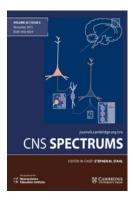
CNS Spectrums

http://journals.cambridge.org/CNS

Additional services for CNS Spectrums:

Email alerts: <u>Click here</u>
Subscriptions: <u>Click here</u>
Commercial reprints: <u>Click here</u>
Terms of use: <u>Click here</u>



Cognitive biases in binge eating disorder: the hijacking of decision making

Valerie Voon

CNS Spectrums / Volume 20 / Issue 06 / December 2015, pp 566 - 573 DOI: 10.1017/S1092852915000681, Published online: 23 November 2015

Link to this article: http://journals.cambridge.org/abstract_S1092852915000681

How to cite this article:

Valerie Voon (2015). Cognitive biases in binge eating disorder: the hijacking of decision making. CNS Spectrums, 20, pp 566-573 doi:10.1017/S1092852915000681

Request Permissions: Click here

CNS Spectrums (2015), **20**, 566–573. © Cambridge University Press 2015. The online version of this article is published within an Open Access environment subject to the conditions of the Creative Commons Attribution-NonCommercial-ShareAlike licence http://creativecommons.org/licenses/by-nc-sa/3.0/. The written permission of Cambridge University Press must be obtained for commercial re-use. doi:10.1017/S1092852915000681

REVIEW ARTICLE

Cognitive biases in binge eating disorder: the hijacking of decision making

Valerie Voon*

Department of Psychiatry, University of Cambridge, Cambridge, UK; Behavioural and Clinical Neurosciences Institute, Cambridge, UK; Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK

Binge eating disorder (BED) is the most common of eating disorders and is characterized by excessive, out-of-control, rapid food intake. This review focuses on cognitive impairments in BED, which represent an endophenotype that mediates brain function and behavior. Here we focus on reviewing impulsivity, compulsivity, attentional biases to food cues, and executive function. Behavioral regulation in BED appears to be influenced by the context of motivationally salient food cues and the degree of obesity. Deficits in delay discounting and risk taking under ambiguity are impaired in obesity irrespective of BED status. However, in BED subjects with milder obesity, greater risk seeking under explicit probabilistic risk is observed to monetary rewards, whereas this shifts to risk aversion and enhanced delay discounting in more severe obesity. Relative to non-BED obese subjects, BED is characterized by enhanced behavioral inflexibility or compulsivity across multiple domains, with subjects selecting the same choices despite change in relevance (set shifting), being no longer rewarding (habit formation), or irrespective of outcome (perseveration). The context of food cues was associated with multiple attentional and early and late inhibitory impairments and enhanced memory bias, although BED patients also have generalized cognitive interference in working memory. These findings may help explain the phenotype of binge eating. Motivationally salient food cues provoke attentional and memory biases along with impairing response inhibitory processes. Those with BED are also more susceptible to cognitive interference and have impaired decisional impulsivity, with the tendency to inflexibly stick with the same choices irrespective of changes in context. These findings suggest critical cognitive domains that may guide therapeutic interventions.

Received 20 May 2015; Accepted 22 September 2015

Key words: Attentional bias, binge eating disorder, cognition, compulsivity, impulsivity, motivation, obesity.

Introduction

Binge eating disorder (BED) is the most common of eating disorders¹ and is characterized by excessive and rapid food intake without concomitant purging behaviors. BED is commonly associated with obesity but also occurs without obesity. A range of cognitive abnormalities has been reported in BED. The study of cognitive processes allows us to address several issues of relevance to BED. First, cognitive processes have well-defined neural correlates from animal and human studies and represent powerful intermediate endophenotypes that mediate brain function and behavior.³

Dr. Voon is funded by the Wellcome Trust (093705/Z/10/Z).

Thus, cognitive impairments may reflect underlying impairments in corresponding brain substrates. Second, demonstrating similarities across differing pathological disorders provides insights into dimensional mechanistic similarities that might cut across seemingly differing behaviors and assist with further conceptualization of a disorder.4 How BED might compare with other eating disorders, obesity without BED, and disorders of addiction or impulse control may help with conceptualization of BED.5-8 This converges with the trend toward dimensional psychiatry⁴ by conceptualizing binge eating beyond the simple phenomenon of eating behavior (eg, anorexia nervosa or bulimia nervosa), to identifying biological or cognitive endophenotypes that may link this behavior of persistent, out-of-control, rapid consumption of a highly palatable natural reward (food) with other potentially relevant behaviors. Third, differentiating between BED and non-BED obese subjects can further

^{*} Address for correspondence: Valerie Voon, Department of Psychiatry, University of Cambridge, Addenbrookes Hospital, Cambridge CB2 0QQ, UK.(Email: voonval@gmail.com)

help with defining subtypes of obesity and help particularly with characterizing the heterogeneity of obesity. Thus, understanding cognitive processes underlying BED may help elucidate underlying neural networks, mechanisms leading to aberrant behaviors, and also help with conceptualization of BED and differentiating BED as a subtype of obesity. Aberrant cognitive processes may also represent a marker as a predictor for outcomes, for treatment targets, and to assess therapeutic outcomes.

