movement behavior might mainly reflect the incentive salience of the predicted reward (see **Figure 1B**). We found that individual differences during Pavlovian conditioning (i.e., "low" versus "high eye index") interacted with the weight category to influence PIT.

In both the normal-weight and obese groups, the "high eye index" group exhibited a stronger PIT effect triggered by reward cues than the "low eye index" group. By contrast, in overweight participants we observed a high PIT effect irrespective of whether individuals exhibited high or low eye index tendencies during conditioning. However, these data have to be interpreted with caution because the subgroups were quite small. One possible explanation for individual differences in the PIT effect is that not only incentive salience, but also inhibitory control has an impact on how goal-directed behavior is influenced by Pavlovian cues. Normal-weight and obese individuals expressing a "low eye index" might show a smaller PIT effect because they express an inhibitory control mechanism, which regulates the influence of reward-related cues on goal-directed behavior. However, in overweight expressing a "low eye index" this inhibitory mechanism might be altered so that they express a stronger PIT effect, which means that these participants are more susceptible to the influence of cues. Response inhibition for example with a Go/Nogo task was not tested in the present study. Nevertheless, reduced response inhibition was previously shown to be related with overeating and unsuccessful dieting (101, 102). Our finding is also in line with Trick et al. (103) who have shown that a higher conditioned response measured during Pavlovian conditioning is not automatically translated into a higher PIT. The same applies to electrophysiological responses (i.e., P300) that were not correlated with the PIT effect in social drinkers (96).

Furthermore, we found that normal-weight expressing a "high eye index" showed an increased BMI within the healthy range. This could be linked to previous research suggesting that an increased attentional bias toward food cues as a risk factor for gaining weight (37). However, a recent review of the literature has shown that attention to food or drug cues is a weak index of the problem behavior (104).

Interpretational Issues

Our research paper presents a novel view on how food-related cues influence eye movements and goal-directed behavior in overweight and obese individuals. However, the interpretation of our findings is subject to specific limitations.

First, individual differences in reward valuation could have influenced cue-controlled behavior. We tried to overcome this issue by testing all participants in the same dietary state (i.e., hungry) and by letting them choose their favorite snack out of four options. Reward liking based on a visual analog scale was not different between groups (WEIGHT CATEGORY, FIXATION STYLE) and has not influenced the conditioned eye response nor PIT.

Second, our experiment does not enable us to determine whether the overweight individuals' sensitivity to environmental cues holds only for food-specific cues or whether these individuals show a generally increased sensitivity to reward-predicting cues. Both general and substance-specific effects of reward have been found in previous studies on alcohol-dependent patients (45, 48) and smokers (95). Thus, although the dissociation of general and food-specific reward effects was not the focus of the present study, it represents an important question for future research.

Physiological Mechanism and Open Questions

What exactly might be the underlying mechanism for finding differences in the conditioned eye response and probably also the goal-directed behavior in normal-weight, overweight, and obese individuals? It is well-established that eating palatable food increases brain activity in regions implicated in reward processing (i.e., striatum, midbrain, amygdala, orbitofrontal cortex) and leads to a dopamine release in the dorsal striatum. The amount of dopamine is related to the pleasantness ratings (i.e., "liking") and the caloric density of the reward/food [for reviews, see Ref. (20, 21)]. Anticipated food intake or exposure to cues/food images increases activity within brain regions known for incentive reward valuation (i.e., amygdala, orbitofrontal cortex) (21, 105, 106) and results in a similar dopamine release as rewards (107). The incentive sensitization model posits that repeated intake of high-calorie palatable food leads to an increased brain activity in regions involved in incentive valuation to cues that are associated with palatable food intake *via* conditioning, which prompts craving and overeating when these cues are available (15, 17, 20, 21). There is strong evidence that dopaminergic neurons projecting to the striatum and ventral pallidum respond to the receipt of palatable food, but after repeated pairings between food and a cue, fire in response to the food-related cue and no longer in response to the receipt of food [for review, see Ref. (107)]. This shift during stimulus-outcome learning attributes value to the cues themselves and thereby guides motivated behavior (59, 107–109). This process is likely to contribute to overeating and lead to weight gain. Consistent with the incentive sensitization theory, obese humans showed an increased activity in brain regions associated with reward and motivation, brain regions associated with motor responses and brain regions associated with attention to food pictures, food cues, or food commercials (20, 21, 27, 110–114). This greater responsivity to food-associated cues could be reflected in the increased conditioned eye response in obese individuals observed in our experiment. A food-related cue attributed with incentive salience can then trigger actions to obtain the food (i.e., increased "wanting") (20). In our study, this increased "wanting"/motivation due to food-associated cues is a potential reason for observing stronger PIT effects in overweight. However, our study suggests that this is probably not the case for obese participants. There is some evidence from animal and human experiments that habitual intake of high-fat diets decreases dopamine signaling in the reward circuitry (21, 115, 116). This is in agreement with experiments on cocaine and alcohol-dependent individuals (117, 118). However, habitual processes were not measured with our experimental paradigm.

A combination of our behavioral paradigm with additional methods such as neuroimaging or pharmacological interventions would allow better understanding of the underlying mechanism. This would also facilitate the integration of our findings into animal research on individual variation, conditioned motivation, overeating, and addiction. Furthermore, it would be interesting to investigate the influence of environmental cues in a group of patients after bariatric surgery or after other interventions (i.e., diet, behavioral training, see Clinical Implication).

Clinical Implication

Our findings may prove to be of practical relevance because we show that the overweight group's conditioned eye response and goal-directed behavior is generally more susceptible to the influence of environmental cues. Thus, it might be beneficial to address mental strategies to resist food-related cues also in the psychological/behavioral treatment of overweight individuals [e.g., extinction training, attentional control training, response training (60, 119–121)]. Manipulating the attentional bias to drug cues *via* attentional control therapies was shown to reduce some of the behavioral control drug cues have over addicts (60, 122–124). To the best of our knowledge, there is only one study, which applied the attention bias modification (ABM) program as used in addictive disorders to overweight and obese individuals (i.e., binge eaters) (125). This study revealed a decrease in weight, eating disorder symptoms, binge eating, and loss of control and responsivity to food after an 8-week ABM training (125). However, these results should be interpreted with caution because of the low sample size and single-group open label trial. A combination of food response and attention training has successfully downregulated reward and attention brain networks and reduced body fat (120, 121). For obese individuals, which in our study did not differ from normal-weight controls regarding the influence of external cues on goal-directed behavior, other treatments are possibly more appropriate because maladaptive eating behavior has already been consolidated [e.g., cognitive behavioral therapy, motivational interviewing, habit reversal training, inhibition control training (102, 126)]. The finding of the present study together with previous studies (8, 9, 14, 57) should also be considered when new policies and guidelines for food advertisements will be drafted.

CONCLUSION

We found that PIT effects for food rewards differed as a function of weight status. In particular, overweight individuals were more strongly influenced by food-associated stimuli than both obese and normal-weight individuals. Eye movements during Pavlovian conditioning were not related to the strength of the PIT effect in overweight or obese individuals. However, normal-weight individuals with a stronger conditioned response toward the reward location showed a stronger PIT effect and are possibly at risk to gain weight. Our findings are generally in line with the incentive sensitization theory predicting that overweight individuals are more susceptible to food-related cues than normal-weight controls. We speculate that this hypersensitivity might be reduced in obese participants due to habitual/compulsive overeating or differences in reward valuation.

ETHICS STATEMENT

All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the Canton Zurich.

AUTHOR CONTRIBUTIONS

All authors conceived of and designed the experiment; RL programmed the experiment, analyzed the data, wrote the main manuscript text, and prepared the figures; AB collected the data; all authors read, corrected, and approved the final manuscript.

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Application of Intelligent Recommendation Techniques for Consumers' Food Choices in Restaurants

Xinke Li[1,2]*, *Wenyan Jia*[2], *Zhaofang Yang*[2,3], *Yuecheng Li*[2], *Ding Yuan*[4], *Hong Zhang*[4] and *Mingui Sun*[2,5]

[1] College of Communication Engineering, Chongqing University, Chongqing, China, [2] Department of Neurosurgery, University of Pittsburgh, Pittsburgh, PA, United States, [3] College of Computer & Information Science, Southwest University, Chongqing, China, [4] Image Processing Center, School of Astronautics, Beihang University, Beijing, China, [5] Department of Electrical and Computer Engineering, University of Pittsburgh, Pittsburgh, PA, United States

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***Correspondence:**
Xinke Li
lxk@cqu.edu.cn

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Currently, there has been a new trend in applying modern robotics, information technology, and artificial intelligence to restaurants for improvements of food service, cost-effectiveness, and customer satisfaction. As robots replace humans to serve food, there is a clear need for robotic servers to help consumers select foods from a menu that satisfies their preferences such as taste and nutrition. However, currently, little is known about how eating behaviors drive food choices, and it is often difficult for consumers to make choices from a variety of foods offered by the typical restaurant, even with the assistance from a human server. In this paper, we conduct an exploratory study on an intelligent food choice method that recommends dishes by predicting individual's dietary preference, including ingredients, types of spices, price, etc. A multi-attribute relation matrix tri-factorization (MARMTF) technique is developed for a relation-driven food recommendation system. First, the user's ordering history and their rating scores of the foods in the menu are gathered and represented by a user-dish rating matrix. Next, the attribute relations of the ingredients, spicy level, and price of each food choice are extracted to construct a group of the relation matrices. Then, these matrices are integrated into a large block matrix. In the next step, a matrix tri-factorization algorithm is employed to decompose the block matrix and fuse the complex relationships into matrix factors. Further, a set of approximation block matrices are constructed and the predicted food rating matrix is generated. Finally, the foods (dishes) with sufficiently high preference scores are recommended to the consumers. Our experiments demonstrate that the MARMTF technique can provide effective dish recommendation for customers. Our system significantly simplifies the daunting task of making food choices and has a great potential in providing intelligent and professionally trained non-human waiters and waitresses for employment by future restaurants.

Keywords: food choice, consumer preference, eating behaviors, food's attributes, matrix tri-factorization, food recommendation system, robotic restaurant, non-human waiter/waitress

INTRODUCTION

In recent years, there has been an interesting new trend to apply modern robotics, information technology and artificial intelligence (AI) to restaurants. Tablet computers for food ordering have been widely utilized in many countries (1–3). Robotic restaurants without human waiters and waitresses have been in operation, such as those in Canada (4), Japan (5), and Singapore (6). Although these trends have great potential in improving restaurant service, reducing cost, and enhancing customer satisfaction, the reduction or elimination of human interaction with customers on food choices significantly increases the problem in selecting a dish from a long restaurant menu. Although food flavor and appearance have been important features for consumers choosing their favorite foods (7–10), for meal ordering service in restaurants, it is also very important to understand what drives consumers' food choices and give recommendations through computational analysis of the variables collected both historically and at the tableside. Personalized recommendation systems using information and communication technologies (ICT) have been reported (11, 12). At present, these systems mainly satisfy specific needs expressed by consumers (13), such as healthy diet (14), balanced nutrition (15), and food taste (16). With the recent developments of machine learning, artificial intelligence, and cloud computing technologies, the development of smart food recommender systems for the general customers has been reported. For instance, a cloud-based smart restaurant management system (17) can provide easy-to-use interfaces to its users for food menu recommendation. Using advanced algorithms and Amazon Web Services (AWS), not only consumers can easily find their favorite food, but also restaurants can improve service, productivity and profits. Therefore, developing an intelligent menu recommender engine is an important task with promising applications to the enormous food service industry.

Beyond the field of dietary recommendation, many systems have been developed to predict people's interests (18). Personalized recommender engines play an increasingly important role in helping people make selections from overwhelming numbers of choices. For example, online stores such as Amazon, Netflix, and Pandora can recommend books, digital products, and other commodities. There have also been considerable recommenders in the academic field for students to choose schools, majors and classes (19–21). Regardless applications, existing recommender systems can typically be classified into three categories (22): (1) content-based, (2) collaborative, and (3) hybrid systems. The first category makes recommendations by matching item features; the second category makes predictions by analyzing rating data; and the last category possesses both content-based and collaborative features. Among different recommendation algorithms, the collaborative filtering (CF) algorithm and its variants have been used most widely (23). The CF-based algorithms can be further divided into memory-based and model-based algorithms (22, 24). It has been reported that, using a hybrid content-based collaborative filtering (CCF), the recommendation performance can be improved (25, 26). Recently, there has been a new progress in using matrix-factorization (MF)-based methods with high performance and scalability (27). The earliest version of the MF approach was based on singular value decomposition (SVD) (28). Lately, MF-based methods employed customer rating data to extract features and train a recommender based on predicted user preferences (29). There have also been cross integrations of CF recommender systems with regularized MF which have appeared at the Netflix prize competition (30). CF and MF based methods, along with their variations, have found various industrial applications (31–37). Relative to other fields, restaurant menu recommenders are less developed but some works have been reported. A real-time system was developed to monitor dining activity by videos (38). The system recommends additional dishes when the customers finish the existing ones and want more. Tan et al. (13) utilized the radio frequency identification (RFID) technology to improve food service. Elahi et al. (39) used tags and latent factors to design an interactive food recommendation system. Shaikh et al. (40) described a mobile recommendation system using context and user-profile information.

Some dietary recommendation systems pay special attention to the needs of customers who are patients. A system was developed to recommend foods based on user's illness and demographic information (41). Achieving a balanced nutrition was the focus of the recommender established using consumers' dietary records (42). Similarly, a recipe recommendation system was developed to help customers achieve fitness goals (43).

There were other recommender studies focusing on ingredients. Freyne et al. (44) and Feng et al. (45) extracted ingredients, which were individually rated by users, from menus. Recommendations were produced by weighting each ingredient. He et al. (46) used tastes (sour, sweet, bitter, spicy, and salty) to compose a vector of flavors for each dish. Then, customers' food ordering records and the established flavor vectors were used to make recommendations.

Incorporating other content information from recipes, MF-based recommenders generally achieved better preference prediction for users. Forbes and Zhu (47) proposed an algorithm incorporating the ingredient information into the MF method and improved the recipe recommendation performance. Lin et al. (48) employed main ingredients, courses, cuisines, etc. to obtain a recommender model. Although these food recommendation systems enhanced prediction accuracy, they directly incorporated the content information into item vectors for matrix factorization without revealing the hidden associations among these factors. As a result, these systems can only exploit explicit information about users' preferences. In order to reveal associations of food components, consumers' needs, and other related factors to produce better recommendations, we present a multi-attribute relation matrix tri-factorization (MARMTF) technique in this work. We first represent heterogeneous information as multi-type relation matrices. In addition to including users' ordering record and ratings for the dishes, we construct a set of relationship matrices, which reflects ingredients, spicy level, and price and integrate it into the recommendation framework. The multi-variant matrices are then integrated by data fusion using an advanced MF algorithm (49).

This paper is organized as follows. We introduce the recommendation strategies and methods in section Recommendation Strategies and Methods, where attribute relations for the food recommendation system are described. In section Experimental Studies, our experimental studies are presented which employ the multi-attribute relation matrix tri-factorization (MARMTF) framework to produce menu recommendation. Then, the performance of our recommendation system is discussed in section Results and Discussion. Finally, we draw conclusions in section Conclusion.

RECOMMENDATION STRATEGIES AND METHODS

Theoretical Background

It has been proven that Matrix factorization (MF) is both accurate and scalable for recommendation systems (27, 29). In this framework, a user-rating matrix is initially filled with the input data representing the collected information. Let the numbers of users and the pieces of information be n and d, respectively. Let $\mathbf{R}$ be a relation matrix describing the usefulness of the information items to the users. Thus, $n \times d \rightarrow \mathbf{R}$. Normally, this matrix $\mathbf{R}$ is sparse. Next, the rating matrix is factorized into two low-rank factor matrices. Finally, we estimate the unknown entries using the inner products of the matrices and the entries with the highest values are used to produce recommendations.

