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Goal Directed and Self-Control Systems in Bulimia Nervosa: An fMRI Study

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ABSTRACT

Background: Binge eating is apparently the opposite of the strict control over food intake typically set by "maladaptive dieters". Using functional magnetic resonance imaging (fMRI), we investigated the role of goal-directed behaviors, and the related use of self-control, in binge-related food choices in patients with Bulimia Nervosa (BN).

Method: While undergoing fMRI, women aged 18–35 with BN ($N = 35$) and healthy control women ($N = 26$) rated foods for healthiness and tastiness and then made food choices on a 5 points Likert scale between two conflicting options: one food with lower healthiness and higher tastiness (defined as uncontrolled choice) than the other food (defined as controlled choice).

Results: BN and healthy participants made more uncontrolled than controlled choices (63% vs 24% and 65% vs 18% respectively). While healthy participants used only food tastiness (chose tastier foods more often) to make food choices ($p < .001$), BN patients used both food healthiness (chose unhealthy food more often, $p < .001$) and food tastiness ($p < .001$) to make binge-related food choices. Activity in the ventromedial prefrontal cortex (vmPFC), which correlated with food choices ($p_{FWE} = 0.02$), reflected this difference in the integration of food healthiness and food tastiness into a decision value. Functional connectivity analysis showed that the activity in the dorsolateral prefrontal cortex was coupled with vmPFC activity in uncontrolled food choices ($p_{FWE} = 0.03$).

Interpretation: Contrary to what might be expected, not only food tastiness but also unhealthiness (a more abstract cognitive-based attribute than food tastiness) plays a role in uncontrolled choices in BN. These choices are likely goal-directed behaviors and recruit self-control.

1. Introduction

Binge eating episodes impact 4% of women [1]. They are periods of rash overeating experienced as a loss of control, and constitute a break in the strict control over food intake observed in Bulimia Nervosa (BN) [2–4] among other disorders. An important question is whether binges are compatible with patients' long-term goal of strict control over food intake; and more specifically whether the implementation of a binge may represent goal-directed behavior, thus recruiting control processes. Recent behavioral results show that BN patients recruit control processes during binges [5, 6], and clinical observations indicate that BN patients are able to stop transiently a binge and resume it later and to postpone a binge if conditions are not met (environment or current available foods) [2, 5–7]. Additionally, during binges BN patients mainly ingest foods that are restricted outside binging periods [2]. This suggests that, both during binges and the period of strict control over food intake, patients choose foods according to their subjective goal-directed value.

The attribute integration theory postulates that during goal-directed behaviors [6, 8, 9], which involve value-based decisions, the values of the choice attributes, like food healthiness and tastiness, are integrated into a decision according to the ongoing goal [8–11]. This integration is performed in the ventromedial prefrontal cortex (vmPFC) and may be modulated by the left dorsolateral prefrontal cortex (dlPFC) [12–14] a

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Research in context

Evidence before the study

Binge eating episodes constitute a break in the strict control over food intake observed in several disorders like Bulimia Nervosa (BN). However, clinical observations and recent studies have suggested that binging patients recruit self-control during binges. Because self-control is recruited according to a goal, an important question is whether binges and more specifically food choices during binges may represent a goal directed behavior. We therefore reviewed the literature for evidence about the recruitment of goal-directed and self-control processes during binge food choices. We searched PubMed and google scholar with "ventromedial prefrontal cortex", "dorsolateral prefrontal cortex", "goal-directed", "self-control", "cognitive control", "control process", "binge eating", "bulimia nervosa", "eating disorders", "food choice", "food stimuli" and "fMRI" up to July 31, 2017. In the meantime, we reviewed the articles that cited the paper by Hare & al. that described for the first time the task we used. This search was updated shortly before publication. We also looked for books with "handbook", "eating disorder", "binge eating" or "bulimia" in their title. The search showed that:

- Two studies assessing eating disorder patients using the food choice task we used focused exclusively on anorexia nervosa patients who made almost exclusively food choices typical of a diet and not of binge eating.
- Out of the numerous studies assessing self-control in bulimia nervosa, very few used food stimuli and only one used neuroimaging and food stimuli concomitantly but almost all only investigated attention processes and none linked results to food choices.
- Other studies using food cues in BN investigated the neural correlates of passive viewing of food cues but none of them assessed food choices.
- Studies investigating food intake during binges focused on the nutritional content of the binge but not on the neural correlates of binge food intake nor on potential decision making processes underlying binge food selection.
- the use of self-control and goal-oriented processes during the binge have been reported in clinical observations but they were never quantified and their neural correlates were not investigated.

Therefore, there is an obvious lack of data on the behavioral and brain correlates of how binging patients such as BN make binge food choices.