This review focuses on the cognitive domains that are affected in studies comparing BED [as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)] and non-BED obese subjects or matched healthy controls. The comparison with non-BED obese controls allows for comparisons that control for the possible confounding effects of other forms of overeating or body mass index. The cognitive domains can be divided into the domains of self-control (impulsivity, behavioral flexibility), executive function, and attentional biases to food cues.

Methods

The review focuses on laboratory-based rather than selfreport measures and particularly on BED and the comparison with non-BED obese subjects or healthy controls. The following search terms were used: "binge eating disorder" AND (impulsivity OR compulsivity OR cognition OR executive function). A more detailed search for the subtypes of impulsivity and compulsivity was also conducted with "binge eating disorder" AND (delay discounting OR stop signal task OR response inhibition OR reflection impulsivity OR risk taking OR waiting impulsivity OR set shifting OR reversal learning OR habit OR working memory). The search encompassed articles to August 2015.

Impulsivity

Impulsivity is the tendency to act rapidly without forethought and without regard of the negative consequences, or the reduced ability to withhold a behavior when inhibition is the appropriate or adaptive response.⁹ Impulsivity is heterogeneous and can be subdivided into motor and decisional domains, which have overlapping, yet discrete, neural substrates. 10 Differing subtypes of impulsivity are affected differentially across a range of disorders. Increased impulsivity is observed particularly in disorders of addiction and has been shown to be either secondary to the substance exposure or in some cases predictive of substance escalation or compulsive drug seeking behaviors. 10 Motor impulsivity includes motor response inhibition and waiting impulsivity, otherwise known as premature responding. The former captures the capacity to inhibit a prepotent response, and the latter the tendency to respond before target onset. Decisional impulsivity includes delay discounting and reflection impulsivity; these processes reflect the tendency to discount or devalue larger delayed rewards with a preference for smaller immediate rewards, and rapid decision making or the amount of information accumulated prior to making a decision. Risk taking can also be considered a form of impulsivity and can occur in the context of risk (or known probability) or uncertainty (in which the probability is unknown).

Response inhibition

Response inhibition is the capacity to inhibit prepotent motor responses, which can span the processes of action restraint (eg, tested using the "go/no-go" task, in which actions that are not yet initiated are inhibited) or action cancellation (eg, tested using the "stop signal" task, in which actions that are already initiated are inhibited). 10 These are common measures of response control, with meta-analyses showing deficits in attention-hyperactivity disorder, a disorder associated with impulse control impairments¹¹; substance use disorders, particularly to stimulants, nicotine, and alcohol, but not to opioids or cannabis; and pathological gambling.12 Impairments in the stop signal task have also been shown in unaffected siblings of stimulant-dependent subjects, which suggests an endophenotypic risk factor for the development of addiction. 13

Studies comparing obese BED patients against obese controls or against age- and gender-matched, healthy, non-obese controls suggest that response inhibition tested using the go/no-go task or stop signal task are impaired in BED only if paired with food cues. In one study using a go/no-go task with food and body words, BED subjects made more commission errors to both food and body words compared to non-BED obese subjects. 14 Similarly, another study showed that BED compared to non-BED obese subjects had prolonged stop signal reaction time in a stop signal task involving food images. The study also showed that BED had greater commission errors to food versus non-food images. 15 In contrast, 2 studies comparing BED versus their own healthy volunteers did not show an impairment in a neutral stop signal task without food cues. ^{16,17} In these same studies, although the stop signal task was not impaired in BED subjects, subjects with bulimia nervosa had impaired response inhibition compared to healthy volunteers¹⁶ and non-BED obese subjects, and those with alcohol use disorders had impaired response inhibition compared to healthy volunteers. 17 These studies thus suggest that response inhibition in the context of neutral cues may not be impaired in BED; however, in the context of food (and body) cues, both early and late response inhibition

Delay discounting

Delay discounting tasks in both animal and human studies involve the selection of an immediate smaller reward and a larger delayed reward with variations in either the delay to the reward or the magnitude of the reward to calculate an indifference point in which the 2 options are selected equally. This represents the value attached to the delayed reward. Greater delay discounting is observed in ADHD¹⁸ and across a range of substance use disorders.

In studies of BED subjects with mild obesity of mixed gender [body mass index (BMI) 33-35]17 to moderate obesity in women (BMI 36-38),²⁰ both BED and non-BED obese subjects had greater discounting of delayed rewards compared to healthy volunteers. In contrast, in a study in women with higher BMIs (BMI 42), BED subjects had greater discounting to delayed rewards in multiple domains, including food, money, sedentary activity, and massage time compared to non-BED obese subjects. 21 Thus, in the domain of delay discounting, an influence of severity of obesity appears to play a role: greater devaluation of the delayed reward appears to be common across BED and non-BED obese subjects, with mild to moderate BMI levels suggesting a core common cognitive deficit. However, in those with morbid obesity, BED subjects discount delayed rewards to a greater extent than non-BED obese subjects, suggesting a potential interaction between BED and severity of obesity resulting in greater impairments.