During the MF process, the non-negativity matrix factorization (NMF) is critically important. NMF aims to find two non-negative matrix factors $\mathbf{U}$ and $\mathbf{V}$ from a non-negative matrix $\mathbf{X}$, i.e.,

$$\mathbf{X} = \mathbf{U}\mathbf{V}^T \tag{1}$$

where $\mathbf{X} \in \mathbb{R}_+^{n\times d}, \mathbf{U} \in \mathbb{R}_+^{n\times c}$ and $\mathbf{V} \in \mathbb{R}_+^{d\times c}$ [$\mathbb{R}_+^{d\times c}$are all d-by-c matrices whose entries are non-negative. The rank c usually satisfies$c \ll \min(n, d)$].

Ding et al. (50) provided a systematic analysis of the NMF. It was shown that the NMF performs spectral clustering and the orthogonal NMF is equivalent to K-means clustering. Furthermore, Ding et al. (51) proposed a bi-orthogonal 3-factor NMF:

$$\min_{\mathbf{F}\geq 0, \mathbf{S}\geq 0, \mathbf{G}\geq 0} ||\mathbf{X} - \mathbf{U}\mathbf{B}\mathbf{V}^T||^2, \ \ s.t., \mathbf{U}\mathbf{U}^T = \mathbf{I}, \ \mathbf{V}^T\mathbf{V} = \mathbf{I} \tag{2}$$

where $\mathbf{X} \in \mathbb{R}_+^{n\times d}, \mathbf{U} \in \mathbb{R}_+^{n\times k}, \mathbf{B} \in \mathbb{R}_+^{k\times l}$ and $\mathbf{V} \in \mathbb{R}_+^{d\times l}$. Equation (2) can be called orthogonal non-negative matrix tri-factorization (ONMTF) which has a better capability in simultaneously clustering rows and columns of the data matrix. As an effective co-clustering tool, ONMTF was applied to collaborative filtering with improved performance (52).

Wang et al. (53) presented a novel symmetric penalized matrix tri-factorization (tri-PMF) framework which employs penalized terms for dyadic constrained co-clustering.

$$\min_{\mathbf{G}_1\geq 0, \mathbf{G}_2\geq 0} ||\mathbf{R}_{12} - \mathbf{V}_1\mathbf{B}\mathbf{V}_2^T||^2 + P(\chi_1) + P(\chi_2) \tag{3}$$

where V_1 and V_2 denote the cluster indicator matrices of χ_1 and χ_2, respectively, and $P(\chi_1)$ and $P(\chi_2)$ correspond to the penalties on χ_1 and χ_2. Here the tri-PMF is extended to symmetric penalized matrix tri-factorization in order to cluster multi-type data objects simultaneously. Wang et al. (54) also proposed a symmetric non-negative matrix tri-factorization (S-NMTF) method to co-cluster multiple types of relational data.

Multi-Attribute Relation Fusion for Food Recommendation

Besides the user-dish rating data, our dish recommendation system also combines other relational data including dish-ingredients, dish-spices, and dish-price. Additional food-choice related factors, such as consumer's age, physical/medical condition, native region, meal time, season of the year, etc., may also be included. Based on the matrix tri-factorization techniques, we present a multi-attribute relational information fusion scheme which integrates available data sources to predict consumers' preferences.

Factorization Model

In our recommendation model, the input data are relation matrices. If the i-th and j-th object types constitute a relation matrix $\mathbf{R}_{ij}$, then all relation matrices can be integrated to a block matrix $\mathbf{R}$, given by

$$\mathbf{R} = \begin{bmatrix} * & \mathbf{R}_{12} & \cdots & \mathbf{R}_{1r} \\ \mathbf{R}_{21} & * & \cdots & \mathbf{R}_{2r} \\ \vdots & \vdots & \ddots & \vdots \\ \mathbf{R}_{r1} & \mathbf{R}_{r2} & \cdots & * \end{bmatrix} \tag{4}$$

where the relation matrices between the same type of objects are denoted by the asterisk ("*"). For our recommendation system, if some relation matrices, such as user-ingredient, and ingredient-price, are not directly modeled, we let the corresponding locations be blank. Obviously, the relation matrices may not be symmetric, i.e., $\mathbf{R}_{ij} \neq \mathbf{R}_{ji}^T$.

Let us consider constraints of the relation between the same types of objects. Suppose that there are r data sources represented by a set of constraint matrices $\mathbf{P}_i$ for $i \in \{1, 2, \cdots, r\}$. Constraints are collectively encoded in a set of constraint block diagonal matrices $\mathbf{P}$

$$\mathbf{P} = Diag(\mathbf{P}_1, \mathbf{P}_2, \cdots, \mathbf{P}_r) \tag{5}$$

where $Diag(\cdot)$ denote the diagonalization for the block diagonal matrix $\mathbf{P}$. In order to use all modeled relation matrices to obtain a fused block matrix, we first use matrix tri-factorization to decompose the original block matrix $\mathbf{R}$ into integrant block matrix factors $\mathbf{V}$ and $\mathbf{B}$:

$$\mathbf{V} = Diag(\mathbf{V}_1^{n_1\times k_1}, \mathbf{V}_2^{n_2\times k_2}, \cdots, \mathbf{V}_r^{n_r\times k_r}) \tag{6}$$

$$\mathbf{B} = \begin{bmatrix} * & \mathbf{B}_{12}^{k_1\times k_2} & \cdots & \mathbf{B}_{1r}^{k_1\times k_r} \\ \mathbf{B}_{21}^{k_2\times k_1} & * & \cdots & \mathbf{B}_{2r}^{k_2\times k_r} \\ \vdots & \vdots & \ddots & \vdots \\ \mathbf{B}_{r1}^{k_r\times k_1} & \mathbf{B}_{r2}^{k_r\times k_2} & \cdots & * \end{bmatrix} \tag{7}$$

Block matrix $\mathbf{B}$ has the same structure as $\mathbf{R}$ in Equation (4). From Equations (6, 7), we can reconstruct the block structure as $\mathbf{VBV}^T$:

$$\mathbf{VBV}^T = \begin{bmatrix} * & \mathbf{V}_1\mathbf{B}_{12}\mathbf{V}_2^T & \cdots & \mathbf{V}_1\mathbf{B}_{1r}\mathbf{V}_r^T \\ \mathbf{V}_2\mathbf{B}_{21}\mathbf{V}_1^T & * & \cdots & \mathbf{V}_2\mathbf{B}_{2r}\mathbf{V}_r^T \\ \vdots & \vdots & \ddots & \vdots \\ \mathbf{V}_r\mathbf{B}_{r1}\mathbf{V}_1^T & \mathbf{V}_r\mathbf{B}_{r2}\mathbf{V}_2^T & \cdots & * \end{bmatrix} \tag{8}$$

Objective Function and Data Processing Procedure

The objective function aims at the closest approximation of the input data by the following minimization:

$$\min_{V \geq 0} J(\mathbf{V}; \mathbf{B}) = \sum_{\mathbf{R}_{ij} \in \Re} ||\mathbf{R}_{ij} - \mathbf{V}_i\mathbf{B}_{ij}\mathbf{V}_j^T||^2 + tr(\mathbf{V}^T\mathbf{PV}) \tag{9}$$

where $\|\cdot\|$ and $tr(\cdot)$ denote the Frobenius norm and trace, respectively, and $\Re$ is the set of all relations included in our model. We can compute the factorization to obtain the latent factors $\mathbf{V}$ and $\mathbf{B}$ by solving the minimization problem with Equation (9). The factorization algorithm can be simply described as follows. Firstly, the matrix factors $\mathbf{V}$ and $\mathbf{B}$ are initialized (section Initialization of Decomposition Factors). Next, alternating between fixing $\mathbf{V}$ and updating $\mathbf{B}$, and then fixing $\mathbf{B}$ and updating $\mathbf{V}$, until the results achieve convergence to iteratively refine the latent matric factors. The update functions of $\mathbf{B}$ and $\mathbf{V}$ can be derived by multiplicative updating rules (49). For convergence criterion, run for a fixed number of iterations (section The Number of Iterations) is adopted in this study. Finally, we can use the convergent $\mathbf{B}$ and $\mathbf{V}$ to compute the approximation of input block matrix $\mathbf{VBV}^T$.

To predict users' preference ratings of different dishes, we reconstruct the rating matrix from the observed relation matrices. The whole processing procedure can be represented in **Figure 1**. In the step of matrix tri-factorization and fusion, we can use the multi-type relation matrices to obtain matrix factors $\mathbf{V}$ and $\mathbf{B}$. Finally, the predicted rating matrix $\hat{\mathrm{R}}_{ij}$ can be extracted from the reconstructed block matrix $\hat{\mathrm{R}}$.

After the new user-dish rating matrix is generated, each dish is assigned with a predicted value. Then, the system will make the recommendation for users according to the ranking of dishes with adequate scores (determined empirically).

EXPERIMENTAL STUDIES

Materials and Datasets

Our experimental study was performed using Chinese foods which are renowned for their wide choices and varieties. First, we generated a list of Chinese foods commonly found in Chongqing, a major mid-west city of over 10 million, well-known for its spicy Sichuan cooking style. The foods selected were mostly in the low or moderate price range. Therefore, they have a large customer base. We recruited 37 adult evaluators (22 males and 15 females) who were all ethnic Chinese but were from different regions in China, not limited in Chongqing. They were healthy (based on their own evaluation), and their ages were between 20 and 60, for a better generalizability of our study. Each evaluator was presented with a list of 289 foods (dishes). He/she gave a rating for each dish according to his/her preference. The rating grades were integers within the range of 1–5, representing "hate," "dislike," "neutral," "like," and "love," respectively. If the evaluator has no experience about a particular dish or was not sure because of a poor memory recall or other reasons, he/she simply left a blank for the dish. After all lists were collected, we integrate them to form the initial user-dish rating matrix exemplified in **Table 1**. For compactness of the table, we represent each dish with a sequential number. It can be seen that the matrix is, as it is normally, quite sparse.

As stated previously, food ingredients represent an important attribute for dishes. It is also one of the key factors driving consumers to choose their preferred dishes (55, 56). Therefore, we incorporated the ingredient-dish information, as exemplified in **Table 2** where the dishes were classified into six main food ingredients: meat, poultry, vegetables, aquatic products, soybean products, and cereals. We used Boolean values to indicate whether a dish contains the particular ingredient ("1") or not ("0").

For the Sichuan and many other Chinese cuisine systems, the degree of spiciness is important for people to make food choices (57). Some studies have been conducted on the factors that influence consumers' behavior of eating spicy food (58–60). Therefore, we also utilized spiciness as an important factor for consumers' food choices. The spicy level of each dish is commonly available in restaurants' menus (e.g., indicated by the number of hot pepper symbols). Using this information, the dishes were classified in four levels: "not spicy," "slightly spicy," "medium spicy," and "very spicy." **Table 3** describes the relationship matrix of the dishes and their spiciness.

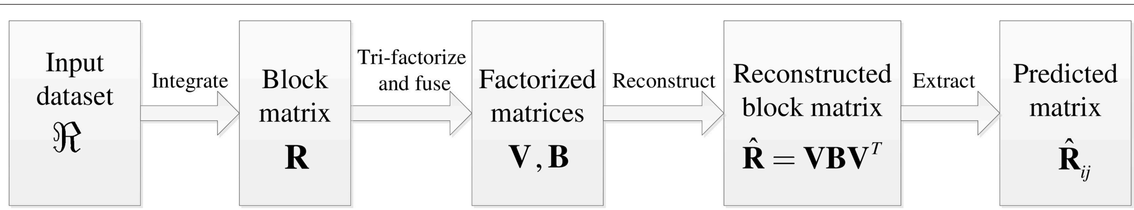

FIGURE 1 | Flowchart of the recommendation system.

TABLE 1 | The user-dish rating matrix.

	*Dish*1	*Dish*2			•••			*Dish*n	
*User*1								2	
*User*2					5				
			5	5					
		4				4			
•	5						3		
•						1			
•		4						3	
							2		
		2							
*User*m				3					4

TABLE 2 | The relationship matrix between the dishes and the food ingredients.

	Meat	Poultry	Vegetables	Soybean products	Cereals	Aquatic products
*Dish*1	1	0	0	0	0	0
*Dish*2	0	0	0	0	1	0
	0	1	1	0	0	0
	0	0	0	1	0	0
•	1	0	0	1	0	0
•	0	0	1	0	0	1
•	0	0	0	1	0	1
	1	0	0	0	0	0
	1	0	0	0	1	0
*Dish*n	0	0	1	0	0	0

TABLE 3 | Relationship matrix of the dishes and their spicy levels.

	No spicy	Slightly spicy	Medium spicy	Very spicy
*Dish*1	0	0	0	1
*Dish*2	0	0	1	0
	0	1	0	0
	0	1	0	1
•	0	0	1	1
•	0	1	0	0
•	0	0	0	1
	1	0	0	0
	1	0	0	0
*Dish*n	0	0	1	0

Additionally, price is an undeniable factor influencing food choices, especially for low- and middle-income consumers (61, 62). For people dining away from home, food consumption is largely responsive to price change (63). Therefore, we incorporated food price into our recommendation system, as shown the dish-price relation matrix in **Table 4** where three price levels were extracted from the restaurant menu: "low price," "medium price," and "high price."

TABLE 4 | Relationship matrix between the dishes and the price levels.

	Low price	Medium price	High price
*Dish*1	1	0	0
*Dish*2	0	1	0
	0	1	0
	1	0	0
•	0	0	1
•	1	0	0
•	0	0	1
	0	1	0
	0	1	0
*Dish*n	0	0	1

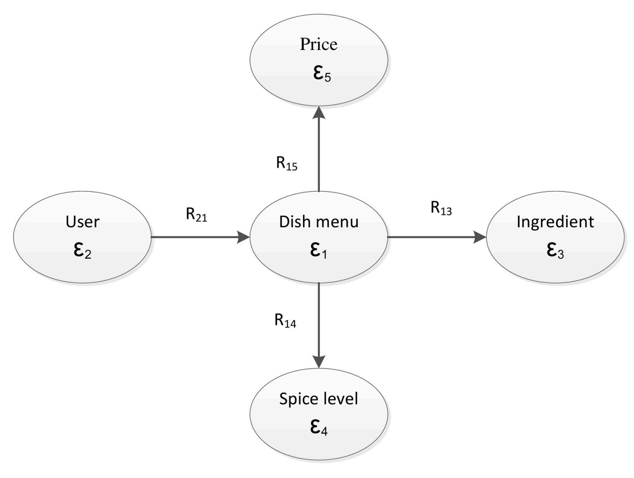

FIGURE 2 | Relation fusion graph of the system.

Relation Integration

In terms of mathematical modeling, we have formed 5 object types, ε_1 through ε_5, corresponding to "dish," "user," "food ingredient," "price level," and "spicy level." For convenience in implementation, each relationship matrix was represented in the Comma Separated Value (CSV) format. From these data sources, we integrated them into a relation graph as shown in **Figure 2**. The attribute relations of user-dish, dish-ingredient, dish-price, and dish-spicy were represented by $\mathbf{R}_{21}$, $\mathbf{R}_{13}$, $\mathbf{R}_{14}$, and $\mathbf{R}_{15}$, respectively. We used these relation matrices as input data for the matrix tri-factorization model.

Data Processing and Analysis

We collected input data from 37 evaluators for 289 dishes (described in section Materials and Datasets), along with the preparation of the relation matrices described above. The user-dish rating dataset was then divided into two sets, training set (83.3% of data) and test set (16.7% of data).

Evaluation Metrics

The root mean-squared error (RMSE) and mean absolute error (MAE) were utilized to evaluate the performance of our recommendation systems (18), given by

$$RMSE = \sqrt{\frac{1}{|T|} \sum_{(u,i) \in T} (r_{ui} - \hat{r}_{ui})^2} \qquad (10)$$

$$MAE = \frac{1}{|T|} \sum_{(u,i) \in T} |r_{ui} - \hat{r}_{ui}| \qquad (11)$$

where r_{ui} and $\hat{r}_{ui}$ denote the ratings given by the user u and the recommendation system for item i, respectively, and $|T|$ denotes the number of elements in rating set T.