Risk, ambiguity, and sensitivity to value

Studies on risk taking involve either testing under conditions of risk (in which the probabilities are known) or ambiguity (in which the probabilities are not known). Converging evidence suggests differences in obese BED subjects during risk taking under both conditions of risk and ambiguity. For instance, both BED and non-BED obese subjects are similarly impaired on the "Iowa gambling" task, in which subjects choose one of 4 decks of cards which are either "bad" or "good" decks based on a differing distribution of probabilities of wins or losses over time. This task tests decision making under ambiguity and requires learning from feedback. 20,22 Similarly, patients with BED and patients with anorexia nervosa performed equally poorly on the Iowa gambling task compared to healthy volunteers. 23

In contrast, in studies involving explicit risk, in BED subjects with low to moderate BMI, BED subjects appear to be more risk seeking to reward outcomes than non-BED obese controls. In a study using the "game of dice"

task with feedback testing risk with explicit probabilities, ²⁴ BED subjects (BMI 31-33) made more risky choices compared to non-BED obese controls. In the game of dice task, subjects must guess which number will occur with the throw of a dice and are allowed the option of a combination of numbers associated with fixed probabilities of winning or losing. These findings are consistent with another study that compared certain versus risky choices with explicit probabilities (ie, choosing between a sure amount or a risky amount in which the probability of winning or losing is known) using an adjustment procedure in which BED subjects (BMI 33-35) had greater risk seeking to monetary reward anticipation reflected in greater probability weighting (subjective weighting of the objective probability) and greater convexity of the probability weighting curve.25 A dissociation was observed as a function of reward and loss valence, with binge eating severity scores positively correlated with probability weighting to reward anticipation (ie, that they subjectively believed a probabilistic reward was more likely to occur than the objective probability) and negatively correlated to loss anticipation.

These findings were similar to those with alcohol and methamphetamine dependence, but BED and alcohol-dependent subjects demonstrated a preference for moderate reward magnitudes, whereas methamphetamine dependence was characterized by a preference for high-risk/high-reward magnitudes. BED subjects, similar to methamphetamine-dependent subjects, also exhibited impaired discrimination of reward magnitude or value. These observations of impaired reward value discrimination are similar to studies in psychostimulant dependence, in that they demonstrate impairments in the sensitivity to monetary reward gradients. ^{26,27} BED subjects also had greater risk preference to low-risk losses, whereas obese subjects were much more risk averse to high-risk losses.

These findings contrast with another study that investigated subjects with more severe obesity (mean BMI 42) in which BED subjects were more risk averse, in that they discounted probabilistic rewards in multiple domains (food, money, sedentary activity, or massage) without feedback. 21 The study design similarly compared certain versus risky choices with an adjusting procedure to determine when the certain and risky choices were chosen equally and thus valued equally, and was conducted in conjunction with a delay discounting task with a similar design in which BED subjects also discounted delayed rewards across all domains to a greater extent than non-BED subjects. Thus, in subjects with high BMIs, greater discounting to both delayed and probabilistic rewards was observed, with greater impulsive choice preference but also greater risk aversion.

Waiting impulsivity, reflection impulsivity, and conflict

Waiting impulsivity measures the anticipatory response to a cue that predicts reward. In rodent studies using the 5-Choice Serial Reaction Time task, elevated waiting impulsivity is predictive of compulsive cocaine use.²⁸ In a translational study using the recently developed human 4-Choice Serial Reaction Time task, no differences were observed in waiting impulsivity between BED and non-BED obese controls compared to healthy volunteers. 29,30 In the task, subjects held down a space bar while performing a serial reaction time task in which they released the space bar to touch the square on the touch screen in which a target appeared. The main outcome was premature responses prior to target onset. In contrast to the BED findings, the same study demonstrated enhanced waiting impulsivity across multiple disorders of substance addiction (abstinent methamphetamine, alcohol-dependent, and cannabis users, and current smokers) and binge drinkers. This study suggests that waiting impulsivity, unlike that observed in disorders of addiction, is not impaired in obese subjects with or without BED. However, in this study, the degree of obesity was mild to moderate, and the task was not tested in the context of food cues or premature responding in BED, both of which may influence outcomes.

In a study on reflection impulsivity, which assesses the amount of evidence accumulated prior to a decision, there were no differences between either BED or non-BED obese subjects and healthy volunteers tested using the Information Sampling Task. 17 The information sampling task involves probabilistic inference, in which subjects are shown 25 squares and must use the accumulated evidence (sequential opening of the square color) to decide whether the squares are predominantly blue or pink.

In the Stroop word-color interference task, subjects must report the color in which the word is printed rather than the meaning of the word itself. The task is a complex task that assesses multiple elements, including the capacity to inhibit responding to a conflicting prepotent response, assess conflict, and shift responding. Studies investigating Stroop word-color interference (ie, to non-food related stimuli) report no differences between BED and non-BED obese subjects, suggesting that there is not a fundamental impairment in cognitive control of conflict at least as measured using the Stroop. 31,32 In a functional MRI study using the Stroop word-color task, BED subjects had lower activity in regions implicated in self-control, including the ventromedial prefrontal cortex, inferior gyrus, and insula, compared to non-BED obese controls, although no behavioral differences were observed.³³

Summary of impulsivity studies

These studies converge with and extend an early metaanalysis³⁴ that had identified 2 studies of BED^{16,31}

involving 2 differing impulsivity constructs measured using the stop signal task and Stroop interference task. The authors showed that BED was not associated with impairments in impulsivity, whereas bulimia nervosa was associated with a clear elevation in impulsivity (response inhibition and cognitive interference control) along with a marked increase in impulsivity in the context of food cues.

Put together, decisional impulsivity appears to be impaired: delay discounting and risk taking under ambiguity are impaired across both BED and non-BED obese subjects, suggesting core deficits as a function of obesity. The severity of obesity and the context of food cues appear to play important roles in behavioral regulation. In BED subjects with lower BMIs, greater risk seeking under explicit probabilistic risk is observed to monetary rewards, whereas this shifts to risk aversion in BED subjects with higher BMIs. Similarly, greater discounting of delayed rewards is observed in BED subjects with more severe obesity compared to their obese non-BED counterparts. The capacity to inhibit motor responses appears to be impaired to a greater extent in BED compared to non-BED obese controls; however, this is only true in the context of a motivationally salient food cues, not with neutral cues. Thus, the broader range of impulsivity subtypes does not appear to be as consistently impaired across multiple domains as reported in disorders of addiction. As drugs of abuse are known to influence impulsivity, one possible reason for the different results may be that food is less likely to have a state-specific influence on impulsivity measures. Whether these measures reflect state-specific or traitspecific predictive markers of BED cannot be determined from these cross-sectional studies.

Behavioral Flexibility or Compulsivity

Behavioral flexibility or compulsivity is defined as the capacity to change or shift choices in the face of differing rules, changes in contingencies, or uncertainty. Greater compulsivity commonly presents as the tendency to make repeated choices or actions despite negative consequences¹⁰ or in the face of changes in context. Impulsivity and compulsivity are believed to be overlapping constructs that might sit at opposite ends of a spectrum: for example, models of addiction posit that impulsivity transitions to compulsivity over the course of addiction 10,35; they also have overlapping processes and neural substrates, and can co-exist within the same disorder. Compulsivity, similar to impulsivity, also consists of heterogeneous subtypes with discrete but overlapping neural substrates between subtypes and can be either simple or complex. On a simple level, flexibility includes stereotypies, perseveration or impaired switching. On a more complex level, subtypes can include attentional set shifting, reversal, habit, or exploration behaviors as reviewed in the following sections.

Set shifting

Set shifting assesses a higher order capacity to shift between differing abstract rules or sets. There are several tasks that measure set shifting. In the Wisconsin Card Sorting Task, subjects must match cards to 1 of 4 cards, which differ by specific dimensions (color, shape, or number) based on specific rules that change over time. In the Trail Making Test (TMT), Trail B, which tests the capacity to alternate between numbers and letters, subjects draw must draw a line to connect a series of numbers and letters in order.

A meta-analysis investigating set shifting across multiple task types in 3 different eating disorder populations (BED, anorexia nervosa, and bulimia nervosa) identified impaired set shifting with a small to moderate effect size across all 3 populations (BED effect size: g = -0.53). A moderate effect size was shown in studies of obesity (g = -0.61) but not in overweight studies (g = -0.07). The meta-analysis included only 2 BED studies with a total of 53 BED subjects. Further analysis of the 2 studies and other recently published studies suggests there may be differences between BED and obesity as a function of BMI. In one study with mild obesity (BMI 31-32) assessing the TMT, Trail B, processing time was impaired in BED compared to non-BED obese subjects.²⁴ In another study comparing moderate obesity (BMI 36) using the Wisconsin card sorting task, perseveration errors and the failure to maintain set were both more impaired in BED compared to non-BED obese controls but not TMT, Trail B. 31 In contrast, in a recent study with high BMI (BMI 45), no differences were observed between BED and non-BED obese controls in Trail B.32 A study comparing BED (BMI 35) and anorexia nervosa with healthy controls showed that BED was associated with greater set shifting impairments compared to anorexia nervosa as measured during TMT Trail B and failure to maintain set in the Wisconsin card sorting task.23 Thus, although the literature is limited, those with BED appear to be impaired in set shifting with greater impairments relative to non-BED obese controls when BMI is low but possibly with similar impairments when BMI is high.