Initialization of Decomposition Factors

The initialization of factor matrix **V** in Equation (1) is important because system performance is sensitive to **V**. The initialization also influences the convergence of the algorithm. We adopt the random Acol method (64) to initialize **V** in which the initialization of each column of **V** is formed by averaging random columns of **R**. Our algorithm derives factors **B** in Equation (2) from **V**, as described in section Objective Function and Data Processing Procedure. In addition to the initialization, there are two important parameters, the factorization rank and the number of iterations, to be discussed below.

Factorization Rank

In matrix tri-factorization formula $\mathbf{R}_{ij} - \mathbf{V}_i \mathbf{B}_{ij} \mathbf{V}_j^T$, the dimensions of $\mathbf{R}_{ij} \in \mathbb{R}^{n_i \times n_j}$ and $\mathbf{B}_{ij} \in \mathbb{R}^{k_i \times k_j}$ are $n_i \times n_j$ and $k_i \times k_j$, respectively. k_i and k_j are factorization ranks which are smaller than n_i and n_j. Therefore, the matrix factor $\mathbf{B}_{ij}$ can be considered as a compressed version of the original matrix $\mathbf{R}_{ij}$ (65). The factorization ranks determine the degree of dimension reduction for the object types. In our study, we use the dimension compression ratios ${}^{k_i}/_{n_i}$ and ${}^{k_j}/_{n_j}$ to denote the degree of dimension reduction determined by the selected factorization ranks k_i and k_j. The ratios affect the performance of our data fusion model. For each ratio, if it is too large, the clustering becomes overly fine. On the other hand, if it is too small, the clustering tends to be rough. In order to simplify parameter tuning, we let ${}^{k_i}/_{n_i} = {}^{k_j}/_{n_j}$ for all i and j. To find the dimension compression ratio that optimizes the quality of the system, we fixed the number of iterations at 200, varied the unified compression ratio between 0 and 1, and utilized the RMSE and MAE defined in (10) and (11) to measure performance. Our result is shown in **Figure 3**. It can be observed that the optimal value of the compression ratio is ∼0.4 which was selected.

The Number of Iterations

The objective function $J(\mathbf{V};\mathbf{B})$ given by Equation (9) can be minimized by multiplicative updating for **V** and **B**. Since it is an iterative process, the number of iterations must be determined. We determined it experimentally by observing the convergence of our system. It can be seen from **Figure 4** that both RMSE and MAE decrease as the number of iterations increases. However, when it reaches 100, the error reduction becomes insignificant. We therefore selected the number of iterations to be 200 with a sufficient safety margin.

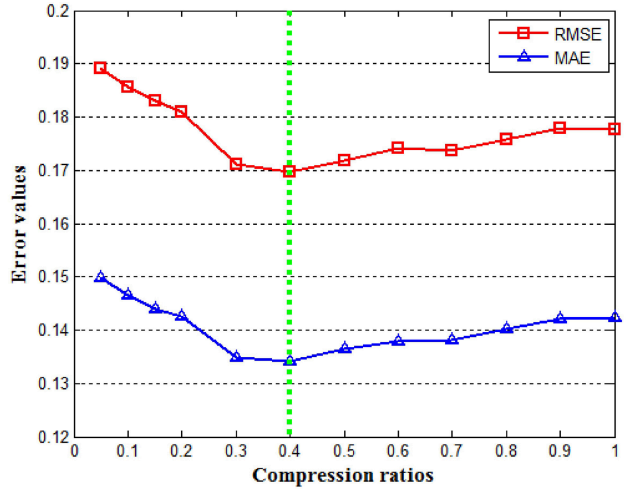

FIGURE 3 | Effect of the different factorization ranks. Both the RMSE and MAE are minimized at a compression ratio near 0.4.

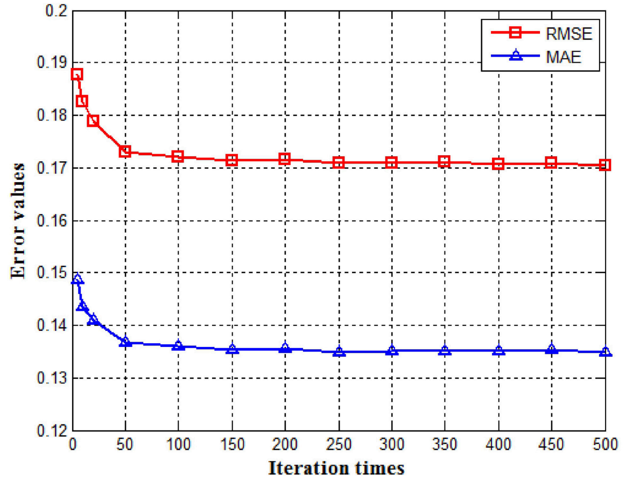

FIGURE 4 | RMSE (top curve) and MAE (bottom curve) vs. the number of iterations.

We implemented our 3-factor matrix factorization algorithm (unoptimized) in Python 3.5 edition on a laptop with an i5 core. The execution time was ∼15 s. Despite the relative slowness in this implementation, we believe that the computational efficiency can be reduced significantly by optimizing the algorithm and utilizing a parallel processor, such as a GPU.

RESULTS AND DISCUSSION

Using the optimally determined parameters, we constructed our recommendation system using the training set, which was composed of 83.3% of the total data. Once constructed, we utilized the test set, composed of the rest of collected data, to

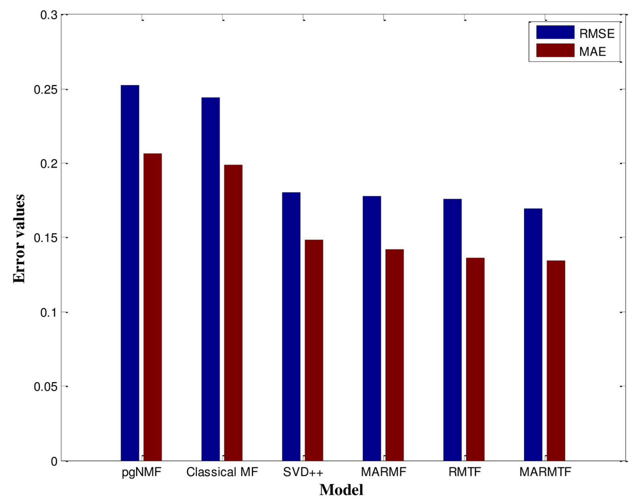

FIGURE 5 | RMSE and MAE for different models.

TABLE 5 | Accuracy comparison of recommenders.

Model	RMSE	MAE
pgNMF	0.2527	0.2067
Classical MF	0.2443	0.1989
SVD++	0.1805	0.1482
MARMF	0.1776	0.1422
RMTF	0.1757	0.1365
MARMTF	0.1693	0.1342

evaluate performance based on the RMSE and MAE metrics. For reliability of the output, the test procedure was repeated 10 times, and we took the average of the evaluation results.

Additionally, we compared our method with several commonly used methods, including projected gradient NMF (pgNMF) (66), classical matrix factorization (MF) (29), and SVD++ (67). Furthermore, we compared our current use of 3-factor matrix factorization (MARMTF) with an alternative of using 2-factor matrix factorization based on the same multi-type relation dataset. Finally, in order to validate our approach of using multi-type relation data, we performed the matrix tri-factorization using only the user-dish rating matrix. The comparison results can be observed in **Figure 5**. The MARMTF model achieve the best prediction rating accuracy.

For more details, our results are listed in **Table 5**. It can be observed that the RMSE and MAE have the minimum values at 0.1693 and 0.1342, respectively, indicating that the MARMTF method outperformed other algorithms. The next performers are the rating matrix tri-factorization (RMTF) and multi-attribute relation matrix factorization (MARMF) methods which are better than the traditional methods, including SVD++, classical MF, and pgNMF.

In this comparison, the recommendation models utilize different amounts of information and/or treated the information differently. For example, the projected gradient NMF model assumes that an absence of rating implies an unfavored item, and the classical MF model only utilizes the rating matrix (68). In contrast, the SVD++ is a matrix factorization model that can combine mean rating, user-item bias, and implicit feedback information (69). As a result, the prediction accuracies of the SVD++ and other multi-attribute methods are higher than those of the projected gradient NMF and Classical MF. Thus, our results agree with a previous report that a recommendation model generally achieves a better performance if it incorporates more background information (67). However, it is difficult for the existing techniques to fuse a large number of attributes from a wide variety of resources.

With regard to making dish recommendations for consumers in restaurants, the relation matrices must be constructed with multiple attributes. Therefore, it is important to integrate and fuse the information from different sources. Our MARMTF model decomposes all the relation matrices systematically for the reconstruction of the rating prediction matrix. In addition, this model achieves a better clustering accuracy by simultaneously co-clustering multiple attributes simultaneously. Due to these valuable properties, the prediction accuracy of the MARMTF overperforms the MARMF which adopts 2-factor matrix decomposition. Overall, the MARMTF can better "understand" complex underlying relationships from different sources to produce more relevant recommendations for consumers.

Despite the advantages, we point out that the current version of the MARMTF has certain limitations. The evaluation was performed in a particular region (Chongqing) where foods tend to be spicy. As a result, there is a tendency that our food choice preferences are biased toward spicy foods and our results are subject to regional limitations. Additionally, we adopted only food ingredients, spicy levels, and price levels as the factors to help consumers choose food. Therefore, the attributes utilized are limited. In future studies, we plan to enhance our recommendation model by considering additional attributes, such as time of meal, season of the year, native region of the consumer, etc., under the MARMTF framework. Finally, food recommendations for healthy diet and balanced nutrition are of great interests for people with chronic diseases or being overweight. In order to produce health-awareness recommendations, we plan to use both food preference and demographic/medical data [e.g., age, body mass index (BMI), existing chronic conditions, etc.] and apply the MARMTF model to make dietary recommendations.

CONCLUSION

With improvements in food production and services, consumers are facing with increased food products and diverse eating environments which make food-choice decisions more complex (70). In order to provide an effective meal selection tool for consumers in restaurants, we have developed a food recommendation system incorporating the information about eating behaviors and food attributes. A multi-attribute relation matrix tri-factorization framework has been presented. Based on the user-dish rating matrix, our relation-driven recommendation model utilizes other dish attribute relation matrices, including dish-ingredients, dish-spices, and dish-price, as the input data to predict consumers' food choices. Experimental results using real-world data have shown that the MARMTF model achieved better performance than existing recommendation methods. In the future work, we will incorporate more information and attributes, not only for choosing favorable food, but also for healthy eating and balanced nutrition.

AUTHOR CONTRIBUTIONS

All of the authors contributed to the study conception and design, data collection, and interpretation of findings. XL conducted the statistical analyses and drafted the manuscript. MS performed the study design, interpretation of findings, and revised the manuscript. WJ advised on the statistical analysis and reviewed drafts of the manuscript.

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Impaired Conflict Monitoring to Food Cues in Women Who Binge Eat

Zhenyong Lyu[1*†], Panpan Zheng[2†], Songkai Lu[1] and Mingzhi Qin[1]

[1] School of Education Science, Xinyang Normal University, Xinyang, China, [2] Key Laboratory of Cognition and Personality, Southwest University, Chongqing, China

Previous research demonstrated the associations between cognitive biases toward food cues and binge eating (BE) behavior. To determine the characteristics of conflict monitoring to food cues in women who binge eat and non-eating disordered controls, a flanker task featured high-caloric food and low-caloric food images was used to examine conflict monitoring with measures of accuracy and reaction time. Women who binge eat displayed longer reaction times (RTs) to incongruent trials (i.e., flanked by pictures from the different category) than to congruent trials (i.e., flanked by pictures from the same category), while controls showed no such difference. This finding demonstrated women who binge eat displayed a general flanker effect toward food-related stimuli compared to controls. Faster reaction times in response to high-caloric food images disturbed by low-caloric food images predicted lower self-reported motor impulsiveness in the women who binge eat, but not in controls. These data suggest a relative conflict monitoring deficit in women with BE pathology.

Keywords: binge eating, flanker task, conflict monitoring, motor impulsivity, food cue

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Yonghui Li,
University of Chinese Academy of Sciences (UCAS), China

Reviewed by:
Michael Grady Wheaton,
Barnard College, Columbia University, United States
Michael Leon,
University of California, Irvine, United States

Correspondence:
Zhenyong Lyu
lyuzy@xynu.edu.cn;
lvzheny@126.com

†These authors have contributed equally to this work as co-first authors

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INTRODUCTION

Binge eating (BE) refers to consumption of an objectively large amount of food within a short period of time, accompanied by a perceived loss of control over eating. Frequent BE is a core diagnostic feature of clinical eating disorders, and persistent symptoms increase risk for Binge-Eating Disorder (BED) according to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013). Diagnosis of Bulimia Nervosa (BN) requires regular binge eating and recurrent compensatory responses to such episodes. BE is prevalent among people seeking to lose or maintain weight (Coker et al., 2015), and affects up to 40% of college-age women in United States (Saules et al., 2009). Furthermore, binge eating behavior is increasing in China (Chen and Jackson, 2008; Tong et al., 2014), and over one third of Chinese adolescents and young adults have reported BE (Chen and Jackson, 2008). Indeed, individuals with binge eating often experience depression, interpersonal problems and reduced quality of life (Ambwani et al., 2015; Rosenbaum and White, 2015).

Cognitive models of obesity suggest reduced inhibitory control is an important causal and maintenance factor in obesity and eating disorders (Jansen et al., 2015). Recent studies have linked cognitive impairment toward food-related stimuli to disordered eating behavior, such as binge eating (Mobbs et al., 2011; Svaldi et al., 2014a,b; Manasse et al., 2016; Kollei et al., 2018; Leehr et al., 2018). An essential component of cognitive control is conflict monitoring (Luna et al., 2015). Conflict monitoring refers to the ability to detect information conflict and reactively increase cognitive control recruitment (Botvinick et al., 2001; Teubner-Rhodes et al., 2016). Poor conflict monitoring might contribute to the frequent initiation of eating episodes, which is associated with obesity. Moreover, poor ability to inhibit an already-initiated motor response (e.g., eating) might contribute to the development of BE (Manasse et al., 2016). However, the knowledge about the conflict monitoring in those with BE is still scarce.

The Stroop color-word interference task has been used as a measure of conflict monitoring and response selection among individuals with eating disorders (Duchesne et al., 2010; Galioto et al., 2012; Balodis et al., 2013; Kittel et al., 2017), though mixed findings have been observed between individuals with BE/BED and controls. For example, Kittel et al. (2017) investigated the conflict monitoring in obese individuals with BED as compared to obese individuals without BED and normal weight participants using a Stroop color-word interference task. They found obese individuals with BED and without BED performed worse than normal weight participants, while the obese individuals with BED and obese individuals without BED did not differ (Kittel et al., 2017). The results hint at general impaired conflict monitoring in youth with BED and obesity in comparison with the normal weight group. However null effects are also existed (Duchesne et al., 2010; Galioto et al., 2012). One potential explanation for the mixed findings is that neutral stimuli (e.g., letters of the alphabet) are probably less rewarding and emotionally arousing compared to food-related images or actual food stimuli, reducing the ecological validity of Stroop tasks (Berner et al., 2017). A meta-analysis of the Stroop task on eating disorders demonstrated that individuals with binge/purge eating disorders showed more cognitive control deficits when food-specific stimuli were used compared to controls (Wu et al., 2014). Cognitive control deficits in those with BE may be especially pronounced when relevant stimuli are used, i.e., food cues (Manasse et al., 2016). In a functional magnetic resonance imaging study, Lee et al. (2017) modified the Stroop match-to-sample task using two different conditions, food-related condition and neutral condition, to investigate the effect of food stimuli on cognitive controls in individuals with eating disorder. The cues with different colors consisted of three letters (i.e., XXX). Participants matched the color of the cue (i.e., "XXX") to the written color of a Stroop word target or to the color that the Stroop word means, which appeared after an interference stimulus (e.g., food-related and neutral pictures). No significant differences were observed in accuracy and reaction time between the BED group and control group (Lee et al., 2017). However, BED group demonstrated stronger activations in the ventral striatum in response to food images compared to control group, indicating BED patients exhibited increased reward sensitivity without inhibitory control (Lee et al., 2017). Together, these findings suggest that individuals with BE/BED are likely to show conflict monitoring deficits though mixed findings have been existed.

The flanker task is another paradigm that has been widely used to assess the ability to inhibit distraction and adapt to conflict (Eriksen and Eriksen, 1974). The Stroop-like tasks elicited responses to non-symbolic information (e.g., color of a letter), whereas flanker task elicited responses to symbolic information (e.g., arrow meaning) (Freitas et al., 2007). In the flanker task, participants respond to the "target" stimulus displayed in the middle of the screen, which are flanked on each side by either the same as the target (i.e., congruent, > > > > >) or different from the target (i.e., incongruent, > > < > >). Participants are instructed to attend to the target stimuli and ignore the non-target stimuli. Because of the interference elicited by the incongruent non-target stimuli, participants generally required longer reaction times to incongruent trials than to congruent trials (Eriksen and Eriksen, 1974; Coles et al., 1985). This "flanker effect" phenomenon, that is, slower responses to incongruent trials, provides an index of the conflict monitoring. Due to the lower levels of cognitive control being successfully applied, the flanker effect will be larger, which indicates a greater conflict monitoring deficit (Husted et al., 2016).

Conflict monitoring to food-related stimuli has been examined using flanker task in previous research (Forestell et al., 2012; Meule et al., 2012; Husted et al., 2016). For example, using a flanker task involved high caloric food-cues and neutral pictures, Meule et al. (2012) found restrained eaters responded faster to high-calorie food targets as compared to neutral targets than unrestrained eaters, suggesting a low self-regulatory ability in restrained eaters (Meule et al., 2012).

Based on the literature outlined above, a food-related flanker task with high- and low-calorie food images was introduced to examine the interference from food stimuli on cognitive control in women who binge eat. We hypothesized that the women who binge eat would show greater deficits in response conflict than the control group on both stimulus types of the flanker task.

MATERIALS AND METHODS

Participants

Thirty-one undergraduate women with BE and 33 healthy control participants were recruited from a large Chinese university. Average age was M = 20.91 years (SD = 1.52), and the mean BMI was M = 20.68 kg/m^2 (SD = 2.66). All women who binge eat reported at least one binge eating episode per week over the past 3 months (M = 2.52, SD = 2.12, range: 1–12) on the Eating Disorder Diagnostic Scale (EDDS; Stice et al., 2000) as well as an absence of compensatory behavior following BE episodes. Healthy control participants reported no current nor past eating disorder according to DSM-5 criteria. In order to standardize hunger levels, all participants were instructed to refrain from eating and drinking caffeinated beverages for 12 h before the study which occurred between 8 and 11 am the next day.

Materials

Forty-eight colorful images each of high-calorie foods (e.g., hamburger, doughnuts, and fried chicken wings) and low-calorie foods (e.g., tomatoes, carrots) were used. All images were taken from a set previously used in our studies (Lyu and Jackson, 2016; Lyu et al., 2016, 2017), and edited to be homogeneous with respect to background color.

Procedure

This study was performed in accordance with the guidelines of the International Committee of Medical Journal Editors. The study was approved by the Human Research Ethics Committee of the Xinyang Normal University. Potential volunteers were recruited via the campus electronic bulletin board system and flyers. Screening materials including demographic items and the Eating Disorder Diagnostic Scale (EDDS) were completed (Stice et al., 2000). Participants arrived at the lab individually for their scheduled appointment. Upon arriving, volunteers were informed of the general research focus (i.e., attention toward different kinds of food images) and gave the informed consent prior to their participation. Subjective feeling of hunger were assessed individually on a visual analog scale from 1 to 9 (1: not hungry at all; 9: very hungry).

The flanker task procedures were programmed using E-Prime 2.0. The flanker task comes from prior food flanker studies (Forestell et al., 2012; Meule et al., 2012; Husted et al., 2016). In the food flanker task, the central targets were pictures of either high-calorie foods or low-calorie foods images, which were flanked by pictures either from the same category (congruent condition) or distractors from the other category (incongruent condition). Participants were instructed to respond to the centrally presented picture (i.e., target) as quickly and accurately as possible by pressing a left or right button to indicate whether the target was a high-calorie food or a low-calorie food item (mapping was counterbalanced across participants). A 2 min practice session commenced first to ensure that participants become familiar with the procedure before the formal study. Each trial consisted of a prestimulus baseline during which a fixation cross was presented in the middle of the screen for 1000 ms. This was followed by a stimulus array contained one target picture and two pictures on either side of the target (i.e., flankers) followed by a blank screen. After the target appeared in the center of the screen, participants were instructed to respond as quickly as possible. The target remained on the screen until a response was detected or 1500 ms passed. Pictures for flankers and targets were randomly drawn from the same food image set of high or low calorie. In the congruent condition, target and flanker pictures were the homogeneous: (1) all the pictures were high-calorie foods (HHH); (2) all the pictures were low-calorie foods (LLL). In the incongruent condition, target and flanker pictures differed: (3) the target was a high-calorie food picture and the flankers were two low-calorie food pictures (LHL); (4) the target was a low-calorie food picture and the flankers were two high-calorie food pictures (HLH). Inter-trial intervals varied randomly from 1000 to 3000 ms to avoid time conditioning. The task included 192 trials in total divided in three blocks.

After the flanker task, the self-report scales described below, except the EDDS, were completed in a quiet room. Finally, participants were required to make a guess regarding the main research purpose, and then were debriefed about the study hypotheses. No participants identified BE or response conflict as foci of the experiment. Participants received 20 yuan as compensation.

Questionnaires

Eating Disorder Diagnostic Scale (EDDS; Stice et al., 2000)

The EDDS is a 22-item self-report scale that based on Diagnostic and Statistical Manual-IV criteria for Anorexia Nervosa (AN), BN, and BED. In the present study, EDDS was used to identify individuals with BE as well as to rule an eating disorder diagnosis among the control group members. An overall composite calculated from the sum of z-scores of the first 18 items also provided a symptom severity rating. The scale has satisfactory test–retest reliability, a high level of internal consistency, and excellent concordance with diagnoses based on structured interviews and other self-report measures of eating disturbances (Stice et al., 2000, 2004). The Chinese version of the EDDS also has satisfactory reliability and validity in samples of mainland Chinese adolescents and young adults (Jackson and Chen, 2014, 2015). The consistency was $\alpha = 0.76$ in this sample.

Barratt Impulsiveness Scale-Chinese (BIS-C; Li et al., 2011)

The BIS-C, consisting of attentional, motor, and non-planning impulsiveness subscales, was used to assess rash-spontaneous behavior (Lyu et al., 2016, 2017). BIS-C has satisfactory psychometrics among Chinese undergraduates (Li et al., 2011). For this study, the internal consistency of the overall BIS-C was $\alpha = 0.74$. Alphas values were acceptable for the three subscales ($\alpha s \geq 0.71$).

Uncontrolled Eating Scale (UES; Karlsson et al., 2000)

The binge eating level was assessed by summing seven items from the Three-Factor Eating Questionnaire-R18 in the formal study. The questionnaire has been found to have sound reliability and validity (Anglé et al., 2009; Lyu et al., 2017). Its alpha value was 0.84 in the current study.

Data Analyses

Data were analyzed with IBM SPSS Statistics 20.0. Group differences on demographics, impulsivity, and uncontrolled eating were assessed via t-tests. A 2 (Group: binge eating versus non-binge eating) $\times$ 2 (Food Type: high-calorie food versus low-calorie food) $\times$ 2 (Flanker: congruent versus incongruent) ANOVA was performed to assess accuracy and RT differences. Individual trials on the flanker task with errors and response times more than three standard deviations above or below the mean (i.e., 7% of trials) were excluded from analysis (Forestell et al., 2012). Mean accuracy and reaction times were calculated for each of the 3-picture array combinations (i.e., HHH, LLL, LHL, and HLH) for each participant. Mauchly's test of sphericity was violated in ANOVA analyses; thus, Greenhouse-Geisser corrections were used to reduce risk for Type I errors.

RESULTS

Group Differences on Demographics and Characteristics

As show in **Table 1**, women who binge eat displayed higher levels of motor impulsiveness and uncontrolled eating relative to controls. However, no group differences were observed on age, BMI, year in university, or hunger ratings.

TABLE 1 | Characteristics of binge-eating group versus control group (M ± SE).

	Binge eating (n = 31)	Control (n = 33)	t	Cohen's d
Age	20.00(0.66)	21.15(0.26)	−1.67	−0.41
Body mass index	21.03(0.50)	20.36(0.44)	1.01	0.25
Year in university	2.10(0.16)	2.55(0.17)	−1.91	−0.48
Hunger rating	6.13(0.34)	6.79(0.22)	−1.64	−0.41
EDDS (z-scores)	0.50(0.16)	−0.47(0.15)	−4.45***	1.10
BIS-C total score	96.06(1.39)	92.79(1.87)	1.39	0.35
BIS-C (motor impulsiveness)	29.32(0.83)	25.58(1.42)	2.24*	0.56
BIS-C (attention impulsiveness)	34.55(0.68)	34.06(0.75)	0.48	0.12
BIS-C (non-planning impulsiveness)	32.19(0.80)	33.15(1.11)	−0.69	−0.17
Uncontrolled Eating Scale	23.65(0.50)	18.24(0.74)	5.55***	1.40

*EDDS, Eating Disorder Diagnostic Scale; BIS-C, Barratt Impulsiveness Scale-Chinese; * < 0.05; *** < 0.001.*

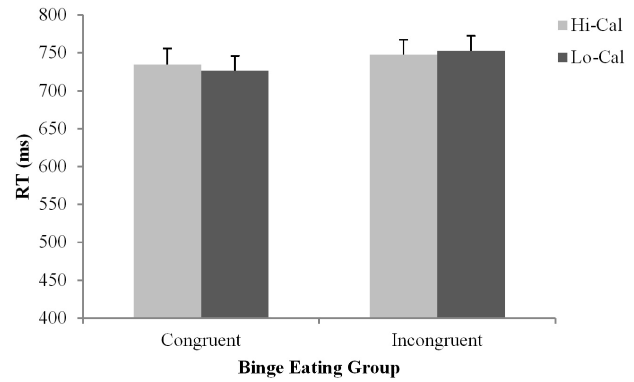

FIGURE 1 | Reaction time data for women with binge eating. Bars represent standard error of the mean (SE). Hi-Cal, High-calorie; Lo-Cal, Low-calorie.

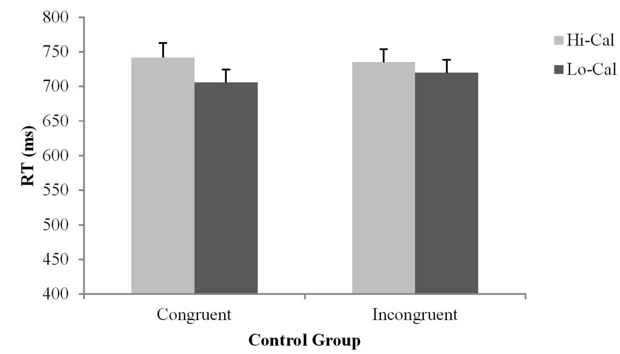

FIGURE 2 | Reaction time data for controls. Bars represent standard error of the mean (SE). Hi-Cal, High-calorie; Lo-Cal, Low-calorie.

Differences in Accuracy

The repeated measures ANOVA performed on accuracy revealed an interaction effect of Food Type × Flanker, $F(1, 62) = 14.42$, $p < 0.001$, $\eta_p^2 = 0.19$. Simple effects analyses indicated that a better performance of judgment was observed for congruent trials ($M = 0.94$, $SE = 0.02$) compared to incongruent trials ($M = 0.91$, $SE = 0.02$) with low-calorie food images as targets ($p = 0.01$), while a better performance of judgment was shown for incongruent trials ($M = 0.94$, $SE = 0.01$) than congruent ones ($M = 0.92$, $SE = 0.02$) with high-calorie food images as targets ($p = 0.01$). No other main effect or interaction effect was significant (p's > 0.05).

Differences in Reaction Time (RT)

A main effect for Food Type, $F(1, 62) = 5.16$, $p = 0.02$, $\eta_p^2 = 0.20$, indicated the sample responded more quickly to low-calorie food compared to high-calorie food images ($M = 726.27$ ms versus $M = 739.99$ ms, $p = 0.03$). As expected, the main effect for Flanker, $F(1, 62) = 14.36$, $p < 0.001$, $\eta_p^2 = 0.19$, evidenced a general flanker effect: congruent trials elicited significantly shorter RTs in the entire sample ($M = 727.28$ ms versus $M = 738.98$ ms, $p < 0.001$).

Simple effects analyses of the Group × Flank interaction, $F(1, 62) = 6.69$, $p = 0.01$, $\eta_p^2 = 0.10$, indicated women who binge eat displayed a significant flanker effect ($p < 0.001$), while no such effect was observed in the controls ($p = 0.39$) (see **Figures 1**, **2**). The Food Type × Flanker interaction, $F(1, 62) = 8.35$, $p = 0.01$, $\eta_p^2 = 0.12$, indicated a strong flanker effect to low-calorie food images ($p < 0.001$), but not to high-calorie food images ($p = 0.45$). Furthermore, shorter RTs were observed to low-calorie food images compared to high-calorie food images in congruent trials ($M = 716.16$ ms versus $M = 738.39$ ms, $p = 0.01$), but no such difference was found in incongruent trials ($M = 736.37$ ms versus $M = 741.58$ ms, $p = 0.43$). For the Food Type × Group interaction, $F(1, 62) = 4.11$, $p = 0.04$, $\eta_p^2 = 0.06$, controls displayed shorter RTs to low-calorie food images than to high-calorie food images ($M = 712.68$ ms versus $M = 738.65$ ms, $p = 0.01$), but no such difference was found in women who binge eat ($M = 741.32$ ms versus $M = 739.85$ ms, $p = 0.87$). No other differences were observed significant.

To disentangle significant relations between flank task responses and self-reported measures, supplementary correlation analyses were performed within group. Women who binge eat displayed negative correlations between self-reported motor impulsiveness score and accuracy rates in different conditions (HHH: $r = -0.41$, $p = 0.02$; LHL: $r = -0.46$, $p = 0.01$; LLL: $r = -0.47$, $p = 0.01$), though a marginally significant correlation was observed (HLH: $r = -0.35$, $p = 0.05$). Conversely, control group members showed no such correlations between self-reported motor impulsiveness and accuracy rates for HHH ($r = 0.01$, $p = 0.99$), LHL ($r = -0.01$, $p = 0.98$), LLL ($r = -0.01$, $p = 0.99$), and HLH ($r = -0.03$, $p = 0.88$). Shorter RTs in response to high-caloric food images disturbed by low-caloric food images (i.e., LHL) were related to higher motor impulsiveness in women who binge eat ($r = 0.44$, $p = 0.01$) but not in controls ($r = 0.03$, $p = 0.87$). No other correlations were observed significant.

DISCUSSION

The present study investigated the conflict monitoring in women who binge eat during exposure to food cues. To the best of our knowledge, this is the first study that used food-related flanker task to assess conflict monitoring in women with BE and controls. Regarding the central research focus, women with BE show greater deficits in response conflict on the food-related flanker task, which support the main hypothesis.

Compared to controls, participants with BE reported higher trait impulsivity and uncontrolled eating, in line with the criterion of BE and previous research (Schag et al., 2013; Svaldi et al., 2014a), especially on motor impulsivity (Nasser et al., 2004; Galanti et al., 2007; Lyu et al., 2016, 2017). The motor impulsivity is defined as acting without thinking (Stanford et al., 2009), and could be used to distinguish eating disorder subtypes (Tillman and Wiens, 2011). Previous research have found the motor impulsivity was positively correlated with test meal intake and mood rated before consuming the test meal (Nasser et al., 2004; Galanti et al., 2007), and positively predicted binge eating and general eating pathology (Meule and Platte, 2015). Motor impulsivity involves the ability to suppress a prepotent yet inapposite motor response (Chamberlain and Sahakian, 2007). On this basis, the negative correlations between motor impulsiveness and performance of judgment indexed with accuracy may reflect poor response inhibition for women who binge eat, which may make them vulnerable to binge eating.