Goal-directed, habitual, and perseverative choices

Goal-directed and habitual behaviors have been examined in BED using the Two-step task which assesses whether individuals make choices based on the likely affective outcomes (model-based) or based on previously reinforced choices (model-free).³⁷ In this task, subjects choose between 1 of 2 choices, which then leads with

fixed probability to 1 of 2 states; selection of the choice at the second stage then leads to a probabilistic reward. Using this task to examine the balance between goal-directed behavior and habit formation, BED compared to non-BED obese subjects had impairment in model-based, goaldirected behavior with a shift toward model-free habitual behaviors.38 Higher binge eating scores correlated positively with the shift toward habit formation. These findings were similar to other disorders, including methamphetamine dependence and obsessive compulsive disorder, suggesting similarities linked by compulsive behaviors. In healthy controls, greater model-based behaviors were associated with greater volumes of the medial orbitofrontal cortex and caudate. In the same study, BED subjects had lower medial orbitofrontal cortex and ventral striatal volumes relative to non-BED obese subjects-a group difference that was lost with the inclusion of the Two-step task outcome as a covariate of no interest, suggesting that these neural regions may mediate the impairment in goal-directed behaviors. More crucially, the same study analyzed perseverative behaviors, showing that BED subjects were markedly more likely to choose the same stimulus irrespective of the outcome. Overall, these findings suggest a shift toward behavioral inflexibility, or choosing the same stimuli whether they have (habit formation) or have not (perseveration) been previously reinforced, rather than being guided by goals and changing outcomes.

Exploration

A recent study focused on the construct of exploration, in which subjects either favored restricted exploitative choices in which the action-outcome contingencies were known or explored the environment in which the contingencies were unknown.³⁹ Thus, exploration occurred as a function of tolerance of uncertainty. In the task, subjects chose the time in which to stop a clock, which then resulted in either random wins or losses. The tendency to stay and exploit the same time choice or explore alternate times was assessed. The study showed a reduction in exploratory behaviors in alcohol use disorders across both gain and loss valences.40 In this same study, although neither obese BED nor obese non-BED subjects scored differently from healthy volunteers when compared to each other, BED were more exploratory in the loss domain compared to non-BED subjects. These findings suggest that BED subjects were less avoidant of uncertainty and more exploratory in the context of losses compared to obese non-BED subjects.

Summary of compulsivity studies

Thus, BED appears to be impaired across multiple domains of compulsivity. BED subjects have greater impairments in set shifting compared to non-BED obese controls, particularly with low BMI with similar impairments across both groups with higher BMIs. BED is also impaired in habit formation and perseveration. In contrast, compared to obese subjects without BED, BED is associated with greater exploratory tendencies, particularly in a loss context, which may be related to greater tolerance of uncertain losses rather than specifically to enhanced exploratory tendencies.

Attentional and Memory Biases to Food Cues

Attentional bias provides a measure of the motivational salience of a stimulus. Although a large number of studies have focused more generally on obesity and attentional bias to food cues, relatively few studies comparing BED and non-BED obese subjects have been conducted. Female BED subjects compared to non-BED obese subjects have longer latency event-related potentials when viewing high calorie compared to low calorie foods.41 Using eye-movement tracking, BED subjects compared to non-BED obese subjects had longer gaze duration to food stimuli and difficulties with saccade away from both food and non-food stimuli in the first saccade and particularly toward food in the second saccade. 42

In studies investigating cognitive interference and memory biases for food cues, BED subjects show a general interference effect on the N-back task with lures and a food cue-specific effect in the recent probes task. Thus, working memory appears to be more susceptible to cognitive interference and is more likely to have a food cuerelated memory bias. 43 Both obese subjects with and without BED also show a bias toward negatively valenced weight or body shape words, whereas BED subjects have a specific impairment in retrieval of positively valenced words. 44

Put together with the response inhibition findings, BED is characterized by enhanced general susceptibility to cognitive interference of working memory and attentional and memory bias and impaired selfregulation in the context of salient food cues.

Mu-Opioid Receptor Antagonism

Few studies have reported pharmacological effects on cognition in BED. One study that showed cognitive and neuroimaging effects in BED was an investigational drug (GSK 1521498 2 mg and 5 mg) selective for mu-opioid receptor (MOR) antagonism administered over a 28-day period in a double-blind, placebo-controlled trial. Although the drug had no clear efficacy on weight, fat mass, or binge eating scores, the drug decreased hedonic responses to consumed sweetened dairy products (specifically to high but not low sugar and fat content), which was negatively correlated with plasma drug levels. 45 The same MOR drug also decreased putaminal and pallidal activity and motivational responding (grip force task)

specifically to viewing high-calorie foods. Although the drug did not increase subjective liking for passively viewed food images, it increased liking for the highcalorie food images in the grip force task, suggesting a potential relationship between liking and wanting related to motivational processes. 46 Although motivation and liking correlated prior to drug administration and in the placebo group, this relationship was lost following mu-opioid antagonism.