Reaction times for incongruent trials in the flanker task were found to be significantly longer in women with BE, indicating a deficit of conflict monitoring in BE. The findings are comparable to the results of a study of combined electroencephalography (EEG) and eye tracking. In the food-related antisaccade task, Leehr et al. (2018) observed smaller N2 latencies in overweight individuals with BED compared with overweight individuals without BED, suggesting that the conflict processing might be less thorough in the overweight individuals with BED (Leehr et al., 2018). Our finding extends evidences of previous literature focusing on conflict monitoring in individuals with binge eat. In previous research, the Stroop color-word interference task was performed to assess the inhibitory control of individuals with eating disorders (Duchesne et al., 2010; Galioto et al., 2012; Balodis et al., 2013; Kittel et al., 2017). The mixed findings mentioned above could be explained by the methodological procedures employed. Corresponding to the differential mechanisms of the interference, the response of the flanker task and Stroop task may reflect different cognitive processes. For example, Tillman and Wiens (2011) assessed effects of variation in proportions of incongruent trials on response conflict in the Stroop and flanker task. ERP findings demonstrated that the flanker N200 and Stroop N450 may reflect different cognitive processes (Tillman and Wiens, 2011). The flanker N200 may reflect attentional control processes used to focus attention on task-relevant aspects of a situation, while the Stroop N450 may reflect the perceptual conflict processing (Tillman and Wiens, 2011). The flanker task contains two sources of conflict, one related to the responses, and the other related to the stimulus itself (Eriksen and Eriksen, 1974). The flankers involve little semantic interference, so the motor conflict may occur faster than does the conflict in the Stroop, which requires also semantic processing (Pires et al., 2014). Women who binge eat with high level of motor impulsiveness displayed longer reaction times in responding to high-caloric food images flanked by low-caloric food images (i.e., LHL) may reflect the poor inhibition of responses in the women who binge eat when exposure to food cues.

One alternative explanation from an evolutionary perspective is that the binge eating behavior may be suitably conceptualized as an "evolutionary mismatch" condition arising from a maladaptive gene–environment interaction (Levitan et al., 2004; Davis, 2015; Abed, 2016; Mayhew et al., 2018). The strong hedonic response to food was an undeniable survival benefit during the huntergatherer era, which mismatched to our current environment (Davis, 2014). The deficit of conflict monitoring in women who binge eat when food stimuli present may reflect an adaptative strategy in early environments.

A number of study limitations should be mentioned. First, given possible gender differences in BE (Rosenbaum and White, 2015), results do not necessarily apply to BE men. In addition, findings may not generalize fully to a wider population. Second, it would be beneficial to replicate these findings in food-related Stroop task. In these tasks, the food or eating words (e.g., cake, cream, and diet) are presented. Participants must name the color in which each word is printed and ignore the meaning of the words (Black et al., 1998; Johansson et al., 2005; Rosenbaum and White, 2015). Some studies have found that the Stroop effect is enhanced when food-related stimuli are primed in restrained eaters (Cooper and Fairburn, 1992; Perpiñá et al., 1993). Further, only high-caloric and low-caloric food stimuli were used, the conflict monitoring of food versus non-food stimuli cannot be revealed. Future research should examine the comparison of food versus non-food stimuli to investigate the food-specific conflict monitoring in the cognitive control processes. Finally, higher impulsive responding was correlated with more calories consumed in average weight samples (Nederkoorn et al., 2009). It would be interesting to investigate the correlation between the response conflict to high- and low-calorie foods and the consumption of these foods in future research.

CONCLUSION

The results provide initial evidence that women who binge eat appear to exhibit greater response conflict deficits with food cues in a flanker task featured high-caloric food and low-caloric food images relative to those who do not have binge eating episodes. These findings suggest that individuals who binge eat tend to rely on automatic processing and respond to processing conflicting food stimuli less effectively. Such an understanding will assist to prevent disordered eating in binge-eating populations, and to develop psychological interventions more effectively.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the ethical guidelines of the American Psychological Association. The protocol was approved by the Human Research Ethics Committee of the Xinyang Normal University. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

ZL designed the project. SL and MQ performed the experiment. ZL and PZ analyzed the data and wrote the manuscript.

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Questionnaire-Based Maladaptive Decision-Coping Patterns Involved in Binge Eating Among 1013 College Students

Wan-Sen Yan[1,2], Ran-Ran Zhang[1], Yan Lan[1], Zhi-Ming Li[1] and Yong-Hui Li[2]*

[1] Department of Psychology, School of Medical Humanitarians, Guizhou Medical University, Guiyang, China, [2] Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China

Binge Eating Disorder (BED), considered a public health problem because of its impact on psychiatric, physical, and social functioning, merits much attention given its elevation to an independent diagnosis in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Similar with substance use disorders, some neuropsychological and personality constructs are potentially implicated in the onset and development of BED, in which poor decision-making has been suggested to facilitate overeating and BED. The objective of this study was to investigate the associations between decision-coping patterns, monetary decision-making, and binge-eating behavior in young adults. A sample of 1013 college students, equally divided into binge-eating and non-binge-eating groups according to the scores on the Binge Eating Scale (BES), were administered multiple measures of decision-making including the Melbourne Decision-Making Questionnaire (MDMQ), the Delay-discounting Test (DDT), and the Probability Discounting Test (PDT). Compared with the non-binge-eating group, the binge-eating group displayed elevated scores on maladaptive decision-making patterns including Procrastination, Buck-passing, and Hypervigilance. Logistic regression model revealed that only Procrastination positively predicted binge eating. These findings suggest that different dimensions of decision-making may be distinctly linked to binge eating among young adults, with Procrastination putatively identified as a risk trait in the development of overeating behavior, which might promote a better understanding of this disorder.

Keywords: binge eating, decision making, reward discounting, personality, young adults

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Yale University, United States

***Correspondence:**
Wan-Sen Yan
yanwansen@163.com

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INTRODUCTION

Compulsive overeating, formally named binge eating disorder (BED) as an independent diagnosis in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (i.e., DSM-5; American Psychiatric Association, 2013), is characterized by consuming large amounts of (mostly highly palatable) food with an overwhelming desire and the associated sense of loss of control (Peat et al., 2017). The lifetime prevalence estimates of DSM-IV BED among adults were 2.8% (3.5% for women and 2.0% for men) in the United States (Hudson et al., 2007) and 1.9% (2.6% for women and 1.1% for men) across 14 WHO World Mental Health (WMH) countries (Kessler et al., 2013). BED is considered a public health problem because it is associated with significant psychiatric and medical complications (Mitchell and Crow, 2010) as well as an increased risk for weight gain and obesity (Stice et al., 2002).

Binge eating disorder has multiple clinical similarities with substance use disorders in some cases, such as the intense cravings for certain foods and a feeling of loss of control even in the face of negative consequences (Davis and Carter, 2009). Besides, BED and addictive disorders share a number of proposed mechanisms including impulsivity and a hyper-reward response to relevant cues (Schulte et al., 2016). There is also substantial overlap between BED and food addiction (Davis, 2017), though the latter topic remains controversial. Akin to addictive disorders, poor decision-making might facilitate overeating. It has been suggested that addictive behaviors are associated with complex cognitive and emotional deficits in the process of decision-making (Redish et al., 2008), thus it is important to acknowledge the possible pathways of decision-making in the onset and development of binge-eating behavior.

Decision making is a complex process involving different choices (e.g., everyday food choices among individuals with BED). There are various decision-making measurements in cognitive neuroscience and behavioral economics. Laboratory cognitive tasks such as the Iowa Gambling Task (IGT; Bechara et al., 1994) mainly test the decision-making abilities of subjects in ambiguity conditions. The Delay-discounting Test (DDT; Kirby et al., 1999) and the Probability Discounting Test (PDT; Madden et al., 2009) primarily measure the individual choice propensity in risk conditions. There are also some self-report personality questionnaires, such as the Melbourne Decision-Making Questionnaire (MDMQ; Mann et al., 1997). The MDMQ characterizes competent decision-making or vigilance as an adaptive appraisal prior to decision-making, while avoiding decisions (i.e., procrastination and buck-passing) or quickly making a choice to escape the uncomfortable feeling of decision making (i.e., hypervigilance) are considered maladaptive traits (Gorodetzky et al., 2011).

Despite scarce evidence, several previous studies have investigated the cognitive profile including decision-making in patients with BED. In one study (Svaldi et al., 2010), women with obesity and BED displayed impaired decision-making in comparison with overweight women without BED on the Game of Dice Task (GDT; Brand et al., 2005), which assesses decision-making under risk with explicit rules for gains and losses. In another study, though female individuals with obesity and BED had worse decision-making performance on the IGT and a Delay Discounting measure compared with normal-weight females, these group differences vanished when education level was taken into account, and there were no task differences between overweight women with and without BED (Davis et al., 2010). Nevertheless, women patients with BED displayed decision-making deficits on the IGT compared to healthy women, which seemed comparable with the poor decision-making performance of women with obesity in this study (Danner et al., 2012). More recently, Aloi et al. (2015) compared decision-making, central coherence and set-shifting functions between women BED patients, Anorexia Nervosa (AN) patients, and healthy controls with a large sample. The results revealed that both BED and AN patients had significantly lower IGT scores compared with healthy controls, showing impaired capacities to advantageously utilize feedback processing in decision making. A functional neuroimaging study of reward-based decision-making in BED has further observed impaired behavioral adaptation in BED patients compared to healthy individuals, accompanied by diminished activation in the anterior insula/ventro-lateral prefrontal cortex (related to exploratory decisions) and reduced representation of ventro-medial prefrontal learning signatures (associated with successful decision-making) (Reiter et al., 2017). Albeit these limited studies and discrepant results, targeting a more precise profile of decision-making in BED may provide a better understanding of the pathogenesis.

The present study thus employed the MDMQ that describes individual decision-coping patterns in daily life at the personality-trait level, as well as the DDT and the PDT that evaluate personal preference in hypothetical money reward choices at the behavioral level, aiming to further investigate the relationships between different dimensions of decision-making and BED with a relatively large sample of general population. It was hypothesized that individuals with binge eating would be more likely to show a steeper delay discounting and a trend toward decreased discounting of probabilistic rewards than individuals without binge eating, and exhibit more maladaptive decision-making patterns on the MDMQ.

MATERIALS AND METHODS

Participants and Procedure

The data were collected in November 2016. Participants included 1050 young adult students, recruited from 12 randomly selected 1st-year courses at a local university in Guiyang, China. All of them were invited to carry out a battery of self-report questionnaires including the demographic information in a 45-min psychology class. The inclusion criteria were: (1) $\geq$18 years of age, and (2) willingness to participate in this study. The exclusion criteria included current/past major psychiatric disorders (e.g., schizophrenia, major depressive disorder), a history of brain injury/trauma, current/past neurological diseases or mental disorders, and current/past use of psychoactive drugs (e.g., cocaine, heroin, and methamphetamine) by self-report. Thirty-seven students were excluded according to one or more of these exclusion criteria. Finally, 1013 students (average age = 18.85, ranging from 18 to 24 years) were included in data analyses. All subjects provided written informed consent and were compensated with a gift equal to RMB ￥50. This study was approved by the Human Research Ethics Committee at the Guizhou Medical University. Our proposed recruitment process, study design, and plans to compensate participants were consistent with the Declaration of Helsinki.

Binge Eating Classification

Binge-eating status was classified by employing the Binge Eating Scale (BES; Gormally et al., 1982), which is used to identify individuals with binge-eating behavior, to evaluate binge-eating severity and also as a parameter of treatment outcome (Freitas et al., 2006). BES is a 16-item self-report questionnaire, with a total score ranging from 0 to 46. Subjects scoring 17 and less on the BES are considered individuals without binge eating, and those with a score ≥18 are considered individuals with binge eating (Marcus et al., 1988; Greeno et al., 1995; Ricca et al., 2000). In our study, the Chinese version of the BES (He et al., 2014; Wu et al., 2015) was used. Cronbach's α for the scale was 0.77. There were 85 persons in the binge-eating group (M_{BES} = 21.49) and 928 persons in the non-binge-eating group (M_{BES} = 7.28) according to BES scores.

Decision-Coping Patterns

The MDMQ (Mann et al., 1997) was used to assess adaptive and maladaptive decision-making traits in the binge-eating and non-binge-eating groups. MDMQ is a 22-item self-report inventory measuring four major coping patterns based on the conflict theory of decision-making (Janis and Mann, 1977). It consists of four subscales (i.e., vigilance, procrastination, buck-passing, and hypervigilance) scoring on a three-point scale: "not true for me" = 0, "sometimes true" = 1, "true for me" = 2. According to Mann et al. (1997), the adaptive or competent decision-making pattern might be characterized by higher scores on the *vigilance* scale (e.g., I like to consider all of the alternatives when making decisions), and avoidant patterns could be indicated by higher scores on the *procrastination* scale (e.g., Even after I have made a decision I delay acting upon it) and *buck-passing* scale (e.g., I prefer to leave decisions to others), while impulsivity and defective decision-making might be indicated by higher *hypervigilance* scores (e.g., I cannot think straight if I have to make a decision in a hurry). In the current study, the Chinese version of the MDMQ (Mann et al., 1998; Zhou et al., 2014) was adopted, and Cronbach's α for the four subscales was 0.73 (vigilance), 0.66 (procrastination), 0.75 (buck-passing), and 0.63 (hypervigilance), respectively.

Reward Discounting Measures

The DDT (Kirby et al., 1999) and PDT (Madden et al., 2009) were employed to assess the discounting degree of delayed or probabilistic rewards in the context of monetary decision-making. The DDT is a 27-item choice questionnaire between immediate but smaller and delayed but larger monetary rewards. Delay discounting implies a trend that subjects prefer a smaller immediate reward to a larger delayed reward, defined as impulsivity in opposition to self-control (Dixon et al., 2003). The hyperbolic equation $V = A/(1+kD)$ was used to calculate the degree of delay discounting. In this equation, V is the subjective value of the delayed reward, A is the nominal amount of the delayed reward, D is the length of the delay, and k is a free parameter of delay discounting (i.e., discounting rate). A larger k-value describes a higher degree of delay discounting. In this study, we used an adapted version among Chinese students (Sun and Li, 2011). Examples for this version are "*A: receiving ¥9000 now; B: receiving ¥10000 one year later*" and "*A: receiving ¥1000 now; B: receiving ¥10000 one year later.*" Consistent with previous literature, k-values were calculated and log-transformed. The PDT is a three-part monetary-choice questionnaire with 10 questions in each part. Participants were instructed to circle their preferred outcome. One outcome was a smaller amount of money delivered "for sure" and the other was a larger amount of money delivered probabilistically (e.g., "$40 for sure" vs. "a 5-in-10 chance (50%) of winning $100"). The degree of probability discounting was calculated by the equation $V = A/(1+h\Theta)$, which uses the parameter $\Theta = (1-p)/p$ to substitute the odds against winning for the delay, describing hyperbolically declining subjective values of probabilistic outcomes (Rachlin et al., 1991). In this equation, the free parameter h refers to the degree of probability discounting. Lower h implies that probabilistic rewards is less steeply discounted, suggesting a reduction in risk aversion. The PDT has been appropriately used among Chinese college students (Yan et al., 2016). In our study, the degree of probability discounting (h) is obtained and analyzed using the similar methods as in previous study (Madden et al., 2009). The h scores were also log-transformed to approximate a normal distribution.

Statistical Analyses

Data were analyzed with the Statistical Package for the Social Sciences for Windows, Version 15.0 (SPSS Inc., Chicago, IL, United States). Chi-square tests were used to test between-group differences on categorical variables (i.e., gender, ethnicity, home locality, smoking, and drinking status), and T-tests were used to test group differences on age and Body Mass Index (BMI). MDMQ, DDT and PDT scores were compared between the groups using a 2 (group: binge-eating, non-binge-eating) × 2 (gender: male, female) multivariate analysis of variance (mANOVA) model. Partial correlations were tested between the MDMQ, DDT, PDT, and BES scores with age, gender, ethnicity, and home locality as the control variables. Complementally, a multivariable linear regression model was also conducted to test the effects of MDMQ, DDT and PDT scores on BES scores. Logistic regression was employed to examine the effects of MDMQ, DDT, and PDT scores on binge eating behavior, with gender as the control variable, given that the group difference on gender was significant. Multicollinearity was not a problem for any variable in theses regression models according to the variance inflation factor (VIF < 10). Statistical significance was set at $p < 0.05$, two-tailed.

RESULTS

Group Differences on Demographics and Decision-Making Measures

Table 1 describes the demographics and decision-making scores of the groups. In keeping with the literature (Dingemans et al., 2002), females were more likely than males to be involved in binge eating ($\chi^2 = 20.547$, $p < 0.001$), thus in further analyses gender was controlled as a between-group variable. No significant between-group differences were observed for age ($t = -0.157$, $p = 0.875$), ethnicity ($\chi^2 = 0.001$, $p = 0.998$), home locality ($\chi^2 = 0.259$, $p = 0.611$), BMI ($t = 0.80$, $p = 0.424$), smoking ($\chi^2 = 0.015$, $p = 0.902$) or drinking ($\chi^2 = 1.750$, $p = 0.626$) status.

On the MDMQ, the 2 (group: binge-eating, non-binge-eating) × 2 (gender: male, female) mANOVA

TABLE 1 | Demographic characteristics and scale scores of the sample (N = 1013).

Variables	Binge-Eating Group (n = 85)	Non-Binge-Eating Group (n = 928)	χ^2/t	p-values
Age, years ($M \pm SD$)	18.84 ± 0.86	18.85 ± 0.84	−0.157	0.875
Gender, Female n (%)	69 (81.2)	518 (55.8)	20.547	0.000
Ethnicity, Hans n (%)	50 (58.8)	546 (58.8)	0.001	0.998
Home locality, Urban n (%)	23 (27.1)	228 (24.6)	0.259	0.611
BMI, kg/m^2 ($M \pm SD$)	21.0 ± 2.58	20.71 ± 3.18	0.800	0.424
Smokers, n (%)	4 (4.7)	41 (4.4)	0.015	0.902
Drinking status, n (%)	Question: How many days you have at least one drink of alcohol during the past 30 days?			
Never	58 (68.2)	589 (63.5)		
1 or 2 days	5 (5.9)	55 (5.9)	1.750	0.626
3–9 days	1 (1.2)	33 (3.6)		
≥10 days	21 (24.7)	251 (27.0)		
BES score ($M \pm SD$)	21.49 ± 3.49	7.28 ± 4.31	35.159	0.000
MDMQ score ($M \pm SD$)				
Vigilance	6.98 ± 2.70	7.37 ± 2.64	−1.315	0.189
Procrastination	5.32 ± 2.40	3.93 ± 2.29	5.318	0.000
Buck-passing	5.84 ± 2.90	4.36 ± 2.82	4.604	0.000
Hypervigilance	5.29 ± 2.28	4.24 ± 2.15	4.311	0.000
DDT score ($M \pm SD$)				
k/log-transformed	0.29 ± 0.22/−0.68 ± 0.38	0.29 ± 0.20/−0.66 ± 0.35	0.009/0.486	0.993/0.627
PDT score ($M \pm SD$)				
Part A ($20 vs. $80): h/log-transformed	5.67 ± 4.94/0.55 ± 0.48	5.20 ± 4.76/0.50 ± 0.48	0.868/0.946	0.386/0.344
Part B ($40 vs. $100): h/log-transformed	3.67 ± 4.06/0.34 ± 0.45	3.26 ± 4.11/0.25 ± 0.47	0.887/1.678	0.375/0.094
Part C ($40 vs. $60): h/log-transformed	3.09 ± 5.15/0.07 ± 0.54	2.26 ± 3.89/0.01 ± 0.47	1.834/1.043	0.067/0.297

BES, Binge Eating Scale; BMI, Body Mass Index; MDMQ, Melbourne Decision-Making Questionnaire; DDT, Delay-discounting Test; PDT, Probability Discounting Test, k represents the delay discounting rate, and h represents the probability discounting rate.

model revealed significant group differences on Procrastination [$F_{(1,1009)} = 13.338$, $p < 0.001$, $\eta_p^2 = 0.013$], Buck-passing [$F_{(1,1009)} = 6.141$, $p = 0.013$, $\eta_p^2 = 0.006$], and Hypervigilance [$F_{(1,1009)} = 4.403$, $p = 0.036$, $\eta_p^2 = 0.004$] except Vigilance [$F_{(1,1009)} = 3.035$, $p = 0.082$]. Simple comparisons displayed that the binge-eating group had higher scores than the non-binge-eating group on Procrastination ($M_d = 1.197$, $p < 0.001$, Cohen's $d = 0.52$), Buck-passing ($M_d = 0.999$, $p = 0.013$, Cohen's $d = 0.35$), and Hypervigilance ($M_d = 0.640$, $p = 0.036$, Cohen's $d = 0.30$). The mANOVA model also showed significant gender differences on Buck-passing [$F_{(1,1009)} = 4.749$, $p = 0.030$, $\eta_p^2 = 0.005$] and Hypervigilance [$F_{(1,1009)} = 10.995$, $p = 0.001$, $\eta_p^2 = 0.011$] but not on Vigilance [$F_{(1,1009)} = 0.807$, $p = 0.369$] or Procrastination [$F_{(1,1009)} = 1.255$, $p = 0.263$]. Simple comparisons found that females scored higher than males on Buck-passing ($M_d = 0.878$, $p = 0.030$, Cohen's $d = 0.31$] and Hypervigilance ($M_d = 1.011$, $p = 0.001$, Cohen's $d = 0.47$). There were no significant interaction effects of group × gender on Vigilance [$F_{(1,1009)} = 1.611$, $p = 0.205$], Procrastination [$F_{(1,1009)} = 0.606$, $p = 0.436$], Buck-passing [$F_{(1,1009)} = 2.930$, $p = 0.087$], or Hypervigilance [$F_{(1,1009)} = 1.984$, $p = 0.159$].

On the DDT, the 2 (group: binge-eating, non-binge-eating) × 2 (gender: male, female) mANOVA model did not find significant group differences on the k-values (log-transformed) [$F_{(1,1009)} = 0.050$, $p = 0.823$]. There were also no significant gender differences or interaction effects of group × gender on the k-values (log-transformed) [$F_{(1,1009)} = 3.725$, $p = 0.054$; $F_{(1,1009)} = 0.109$, $p = 0.741$, respectively]. On the PDT, the 2 (group: binge-eating, non-binge-eating) × 2 (gender: male, female) mANOVA model revealed no significant group differences on the h-values (log-transformed) of Part A ($20 vs. $80), Part B ($40 vs. $100), or Part C ($40 vs. $60) [$F_{(1,1009)} = 0.002$, $p = 0.965$; $F_{(1,1009)} = 3.018$, $p = 0.083$; $F_{(1,1009)} = 0.495$, $p = 0.482$, respectively]. There were also no significant gender differences on the h-values (log-transformed) of Part A, Part B, or Part C [$F_{(1,1009)} = 1.966$, $p = 0.161$; $F_{(1,1009)} = 0.599$, $p = 0.439$; $F_{(1,1009)} = 0.006$, $p = 0.936$, respectively]. The interaction effects of group × gender on the h-values (log-transformed) of the three parts were not significant [$F_{(1,1009)} = 0.910$, $p = 0.340$; $F_{(1,1009)} = 0.317$, $p = 0.574$; $F_{(1,1009)} = 0.079$, $p = 0.779$, respectively].

Partial Correlations and Multivariable Linear Regression

Table 2 displayed the partial correlations between decision-making measures and BES scores, with age, gender, ethnicity,

TABLE 2 | Partial correlations (r_p) between decision-making measures and BES scores (N = 1013).

Variables	1	2	3	4	5	6	7	8	9
(1) BES score	–								
(2) MDMQ Vigilance	−0.051	–							
(3) MDMQ Procrastination	0.243***	0.115***	–						
(4) MDMQ Buck-passing	0.189***	−0.065	0.432***	–					
(5) MDMQ Hypervigilance	0.264***	0.187***	0.477***	0.458***	–				
(6) DDT *k* (log-transformed)	0.031	−0.029	0.005	0.010	0.028	–			
(7) PDT Part A *h* (log-transformed)	−0.011	−0.006	0.001	0.026	−0.037	−0.038	–		
(8) PDT Part B *h* (log-transformed)	0.001	−0.012	0.013	0.028	−0.031	−0.050	0.721***	–	
(9) PDT Part C *h* (log-transformed)	−0.014	0.014	0.026	0.014	−0.031	−0.038	0.464***	0.639***	–

*BES, Binge Eating Scale; MDMQ, Melbourne Decision-Making Questionnaire; DDT, Delay-discounting Test; PDT, Probability Discounting Test, k represents the delay discounting rate, and h represents the probability discounting rate. Control variables: age, gender, ethnicity, and home locality. ***p < 0.001.*

TABLE 3 | Multivariable linear regression analyses of decision-making measures on BES scores (N = 1013).

Models	Standardized Coefficients (β)	t	F	R	R^2	R^2 change
Step 1			92.906***	0.290	0.084	0.084***
Gender (Male = 1)	−0.290	−9.639***				
Step 2			23.808***	0.420	0.176	0.092***
Gender (Male = 1)	−0.253	−8.608***				
MDMQ Vigilance	−0.037	−1.089				
MDMQ Procrastination	0.141	4.149***				
MDMQ Buck-passing	0.087	2.938**				
MDMQ Hypervigilance	0.187	5.264***				
DDT *k* (log-transformed)	0.030	1.030				
PDT Part A *h* (log-transformed)	−0.015	−0.352				
PDT Part B *h* (log-transformed)	0.026	0.552				
PDT Part C *h* (log-transformed)	−0.019	−0.517				

*BES, Binge Eating Scale; MDMQ, Melbourne Decision-Making Questionnaire; DDT, Delay-discounting Test; PDT, Probability Discounting Test, k represents the delay discounting rate, and h represents the probability discounting rate. Dependent variable: BES scores. **p < 0.01, ***p < 0.001.*

and home locality as the control variables. Data revealed significant positive correlations between BES scores and MDMQ Procrastination, Buck-passing as well as Hypervigilance (r_p = 0.189–0.264, *p*s < 0.001). However, no significant associations were detected between BES scores and MDMQ Vigilance, DDT *k*-values (log-transformed), and PDT *h*-values (log-transformed) of Part A, Part B, and Part C (*p*s > 0.05).

A multivariable linear regression model was further used to test the effects of MDMQ, DDT, and PDT scores on BES scores with a 2-step design (i.e., gender was entered in step 1 as the control variable, and the decision-making variables were entered in step 2 as the predictors). **Table 3** displayed that MDMQ Procrastination, Buck-passing, and Hypervigilance were the positive predictors for BES scores after excluding the effects of gender [$F_{(9,1003)} = 23.808$, $p < 0.001$; $\Delta R^2 = 0.092$, $p < 0.001$].

Logistic Regression Outcomes

A binary logistic regression model was conducted fundamentally to test the effects of decision-making measures on binge eating behavior comparing the two groups (i.e., binge eating vs. non-binge eating). A 2-step design was used: gender was entered in step 1 as the control variable, and the four MDMQ dimensions (Vigilance, Procrastination, Buck-passing, and Hypervigilance), DDT *k*-values (log-transformed) and PDT *h*-values (log-transformed) of Part A, Part B, and Part C were entered in step 2. **Table 4** revealed that only MDMQ Procrastination positively predicted binge eating (OR = 1.191, $p < 0.01$; Nagelkerke $R^2 = 0.130$ for the model). However, none of the MDMQ Vigilance, Buck-passing and Hypervigilance, DDT *k*-values (log-transformed), and PDT *h*-values (log-transformed) of three parts displayed a significant predictive effect on binge eating behavior.

DISCUSSION

This study compared different measures of decision-making in young adults with and without binge eating behavior. Our data revealed elevated scores on maladaptive decision-coping patterns of the MDMQ including Procrastination, Buck-passing, and Hypervigilance in the binge-eating group in comparison to the non-binge-eating group. Significant positive associations were found between BES scores and Procrastination, Buck-passing as well as Hypervigilance scores, and Procrastination, Buck-passing, and Hypervigilance were positive predictors of BES scores. More interesting, logistic regression model revealed that only Procrastination positively predicted binge

TABLE 4 | Logistic regression analyses of decision-making scores on binge eating controlling for gender.

Models	Non-Binge Eating vs. Binge Eating[a] (Binge Eating = 1)		
	B	Wald χ^2	OR (95% CI)
Step 1			
Gender (Male = 1)	−1.228	18.525***	0.293 (0.168–0.512)
Step 2			
MDMQ Vigilance	−0.076	3.021	0.927 (0.850–1.010)
MDMQ Procrastination	0.175	8.971**	1.191 (1.062–1.335)
MDMQ Buck-passing	0.075	2.411	1.078 (0.980–1.185)
MDMQ Hypervigilance	0.080	1.404	1.083 (0.949–1.236)
DDT *k* (log-transformed)	−0.007	0.001	0.993 (0.519–1.898)
PDT Part A *h* (log-transformed)	−0.246	0.491	0.782 (0.393–1.555)
PDT Part B *h* (log-transformed)	0.629	2.103	1.875 (0.802–4.387)
PDT Part C *h* (log-transformed)	−0.109	0.114	0.897 (0.478–1.685)

MDMQ, Melbourne Decision-Making Questionnaire; DDT, Delay-discounting Test; PDT, Probability Discounting Test, k represents the delay discounting rate, and h represents the probability discounting rate. CI, confidence interval; OR, odds ratio, [a]*N = 1013, Nagelkerke* $R^2 = 0.130$. $^{**}p < 0.01$, $^{***}p < 0.001$.

eating. These findings support the hypothesis that diverse dimensions of decision-making are distinctly linked to binge eating and specific decision-making trait (i.e., Procrastination) may characterize individuals with binge eating, putatively representing an important vulnerability trait for the development of BED.

Decision-making deficit is considered an important neurocognitive characteristic of addictive behaviors (Redish et al., 2008; Leeman and Potenza, 2012; Yan et al., 2014), and poor decision-making might facilitate overeating since the remarkable clinical parallels between BED and addictions. Though several previous studies have investigated decision-making performance on cognitive tasks (mainly the IGT) among BED patients (Davis et al., 2010; Svaldi et al., 2010; Danner et al., 2012; Aloi et al., 2015), little work has paid close attention to other facets of decision making such as decision-coping traits and reward discounting. To our knowledge, this is the first study to contrast individuals with and without binge eating on a battery of decision-making measurements (i.e., decision-coping styles, delay discounting, and probability discounting). Our data demonstrated that non-clinical individuals with binge eating had more maladaptive decision-coping traits (i.e., Procrastination, Buck-passing, and Hypervigilance) than individuals without binge eating, suggesting a defective decision-making model at the personality level (Gorodetzky et al., 2011). This result is similar with the present findings of maladaptive decision-making styles in other addictions including stimulant and opiate addicts, problem drinking and gambling individuals as well as nicotine and caffeine dependents (Gorodetzky et al., 2011; Phillips and Ogeil, 2011; Phillips and Ogeil, 2015). It is noteworthy that in our study, though the binge-eating group did show higher scores on Buck-passing and Hypervigilance than the non-binge-eating group with medium to small effect sizes (Cohen's d = 0.35, 0.30, respectively), and the partial correlations between Buck-passing, Hypervigilance and BES scores were significantly positive, Buck-passing and Hypervigilance did not display any main effects as a predictor on distinguishing binge eating from non-binge eating behaviors in the logistic regression model. This issue might be partly accounted for by the results that females scored significantly higher than males on both Buck-passing and Hypervigilance, and the proportion of females was significantly higher in the binge-eating group than in the non-binge-eating group (**Table 1**). In addition, the data of DDT and PDT did not reveal significant between-group differences, inconsistent with previous research data showing increased discounting of delayed rewards in women with obesity and BED compared to normal-weight women (Davis et al., 2010) and decreased discounting of probabilistic rewards in pathological gamblers compared with matched controls (Miedl et al., 2012), which might be due to the different methodologies and samples, therefore universal measurements should be adopted in further studies to clarify on the divergence of results. Furthermore, previous research has displayed diminished bilateral ventral striatal activity during monetary reward/loss processing in individuals with BED and obesity relative to non-BED individuals with obesity (Balodis et al., 2013a), suggesting that potential heterogeneity and neural differences of reward processing in these disorders should be taken into consideration in future.