The MOR antagonist also showed a selective decrease in attentional bias to food cues as measured using the visual Dot Probe task. 47 MOR antagonism had a specific effect on later inhibition processes rather than on the earlier facilitation process of the dot probe. There was no effect on a Stroop food-cue task, working memory, or attention. The lack of difference in the Stroop food-cue task but not the dot probe task may reflect the complexity of the Stroop task, as it involves enhanced processing, inhibition, conflict, and shifting. A general mechanism of a decrease in motivational responding to food cues might suggest that both the dot probe and Stroop foodcue tasks might be similarly affected; alternatively, MOR antagonism might have a specific influence by improving inhibitory mechanisms to food cues.

Thus, MOR antagonism appears to play a role in (i) decreasing motivational responding to highly salient food cues, and may thus secondarily improve inhibitory processes toward these cues; (ii) a complex relationship with hedonic response by having no effect to passive viewing of highly salient food cues, increasing hedonic ratings to highly salient food cues for which effort or motivation is expended, and decreasing subjective hedonic ratings to consummation of sweetened foods thus the influence of MOR on hedonic responses is dissociable as a function of motivation (passive versus the object of effort) and stage (e.g. during anticipation compared to consummatory stage); and (iii) improving inhibitory mechanisms to food cues.

The role of the MOR in anticipatory motivational responding to hedonic food cues is extensively discussed in this series. The following briefly discusses the role of the MOR in impulsivity. Morphine, a MOR agonist, increases premature responding or waiting impulsivity in the 5-Choice Serial Reaction Time task and also increases preference for immediate over delayed rewards, with both measures blocked by naloxone, a MOR antagonist.⁴⁸ Naloxone by itself does not affect waiting impulsivity or delay discounting. Morphine, but not naloxone, appears to have a baseline-dependent influence on the stop signal task. MOR antagonism, but not kappa-opioid receptor antagonism, has also been shown to selectively remediate the amphetamine-induced impairments in premature responding, but to have no effect on delay discounting.⁴⁹ The MOR modulating effect on inhibition appears to be in the nucleus

accumbens shell and may interact with the mesolimbic dopaminergic system. Thus, the observation of the improvement by MOR antagonism in the dot probe task to food cues may be related to improvements in anticipatory responding, or a baseline-dependent effect on response inhibition by improving stopping in individuals with impaired stopping abilities.⁴⁸

Summary

Relative to obesity without BED, impulsivity in BED does not appear to be as critically impaired across multiple domains as observed across disorders of addiction. Whereas drugs of abuse have been shown to enhance impulsivity, the pattern of food intake, or food itself, may be less likely to cause impulsivity. Behavioral inflexibility or compulsivity and attentional bias toward food cues are more prominently impaired in BED. Behavioral regulation appears to be influenced by the context of motivationally salient food cues and the degree of obesity. Deficits in decisional impulsivity, including delay discounting and risk taking under ambiguity, are impaired in obesity irrespective of BED status. Whether these forms of impulsivity are predictive of or a consequence of obesity is not known. However, these findings are influenced by the severity of obesity: compared to non-BED obese subjects, in BED subjects with milder forms of obesity, greater risk seeking under explicit probabilistic risk is observed to monetary rewards, whereas this shifts to risk aversion and greater discounting of delayed rewards in BED subjects with more severe obesity. The capacity to inhibit motor responses appears to be impaired to a greater extent in BED compared to non-BED obese controls, only in the context of a motivationally salient food cues. BED subjects exhibit enhanced behavioral inflexibility across multiple domains, with impairments in set shifting, habit formation, and perseveration.

The presence of food cues was associated with enhanced motivation and impaired self-regulation with multiple attentional and early and late inhibitory impairments in BED, including enhanced ERP responses, longer gaze duration, difficulties with saccade away from the cue, and motor response inhibition both with action restraint and cancellation. Thus, food cues appear to impair self-control particularly in BED, possibly through attentional mechanisms, working memory, or cognitive load. An investigational specific mu-receptor opioid antagonist has been shown to influence late inhibitory processes and motivational responses to food cues, with a mixed influence on subjective hedonic ratings suggesting a potential mechanistic role for the mu-opioid receptor in mediating these processes. However, the role of mu-opioid receptor antagonists is not clear as randomized controlled trials report a mixed effect on binge eating.

Thus, rather than flexible responding guided by changing environmental outcomes, binge eating is characterized by enhanced attention and memory biases and impaired self-regulation in the context food cues, along with impulsive choices and difficulties across multiple domains of behavioral inflexibility. These findings suggest critical cognitive domains that may guide therapeutic interventions.

Disclosures

Valerie Voon does not have anything to disclose.