More importantly, this study found that the binge-eating group scored higher on Procrastination than the non-binge-eating group with a medium to large effect size (Cohen's d = 0.52), and only Procrastination positively predicted binge-eating behavior in the logistic regression model controlling for gender. Procrastination refers to a tendency of defensive avoidance that the decision maker escapes conflict by procrastinating decisions to bolster the least objectionable alternative, leading in turn to faulty decisions (Mann et al., 1997). Our study presented the first direct evidence in non-treatment seeking populations showing that specific trait of decision-making (Procrastination) is overtly increased in binge eating as a predictive indicator. The data, together with previous preliminary evidence in drug addiction (Gorodetzky et al., 2011; Phillips and Ogeil, 2011), suggest that Procrastination as a personality trait of decision-making probably characterizes individuals with BED. These findings support the hypothesis that Procrastination is a specific decision-coping trait involved in BED, putatively representing an important vulnerability for this disorder. Nevertheless, it remains unclear whether Procrastination predates BED or is a consequence of the pathology, considering the cross-sectional design of our study. Therefore, longitudinal designs should be adopted in future studies. Moreover, in consideration of the clinical similarity between BED and substance use disorders, the current findings also call into future studies on the potential neurobiological mechanisms of Procrastination in both disorders. Especially, individuals with BED and obesity were partly differentiated by hypoactivity in brain areas involved in inhibitory control (i.e., ventromedial prefrontal cortex, inferior frontal gyrus, and insula) compared to non-BED individuals with obesity and lean comparison participants (Balodis et al., 2013b). Thus further studies employing neuroimaging methods (e.g., functional magnetic resonance imaging, fMRI) should be of help to elucidate the neural basis of Procrastination in BED.

There were several limitations in this study. First of all, the cross-sectional study design was not able to determine causal relationships between the decision-making measures and binge eating behavior. Although the data suggest that Procrastination might increase risk for BED, further longitudinal studies are warranted. Secondly, BED conditions and decision-making dimensions were evaluated by self-report questionnaires, which could be liable to bring bias into the data analyses. Thus, the results should be explained carefully. Thirdly, the participants consisted of university students, and especially, current and lifetime psychiatric and mental disorders that have been exhibited to be mostly comorbid with BED were excluded in this study (primarily for the purpose of directly portraying a "pure" decision-making patterns in binge-eating behavior itself), so the findings cannot be generalized to the whole population of BED, and the differences on decision-making models between different BED samples (e.g., college students, community populations, clinical patients) should be examined in future research. Besides, the current findings mainly focused on the decision-coping aspects in binge eating, but actually, other cognitive mechanisms such as planning abilities and cue-induced risky decision-making could also play an important role underlying BED (Neveu et al., 2014, 2016), which should be encompassed more comprehensively in future studies.

Despite these limitations, our results indicate that Procrastination, Buck-passing, and Hypervigilance are increased among individuals with binge eating compared to those without binge eating, and moreover, Procrastination is a risk factor in predicting binge eating behavior, putatively identified as a vulnerability trait of BED. The findings may be conducive to further absorbing the mechanisms of specific decision-making traits implicated in the development of BED, and facilitating the exploitation of effective prevention and early interventions of compulsive overeating.

ETHICS STATEMENT

The procedures reported in this study were reviewed and approved by the Human Research Ethics Committee at the Guizhou Medical University, and the proposed recruitment process, study design, and plans to compensate participants were carried out in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

W-SY designed the study, wrote the protocols, directed the study, and wrote the first draft of the manuscript. R-RZ performed the assessments and data collection. YL and Z-ML assisted with main data analysis. Y-HL as well as the other authors contributed to the writing and all authors approved the final manuscript.

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The Perception of Time Is Underestimated in Adolescents With Anorexia Nervosa

Carmelo M. Vicario[1,2,3] and Kim Felmingham[4]*

[1] School of Psychology, University of Tasmania, Hobart, TAS, Australia, [2] Dipartimento di Scienze Cognitive, Psicologiche, Pedagogiche e degli Studi Culturali, Messina, Italy, [3] Department of Psychology and Neurosciences Leibniz Research Center for Working Environment and Human Factors, Dortmund, Germany, [4] School of Psychological Sciences, University of Melbourne, Parkville, VIC, Australia

Research has revealed reduced temporal discounting (i.e., increased capacity to delay reward) and altered interoceptive awareness in anorexia nervosa (AN). In line with the research linking temporal underestimation with a reduced tendency to devalue a reward and reduced interoceptive awareness, we tested the hypothesis that time duration might be underestimated in AN. Our findings revealed that patients with AN displayed lower timing accuracy in the form of timing underestimation compared with controls. These results were not predicted by clinical, demographic factors, attention, and working memory performance of the participants. The evidence of a temporal underestimation bias in AN might be clinically relevant to explain their abnormal motivation in pursuing a long-term restrictive diet, in line with the evidence that increasing the subjective temporal proximity of remote future goals can boost motivation and the actual behavior to reach them.

Keywords: anorexia nervosa, time processing, time underestimation, long-term restrictive diet, symptomatic trait

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****Correspondence:***
Carmelo M. Vicario
carmelo.vicario@utas.edu.au

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INTRODUCTION

Anorexia nervosa (AN) is a disorder of unknown etiology, characterized by severe eating restriction and distorted body image (1), which mainly affects young women (2). The estimated incidence of this disorder in the population is around 8 per 100,000 persons per year (3), while the mortality rate is the highest of any psychiatric disorder (4).

An excessive self-control linked to reward processing is considered one hallmark symptom in AN [e.g., Ref. (5–7)]. This is also suggested by recent investigations (8–10) using temporal discounting paradigms referring to a monetary reward (i.e., participants were asked to choose between smaller-sooner and larger-later monetary rewards) that examine the level to which a reward is devalued (discounted) over time (11). In particular, this research has revealed a lower devaluing associated with delayed reward in AN compared with healthy controls AN had significantly lower discount rates (i.e., less steep discounting) in the intertemporal choice task (10). In other words, as explained by Steinglass et al. (8), one dollar in 3 months was worth more for the AN group than it was for the healthy controls group.

Such reduced temporal discounting in AN has been interpreted as proof of enhanced ability (thus higher self-control) to delay a reward, which might help to explain their capacity to maintain a food restriction for a long time, possibly in favor of a future, more attractive reward—i.e., a further weight loss (8). However, the literature is not consistent as no temporal discounting difference between AN and controls has been documented by others [i.e., Ref. (11–13)]. These contrasting results have been explained by methodological discrepancies in task design and/or age of participants (12, 13).

In research on temporal discounting in healthy populations, several scientists have suggested the importance of separating the perception of the value associated with a reward from the perception of a delay in temporal discounting [e.g., Ref. (14–17)]. In support of this suggestion, a study by Kim and Zauberman (18) has shown that the level of overall time contraction (i.e., how long or short individuals perceive time horizons to be overall) contributes to the degree of hyperbolic discounting—i.e., the tendency to choose a smaller-sooner reward over a larger-later reward. These authors found that the individual levels of hyperbolic discounting were positively correlated with the participants' time estimation length, i.e., the longer the time estimation, the higher the tendency to choose a smaller-sooner reward over a larger-later reward. This result has been confirmed in a subsequent work showing that people who overestimate the passage of time hold less value in delayed rewards (19). Moreover, a study by Suo et al. (20) found lower choice percentage for the smaller-immediate reward in participants who tended to underestimate time, compared with participants who tended to overestimate time. Taken together, the evidence of a link between temporal discounting rate and the subjective experience of time suggests a specific prediction about the perception of time in AN. In particular, one might expect a tendency of individuals with AN to underestimate the duration of temporal intervals, as an effect of a reduced temporal discounting in this clinical population (8–10, 21).

Dysfunction in the ability to perceive time duration in individuals with AN can also be predicted in relation to their altered interoceptive functions [e.g., Ref. (22)], in line with evidence that time perception is modulated by interoception [e.g., Ref. (23–25)]. Meissner and Wittmann (26) have found that time estimation accuracy correlates with both the slope of cardiac slowing during the perception of temporal intervals and the conscious awareness of an individual's own heart beats. Moreover, Di Lernia et al. (27) have recently found a temporal underestimation of the duration of interoceptive stimuli in relation to a diminished processing of high salience stimuli from the body. This latter work further supports the prediction of a temporal underestimation in AN, given the evidence of altered processing of interoceptive (22) and body-related (28) information in this clinical population.

The hypothesis that AN might be associated with dysfunctional time estimation is also supported by the neuroimaging literature. Structural and functional data have shown that the frontostriatal pathway, which is known to play a key role in the experience of time [e.g., Ref. (29–33)], is the most susceptible neural structure to cognitively maintained restraint of appetite in AN [Ref. (34), see also Ref. (35), for a review]. The insula is another region considered putatively important for explaining the pathophysiology of individuals with AN [Ref. (32, 33, 35–38) for a review], and the research has demonstrated its direct involvement in time keeping functions [e.g., Ref. (39–41); see Ref. (42) for a review]. The neural factors predictive of potential time keeping alterations in AN include dysfunction in the dopaminergic system, which is also directly implied in the regulation of the mental clock's beats [e.g., Ref. (30, 43–46)]. Evidence of dysregulation in dopaminergic processes in AN is provided by a PET study in subjects who recovered from AN (47). These authors found increased dopamine (i.e., D2/D3) receptor (DRD3) binding in the ventral striatum, a region that modulates responses to reward stimuli (48) and the subjective experience of time (49, 50). Moreover, research suggests a greater dopamine model reward-learning signal in the anteroventral striatum, insula, and in the prefrontal cortex of AN patients (51).

From a clinical point of view, the evidence of a timing alteration in individuals with AN might be helpful in explaining the dietary restriction associated with AN. A time underestimation bias might contribute to the abnormal motivation of AN in delaying or skipping the consumption of a meal (a primary reward) for a longer-term more desirable reward (i.e., the weight loss). In presence of such a bias, individuals with AN might mentally represent their main goal (i.e., losing more weight) as more temporally proximal than how it is in reality. This could explain their strong motivation in keeping a long-term restrictive diet. An alternative, not mutually exclusive, suggestion is that a temporal underestimation might cause a misperception of meal duration and between-meal epochs. In this regard, one might assume that if between-meal intervals seem shorter than they actually are, then the motivation for the next meal is reduced. Evidence in support for such arguments exists in research on obesity (e.g., people eat more often when the interval between meals seem longer), smoking, and technology use (52–55). Interestingly, the use of a temporal discounting paradigm in previous studies in AN did not allow clarifying whether the reduced discounting response selectively reflect the value of the delayed reward, or if it might also be linked to the encoding of temporal information emerging from the execution of such a paradigm. Therefore, testing AN with an explicit timing task might also address this timely question.

Based on this literature, in this study, we tested if there was a time processing deficit in AN by using a supra-second time estimation task of visual stimuli. We also investigated any role played by attention and working memory (WM) skills, which are known to be predictive of temporal performance in healthy humans and clinical populations (30, 56–62). Moreover, we explored the contribution of depression, stress, and anxiety symptoms, which might influence time keeping skills [e.g., Ref. (63)].

PARTICIPANTS

Data from individuals with AN and healthy controls were extracted from the Brain Resource International Database (BRID[1]). This database contains data from multiple laboratories (New York, Rhode Island, Nijmegen, London, Adelaide, and Sydney) that have been acquired using standardized data acquisition techniques for cognitive tasks (IntegNeuro) including the time estimation task. Inter-lab reliability and test–retest reliability measures are high as documented in previous works [e.g., Ref. (64–66)]. The request of data is only granted to scientists who are formally registered to BRID. Access to the database was approved after the evaluation of our research proposal on time perception in AN. The review of our proposal was executed by other colleagues formally registered to BRID. After formal approval, the

[1] http://www.brainnet.net/about/governance-and-management/.

manager of the database provided an excel copy of all the available data on AN and control participants.

The AN participants were recruited from two adolescent inpatient eating disorder programs at associated teaching hospitals of the University of Sydney, Australia (The Children's Hospital at Westmead and Westmead Hospital). Specific inclusion criteria for AN participants included DSM-IV diagnosis of AN, female, aged between 12.5 and 17.5 years and in their first hospital admission at the time of recruitment. The exclusion criteria of this database included a personal or family history of mental illness, brain injury, neurological disorder, serious medical condition, drug/alcohol addiction, first-degree relative with bipolar disorder, schizophrenia, or genetic disorder, no history of bulimia nervosa, or BMI above 17.5 on day of baseline assessment. We adopted the 10th percentile of the body mass index as a cutoff for underweight in the control group (67). From two initial samples of 41 patients and 41 controls, we excluded participants with less than 8 years of education, to make this variable equivalent between the two samples. Furthermore, we did not include participants with missing information with regard to BMI, and participants providing outlier performance (i.e., ±3 SD). Therefore, the final analysis included a sample of 30 AN patients (mean age = 15.43 ± 1.60 SD) and 21 healthy controls (mean age = 15.32 ± 1.81). All participants gave written informed consent to participate in the study. The study was approved by the University of Tasmania, School of Psychology, Research Ethics Committee.

METHOD

Psychometric Measures

Anorexia nervosa diagnosis was made using the clinician-administered DSM-IV criteria (2). To estimate disorder severity and to assess for eating disorder-related psychopathology, individuals completed the Eating Disorders Inventory-3 (68). WM and attention performance were examined by using, respectively, the *Digit Span* (69) and the *Switching of Attention* (70) tasks. To assess for depressed, anxious, and stressed mood, the depression anxiety and stress scale (DASS) was administered (71). A detailed description of the psychometric measures is provided in the following paragraphs.

TASKS AND PROCEDURE

Participants were seated in a sound attenuated room in front of a touchscreen computer (NEC MultiSync LCD 1530V). All participants completed the cognitive tests as part of a reliable and valid computerized test battery (64, 66). Tests were administered using prerecorded task instructions (*via* headphones) and computerized and voice recording was used for answers. All participants performed a practice trial before the formal completion of the proposed tasks. Responses were provided by using the touchscreen.

Digit Span Task

Participants were presented with a series of digits on the touchscreen, separated by a 1-s interval. The subjects were then immediately asked to enter the digits on a numeric keypad on the touchscreen. In the first part of the test, subjects were required to recall the digits in forward order and reverse order in the second. In each part, the number of digits in each sequence was gradually increased from 3 to 9, with two sequences at each level. The dependent measure was the total number of correct trials forward and backward.

Switching of Attention Task

This modified version of the Trail Making Test consisted of two parts. The first, a measure of psychomotor speed, required the connecting of numbers in ascending sequence (i.e., 1-2-3-, etc.) (Switching of Attention – Number). The second, requiring speeded cognitive flexibility, asked participants to connect numbers and letters in an ascending but alternating sequence (i.e., 1-A-2-B, etc.) (Switching of Attention – Number/Letter). Time for completion for each part served as dependent variables.