REFERENCES:

- 1. Hudson JI, Hiripi E, Pope HG Jr, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry. 2007; 61(3): 348-358.
- 2. Kessler RC, Berglund PA, Chiu WT, et al. The prevalence and correlates of binge eating disorder in the World Health Organization World Mental Health Surveys. Biol Psychiatry. 2013; 73(9): 904-914
- 3. Insel TR, Voon V, Nye JS, et al. Innovative solutions to novel drug development in mental health. Neurosci Biobehav Rev. 2013; 37(10 Pt 1): 2438-2444.
- 4. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010; 167(7): 748-751.
- 5. Gearhardt AN, White MA, Potenza MN. Binge eating disorder and food addiction. Curr Drug Abuse Rev. 2011; 4(3): 201-207.
- 6. Hebebrand J, Albayrak O, Adan R, et al. "Eating addiction", rather than "food addiction", better captures addictive-like eating behavior, Neurosci Biobehav Rev. 2014; 47: 295-306.
- 7. Davis C, Carter JC. Compulsive overeating as an addiction disorder: a review of theory and evidence. Appetite. 2009; 53(1): 1-8.
- 8. Ziauddeen H, Fletcher PC. Is food addiction a valid and useful concept? Obes Rev. 2013; 14(1): 19-28.
- 9. Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, Swann AC. Psychiatric aspects of impulsivity. Am J Psychiatry. 2001; 158(11):
- 10. Dalley JW, Everitt BJ, Robbins TW. Impulsivity, compulsivity, and top-down cognitive control. Neuron. 2011; $\mathbf{69}(4)$: 680-694.
- 11. Lipszyc J, Schachar R. Inhibitory control and psychopathology: a meta-analysis of studies using the stop signal task. J Int Neuropsychol Soc. 2010; 16(6): 1064-1076.
- 12. Smith JL, Mattick RP, Jamadar SD, Iredale JM. Deficits in behavioural inhibition in substance abuse and addiction: a meta-analysis. Drug Alcohol Depend. 2014; 145: 1-33.
- 13. Ersche KD, Jones PS, Williams GB, Turton AJ, Robbins TW, Bullmore ET. Abnormal brain structure implicated in stimulant drug addiction. Science. 2012; 335(6068): 601-604.
- 14. Mobbs O, Iglesias K, Golay A, Van der Linden M. Cognitive deficits in obese persons with and without binge eating disorder: investigation using a mental flexibility task. Appetite. 2011; 57(1):
- 15. Svaldi J, Naumann E, Trentowska M, Schmitz F. General and foodspecific inhibitory deficits in binge eating disorder. Int J Eat Disord. 2014; 47(5): 534-542.
- 16. Wu M, Giel KE, Skunde M, et al. Inhibitory control and decision making under risk in bulimia nervosa and binge-eating disorder. Int J Eat Disord. 2013; 46(7): 721-728.

- 17. Mole TB, Irvine MA, Worbe Y, et al. Impulsivity in disorders of food and drug misuse. Psychol Med. 2015; 45(4): 771-782.
- 18. Noreika V, Falter CM, Rubia K. Timing deficits in attention-deficit/ hyperactivity disorder (ADHD): evidence from neurocognitive and neuroimaging studies. Neuropsychologia. 2013; 51(2): 235-266
- 19. Bickel WK, Koffarnus MN, Moody L, Wilson AG. The behavioraland neuro-economic process of temporal discounting: a candidate behavioral marker of addiction. Neuropharmacology. 2014; 76(Pt R): 518-527
- 20. Davis C, Patte K, Curtis C, Reid C. Immediate pleasures and future consequences: a neuropsychological study of binge eating and obesity. Appetite. 2010; 54(1): 208-213.
- 21. Manwaring JL, Green L, Myerson J, Strube MJ, Wilfley DE. Discounting of various types of rewards by women with and without binge eating disorder: evidence for general rather than specific differences. Psychol Rec. 2011; 61(4): 561-582.
- 22. Danner UN, Ouwehand C, van Haastert NL, Hornsveld H, de Ridder DT. Decision-making impairments in women with binge eating disorder in comparison with obese and normal weight women. Eur Eat Disord Rev. 2012; 20(1): e56-e62.
- 23. Aloi M. Rania M. Caroleo M. et al. Decision making, central coherence and set-shifting: a comparison between binge eating disorder, anorexia nervosa and healthy controls. BMC Psychiatry. 2015; 15: 6.
- 24. Svaldi J, Brand M, Tuschen-Caffier B. Decision-making impairments in women with binge eating disorder. Appetite. 2010; 54(1): 84-92.
- 25. Voon V, Morris LS, Irvine MA, et al. Risk-taking in disorders of natural and drug rewards: neural correlates and effects of probability, valence, and magnitude. Neuropsychopharmacology. 2015: 40(4): 804-812.
- 26. Goldstein RZ, Parvaz MA, Maloney T, et al. Compromised sensitivity to monetary reward in current cocaine users: an ERP study. Psychophysiology. 2008; 45(5): 705-713.
- 27. Goldstein RZ, Tomasi D, Alia-Klein N, et al. Subjective sensitivity to monetary gradients is associated with frontolimbic activation to reward in cocaine abusers. Drug Alcohol Depend. 2007; 87(2-3):
- 28. Belin D, Mar AC, Dalley JW, Robbins TW, Everitt BJ. High impulsivity predicts the switch to compulsive cocaine-taking. Science. 2008; 320(5881): 1352-1355.
- 29. Voon V. Models of impulsivity with a focus on waiting impulsivity: translational potential for neuropsychiatric disorders. Curr Addict Rep. 2014; 1(4): 281-288.
- 30. Voon V, Irvine MA, Derbyshire K, et al. Measuring "waiting" impulsivity in substance addictions and binge eating disorder in a novel analogue of rodent serial reaction time task. Biol Psychiatry. 2014: 75(2): 148-155.
- 31. Duchesne M, Mattos P, Appolinario JC, et al. Assessment of executive functions in obese individuals with binge eating disorder. Rev Bras Psiquiatr. 2010; 32(4): 381-388.
- 32. Galioto R, Spitznagel MB, Strain G, et al. Cognitive function in morbidly obese individuals with and without binge eating disorder. Compr Psychiatry. 2012; 53(5): 490-495.

- 33. Balodis IM, Molina ND, Kober H, et al. Divergent neural substrates of inhibitory control in binge eating disorder relative to other manifestations of obesity. Obesity. 2013; 21(2): 367-377.
- 34. Wu M, Hartmann M, Skunde M, Herzog W, Friederich HC. Inhibitory control in bulimic-type eating disorders: a systematic review and meta-analysis. PLoS One. 2013; 8(12): e83412.
- 35. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010; 35(1): 217-238.
- 36. Wu M, Brockmeyer T, Hartmann M, Skunde M, Herzog W, Friederich HC. Set-shifting ability across the spectrum of eating disorders and in overweight and obesity: a systematic review and meta-analysis. Psychol Med. 2014; 44(16): 3365-3385.
- 37. Daw ND, Gershman SJ, Seymour B, Dayan P, Dolan RJ. Model-based influences on humans' choices and striatal prediction errors. Neuron. 2011: 69(6): 1204-1215.
- 38. Voon V, Derbyshire K, Ruck C, et al. Disorders of compulsivity: a common bias towards learning habits. Mol Psychiatry. 2015; 20(3):
- 39. Frank MJ, Doll BB, Oas-Terpstra J, Moreno F. Prefrontal and striatal dopaminergic genes predict individual differences in exploration and exploitation. Nat Neurosci. 2009; 12(8): 1062-1068.
- 40. Morris LS, Baek K, Kundu P, Harrison NA, Frank MJ, Voon V. Biases in the explore-exploit tradeoff in addictions: the role of avoidance of uncertainty. Neuropsychopharmacology. In press. DOI: 10.1038/npp.2015.208.
- 41. Svaldi J, Tuschen-Caffier B, Peyk P, Blechert J. Information processing of food pictures in binge eating disorder. Appetite. 2010; **55**(3): 685-694.
- 42. Schag K, Teufel M, Junne F, et al. Impulsivity in binge eating disorder: food cues elicit increased reward responses and disinhibition. PLoS One. 2013; 8(10): e76542.
- 43. Svaldi J, Schmitz F, Trentowska M, Tuschen-Caffier B, Berking M, Naumann E. Cognitive interference and a food-related memory bias in binge eating disorder. Appetite. 2014; 72: 28-36.
- 44. Svaldi J, Bender C, Tuschen-Caffier B. Explicit memory bias for positively valenced body-related cues in women with binge eating disorder. J Behav Ther Exp Psychiatry. 2010; 41(3): 251-257.
- 45. Ziauddeen H, Chamberlain SR, Nathan PJ, et al. Effects of the muopioid receptor antagonist GSK1521498 on hedonic and consummatory eating behaviour: a proof of mechanism study in binge-eating obese subjects. Mol Psychiatry. 2013; 18(12): 1287-1293.
- 46. Cambridge VC, Ziauddeen H, Nathan PJ, et al. Neural and behavioral effects of a novel mu opioid receptor antagonist in bingeeating obese people. Biol Psychiatry. 2013; 73(9): 887-894.
- 47. Chamberlain SR, Mogg K, Bradley BP, et al. Effects of mu opioid receptor antagonism on cognition in obese binge-eating individuals. Psychopharmacology~(Berl).~2012;~224 (4):~501-509.
- 48. Pattij T, Schetters D, Janssen MC, Wiskerke J, Schoffelmeer AN. Acute effects of morphine on distinct forms of impulsive behavior in rats. Psychopharmacology (Berl). 2009; 205(3): 489-502.
- 49. Wiskerke J, Schetters D, van Es IE, et al. mu-Opioid receptors in the nucleus accumbens shell region mediate the effects of amphetamine on inhibitory control but not impulsive choice. J Neurosci. 2011; 31(1): 262-272.