The Time Estimation Task

A black circle appeared on the screen, turning green for times varying between 1 and 12 s, in steps of 1 s, in pseudo-random order and for a total of 12 intervals. Therefore, the number of trials was 12. Each participant was required to attend to the screen and estimate the duration of the target trace on the screen, using keys on a fixed display touchpad at the bottom of the screen with the duration range between 1 and 12 s. Each temporal switch was presented once. Task duration was approximately 3 min (see **Figure 1** for a schematic representation of the task execution). The task assesses the ability to estimate time intervals without a clock and relates to the ability to pre-plan actions, decide temporal onset, monitor the time course of initiation, and anticipate

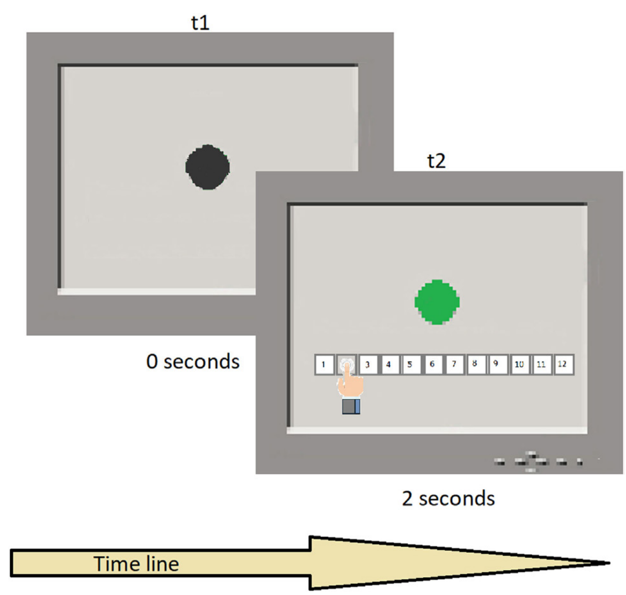

FIGURE 1 | Typical trial sequence. t1 shows the black circle presentation in the screen; t2 shows the color switch after a temporal interval and the participant's response.

outcomes. For more information about the task, refer to Block et al. (72) and Gunstad et al. (73).

DATA ANALYSIS

Participants' task performance was evaluated by considering the *proportional bias* (PB), which provides a measure of the estimation accuracy calculated from the 12 temporal intervals, where the bias for each trial is calculated as a positive or negative percentage of the actual presented interval. PB is estimated from the absolute value of the average difference between the actual duration of the stimulus and the user-estimated duration, weighted by the length of the stimulus. Thus, an overall positive score (i.e., >0) indicates a temporal overestimation; while an overall negative score (i.e., <0) indicates a temporal underestimation. As *post hoc* analysis, we also calculated the *estimation bias variability* (EBV), which represents the SD average of the PB. Timing variability measure reflects how repeated responses are scattered from their target within a particular experimental condition. We have calculated this parameter as a further exploratory measure, with the purpose to explore participants' variability in detecting the duration of temporal intervals.

Proportional bias and EBV scores of our clinical and control samples were compared by using pairwise t-test comparisons. Although we were interested in exploring any role of other variables on time keeping skills, we choose the t-test comparison, instead of the analysis of covariance (ANCOVA), in keeping with the suggestion of a recent work (74) that discourages the use of ANCOVA in the case of classification designs, that is designs that indicate a comparison of different populations such as in our case. The participants PB scores were also compared against the 0 score *via* one sample t-test, to investigate if the timing performance of our two samples significantly deviated from the 0 score, which reflects the timing performance in absence of biases. Finally, *Pearson* correlation analyses were implemented to measure any relationship between the time estimation performance and the cognitive/affective measures collected for our participants. We run separate analyses for AN and controls as the intent of our research was exploring any between groups difference with regard to the several variables included in our research.

The p value was adjusted with Bonferroni correction, as PB and EBV scores were compared with 14 variables (75). Therefore, the corresponding level of significance for the correlation outputs is <0.003 (i.e., 0.05/14, see **Table 2** for details). Data analysis was performed using Statistica software, version 8.0, Stat Soft, Inc., Tulsa, OK, USA.

RESULTS

The sample size was sufficiently large (i.e., ≥46) for the related effect size of Cohen's $d = 0.75$, a statistical power of 0.8 and a probability level of 0.05. The observed *post hoc* statistical power was 0.833. All these analyses were implemented via *Free Statistics Calculator*.[2] **Table 1** presents a summary of means and SDs on demographic, cognitive, and clinical variables for the groups and test statistics for between group comparisons (i.e., pairwise t-test). A significant between groups difference was reported for all clinical measures and the BMI score, while no difference was reported for cognitive and demographic variables (**Table 1** for details).

The t-test on timing performance documented a significant between group difference for the PB score, which was lower for the AN sample (M = −0.072, SD = 0.102), compared with controls (M = 0.027, SD = 0.152) ($t = -2.80$, $p = 0.007$, Cohen's $d = 0.75$), see **Figure 2** for details. The one sample t-test relative to 0 revealed a significant difference for the AN sample ($t = -3.890$, $p < 0.001$, Cohen's $d = 0.69$). By contrast, no significant difference from the 0 score was reported comparing the performance of the control group ($t = 0.817$, $p = 0.423$, Cohen's $d = 0.20$). Finally, we did not find a significant difference for the EBV score ($p = 0.121$).

The correlation analyses of AN and control participants did not reveal significant results according the adjusted p-level (see **Table 2** for details).

[2]https://www.danielsoper.com/statcalc/calculator.aspx?id=49.

TABLE 1 | The table reports the means and the t-test scores for the examined clinical and cognitive affective performance associated to AN and control participants.

	Mean—AN	Mean—controls	t-Test	p-Level
Age	M = 15.43, SD = 1.66	M = 15.33, SD = 1.81	0.217	0.828
Education	M = 10.63, SD = 1.62	M = 10, SD = 1.70	1.341	0.186
Depress	M = 9.72, SD = 5.90	M = 2.47, SD = 2.85	4.904*	<0.001
Anxiety	M = 5.88, SD = 4.12	M = 1.23, SD = 1.17	4.871*	<0.001
Stress	M = 8.52, SD = 4.98	M = 3.42, SD = 3.12	3.810*	<0.001
Digitot	M = 6.25, SD = 2.90	M = 6.70, SD = 2.16	0.228	0.820
Digitsp	M = 5.74, SD = 1.60	M = 5.92, SD = 1.32	0.261	0.794
Rdigitot	M = 4.51, SD = 2.37	M = 3.88, SD = 2.29	1.638	0.107
Rdigitsp	M = 4.71, SD = 1.91	M = 4.40, SD = 1.52	1.505	0.138
Swoadur1	M = 18,656, SD = 4,260	M = 19,652, SD = 4,155	−1.799	0.081
Swoaerr1	M = 0.80, SD = 1.28	M = 0.66, SD = 0.960	0.240	0.811
Esoadur2	M = 40,276.1, SD = 13,273.2	M = 41,076.1, SD = 13,057	−1.070	0.289
Esoaerr2	M = 1.02, SD = 2.00	M = 1.29, SD = 1.56	−0.872	0.387
BMI	M = 16.10, SD = 1.07	M = 21.11, SD = 4.01	−6.485*	<0.001

**A significant result.*

Digitot (digit span forward, correct trials); Digitsp (digit span forward, recall span); Rdigitot (digit span reverse, correct trials); Rdigitsp (digit span reverse, recall span); Swoadur1 (switching of attention, completion time—digits); Swoaerr1 (switching of attention, errors—digits); Esoadur2 (switching of attention, completion time—digits + letters); Esoaerr2 (switching of attention, errors—digits + letters); BMI (body mass index).

TABLE 2 | The table provides details about the correlation results between the PB and estimation bias variability (EBV) scores of the AN and the control groups and their performance with regard to clinical and cognitive measures.

	PB *AN*		**EBV *AN***		**PB *controls***		**EBV *controls***	
	R	***p*-Level**	***R***	***p*-Level**	***R***	***p*-Level**	***R***	***p*-Level**
Age	−0.289	0.120	−0.114	0.546	−0.202	0.378	−0.0381	0.869
Education	−0.306	0.100	−0.063	0.738	−0.270	0.236	−0.117	0.611
Depress	−0.135	0.476	−0.052	0.782	−0.273	0.230	−0.234	0.307
Anxiety	−0.102	0.588	0.054	0.775	−0.035	0.880	−0.023	0.921
Stress	−0.059	0.754	−0.011	0.952	−0.120	0.601	−0.204	0.373
Digitot	0.397	0.032	−0.460	0.012	−0.181	0.430	0.292	0.198
Digitsp	0.427	0.020	−0.495	0.006	−0.361	0.107	0.142	0.537
Rdigitot	0.167	0.385	−0.290	0.126	−0.298	0.188	0.357	0.111
Rdigitsp	0.157	0.413	−0.292	0.123	−0.293	0.197	0.257	0.259
Swoadur1	0.171	0.365	0.001	0.999	0.018	0.9350	−0.072	0.754
Swoaerr1	0.099	0.601	0.271	0.146	0.158	0.493	0.314	0.165
Esoadur2	−0.024	0.898	0.472	0.008	0.217	0.343	−0.023	0.919
Esoaerr2	0.312	0.092	0.427	0.018	0.3100	0.170	0.191	0.406
BMI	0.053	0.779	0.019	0.919	−0.304	0.178	0.075	0.746

Digitot (digit span forward, correct trials); Digitsp (digit span forward, recall span); Rdigitot (digit span reverse, correct trials); Rdigitsp (digit span reverse, recall span); Swoadur1 (switching of attention, completion time—digits); Swoaerr1 (switching of attention, errors—digits); Esoadur2 (switching of attention, completion time—digits + letters); Esoaerr2 (switching of attention, errors—digits + letters); BMI (body mass index).

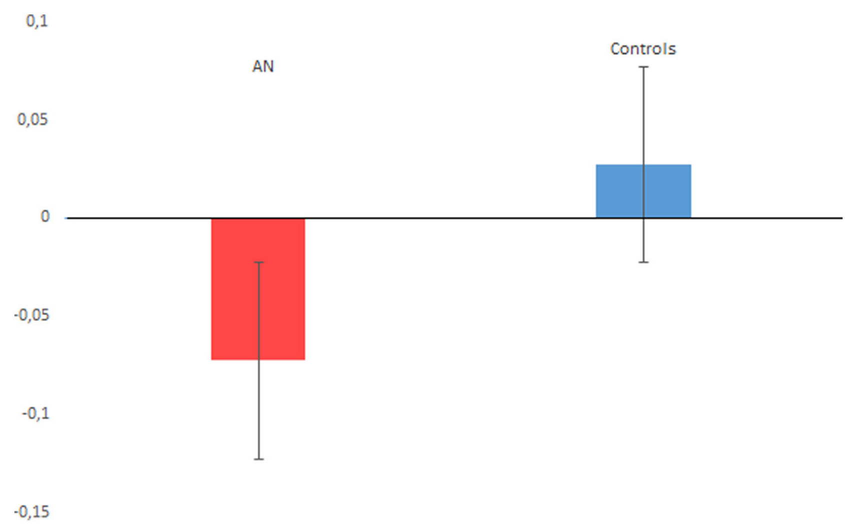

FIGURE 2 | The figure plots the proportional bias performance associated with anorexia nervosa (AN) and control participants. A negative value indicates time underestimation, while a positive value indicates time overestimation. Vertical bars denote ± SEs.

DISCUSSION

In this study, we provided evidence that time perception is underestimated in AN. This result is in agreement with our initial hypothesis based on the research documenting temporal underestimation in the presence of reduced temporal discounting (20) and altered processing of interoceptive/body information (27), which have been documented in AN [e.g., Ref. (8, 10, 22, 28)]. Moreover, the timing performance of the AN group significantly deviated from the 0 score of the PB measure, where the 0 score represents the timing performance in absence of any bias. Therefore, the AN timing performance can also be described as being less accurate than that of the control sample. This result can be explained in relation to the reduced cardiac awareness in AN (76, 77). In fact, the lower the awareness of individual heart beats, the lower the time estimation accuracy (26). However, we did not measure cardiac awareness in our AN participants, and therefore this suggestion remains to be directly tested in future works. As outlined in the Section "Introduction," a possible implication of a temporal underestimation bias in AN is that these patients might perceive their forthcoming goals—such as losing more weight—as more temporally proximal than how they are in the reality. This might contribute to explaining their heightened motivation in keeping a long-term restrictive diet. Such an interpretation is in line with the evidence (78) that increasing the subjective temporal proximity of remote future goals can boost motivation and the actual behavior to reach them, regardless of whether these goals are described in mildly or highly pessimistic terms. In keeping with this interpretation, we suggest that the time underestimation pattern reported in AN might be interpreted as the sign of a *temporal proximity bias*, which might affect their decisions for perspective goals (i.e., the weight loss) or outcomes they are interested in. Importantly, the absence of any correlation with the examined clinical, cognitive, and demographic measures corroborates the suggestion that the AN timing alteration documented in our study might be a symptomatic trait of this psychiatric condition, rather than being the epiphenomenon of other related deficits. Moreover, the evidence of a temporal underestimation in AN suggests that the reduced temporal discounting reported in previous work [e.g., Ref. (8)] might not be a hallmark of this clinical population, but a secondary effect of such timing bias. This is in line with previous evidence in healthy humans [e.g., Ref. (20)] reporting lower choice percentage for the smaller-immediate reward in participants who tended to underestimate time.

There are limitations in this study that should be mentioned. No information about the sub-type of AN condition (*restrictive* or *purging*) was available from the database. This would have been relevant in terms of exploring the possible contribution of impulsivity, as this is known to differ between the two subtypes of AN (79) and can affect timing performance (80). The timing task adopted in our current study did not include AN disorder-specific stimuli (i.e., picture of food stimuli) and/or other reward-related conditions. This would be another interesting aspect to explore in future investigations, as it might clarify whether and how the exposure to a primary reward, which may be perceived as an aversive experience in AN (81, 82), affects time processing. We anticipate that an overestimation response might be predicted in the timing performance of AN in the presence of food stimuli, in line with the evidence of temporal overestimation in response to negative, stressful/fearful outcomes and anxiety [e.g., Ref. (24, 83–85)]. The absence of measures to establish the temporal discounting response and the interoceptive awareness in our AN participants do not allow us to verify whether the reported temporal underestimation pattern is directly related with these measures, as it can be inferred from previous works in this field [e.g., Ref. (20, 26)]. Therefore, the role of temporal discounting and interoception need to be explicitly tested in future investigations.

Strengths of our study are represented by the potential theoretical and clinical implications of the current discovery for the interpretation of AN disorder; the rigid inclusion/exclusion criteria; and the examination of demographic, clinical, and cognitive measures for the interpretation of the reported timing pattern.

CONCLUSION

The results of our study add new insights for the clinical interpretation of AN, suggesting that the temporal underestimation might contribute to the restrictive dietary pattern of this psychiatric disorder. In particular, we suggest that, because of a temporal underestimation bias, AN participants might perceive their future goals (i.e., the loss of further weight) as more proximal. This might contribute to the origin of their extreme motivation in pursuing a restrictive diet for a long time, as increasing the subjective temporal proximity of remote future goals can boost motivation and the actual behavior to reach them (78).

The absence of relationships between cognitive (WM and attention) and timing performance also suggests that the temporal underestimation bias of AN might be a symptomatic trait of this clinical condition. Moreover, the absence of such relationships, together with the absence of significant WM and attention deficits in this AN group, provide insights with regard to the possible neural underpinning of the reported timing alteration. In particular, one might speculate a main role of the insula cortex, over other neural regions, which activity is known to be altered in AN [Ref. (35), for a review]. This suggestion is provided in line with a recent study (86) which has dissociated the role of the insula activity in time processing from the role of basal ganglia for WM and attention processing. The potentially central role of the insula in the timing alteration of AN might make sense also of the food restriction habit of these patients, given the role of this region in regulating hunger/satiety signaling (87, 88).

Future investigations are required to extend this research in adult AN participants. The inclusion of other timing paradigms such as temporal expectation tasks [e.g., see Ref. (89–91), for a review], might allow us to more directly test the hypothesis that AN is affected by a *temporal proximity bias* for forthcoming goals.

ETHICS STATEMENT

All participants gave written informed consent during their recruitment. The study was approved by the Western Sydney Area Health Services Human Research Ethics Committee and by the University of Tasmania, School of Psychology, Research Ethics Committee.

AUTHOR CONTRIBUTIONS

Study concept and design, statistical analysis and interpretation of data, and critical revision of the manuscript: CV and KF. Acquisition of data and drafting of the manuscript: CV. All authors read and approved the version to be published.

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