Added value of the study

For the first time, we used a task which allowed the investigation of how food healthiness and food tastiness are used by BN patients to make uncontrolled (binge related in patients) food choices. While healthy individuals used only food tastiness (i.e. chose tastier foods more often) to make uncontrolled food choices, BN patients used both food healthiness (i.e. chose unhealthy foods more often) and food tastiness to make uncontrolled food choices. Activity in the ventromedial prefrontal cortex (vmPFC), which correlated with food choices, reflected this difference in the integration of food healthiness and food tastiness into a decision value. The activity in the dorsolateral prefrontal cortex, which reflected self-control, was coupled with the activity in the vmPFC. Food choice in a binge context is a goal-directed behavior engaging self-control that uses abstract concepts such as food healthiness.

Implications of all evidence

Our results support reconsidering the view of a cognitive control impairment in behaviors viewed as impulsive, like binge eating. Classical and operant conditioning theories might not be the only main mechanisms at the root of binge eating: therapeutic and neuromodulation interventions might be more efficient if goal-directed processes occurring during binges are tackled. Binges, and potentially breaks of a diet in dieters, would be more deliberative than usually viewed: how BN patients appraise the healthiness of foods should be addressed.

brain region involved in control processes [8], and goal maintenance [12–16].

BN patients showed vmPFC and dlPFC activities during passive viewing of food cues [17–19] suggesting a potential recruitment of goal-oriented valuation and control processes during binges. BN patients may also recruit dlPFC during binges as these patients recruit control processes when primed with binge foods and during binges [2, 5–7, 20]. However neither food choices nor the ratings of the food attributes were collected in studies assessing control processes [5, 6, 17–20]. Therefore, these studies could not determine the current state of BN participants at the time of the assessment: strict control over food intake or binge process. Other studies used tasks requiring passive processing of food rewards without engaging food choices from BN participants [21]; and results showed brain activities in subcortical brain regions [21] that are not directly involved in the attribute integration theory [6, 8, 9]. The assessment of goal-directed processes and their relationships with control processes in binges should therefore be carried out with a food choice task in which BN participants must choose between foods typical of a strict control over food intake or foods typical of a binge.

In the present neuroimaging study, we aimed at investigating whether BN patients have goal-directed behaviors and recruit the aforementioned underlying brain substrate when making binge food choices. The task included a series of choices between two food items. Trials in which one food is deemed tastier whereas the second is deemed healthier are expected to set a cognitive conflict [22]. Among trials with a cognitive conflict, choosing the healthier food item was defined as a controlled choice, and choosing the tastier food item as an uncontrolled choice. The dominant pattern of choices (e.g. making more uncontrolled than controlled choices) can be viewed as a proxy of participant's current goal [22]. This type of task has already been performed in eating disorders but only in patients with anorexia nervosa who made almost exclusively food choices typical of a strict control over food intake and not of binge eating [23].

Given the potential goal-directed behavior in BN, the requirement to appropriately allocate control processes to achieve the current goal [8], and the modulation of the integration of food healthiness and food tastiness values into a decision value by control processes we hypothesized that: [1] vmPFC activity associated with goal-oriented valuation processes would mirror a difference between BN and healthy participants in the association between the decision value and the food attribute values; [2] left dlPFC activity would mirror the patterns of reaction times in uncontrolled and controlled choices; and [3] vmPFC and left dlPFC activities would be coupled.

2. Methods and Materials

2.1. Study Design and Population

In a cross-sectional fMRI study, we recruited two groups of women, aged 18–35 years, right handed, with a body mass index<25 kg/m [2]. Women in the patient group had a current diagnosis of bulimia nervosa

with or without purging behaviors (BN, $N = 37$ eligible and contacted to participate, $N = 35$ assessed, $N = 2$ declined to participate, DSM IV criteria) washed out from any anxiolytic or neuroleptic treatment for at least 12 h to reduce sedation or anxiolytic effects consecutive to the last intake, and women in the healthy control group were free of any eating disorder and diet (healthy controls, $N = 26$ eligible and contacted to participate, $N = 26$ assessed, $N = 0$ declined to participate). At the time of assessment, all patients were stable for antidepressant, anxiolytic and neuroleptic medication for more than one week [24, 25] to avoid interaction with performances. Exclusion criteria for all groups included: any contraindication for MRI, addiction, histrionic personality disorder, psychotic disorder, mental retardation, antisocial personality disorder, attention deficit and hyperactivity disorder, borderline personality disorder. Criteria were assessed by a trained psychiatrist with the MINI (Mini-International Neuropsychiatric Interview) and a structured clinical interview [26].

Patients were recruited from an inpatient unit specialized in the treatment of eating disorders (Lyon, France) and controls through e-mail advertisements. Individuals were included at the same times for the two groups. Note that all patients got three calibrated meals across the day at fixed hours. All participants provided written informed consent before enrolment. A 70€ compensation was provided for the participation. The study was approved by an independent ethical committee, Comité de Protection des Personnes Sud Est IV.

2.2. Assessment

Within each group, participants were randomly allocated to morning or afternoon assessments to account for circadian variations in binge occurrence [27].

We adapted the task from Hare et al. [22] because BN patients may avoid to make binge food choices, and for statistical reasons (see supplementary method 1 for more details). Indeed, just as patients with binging anorexia nervosa did in the same task, BN patients may avoid making binge food choices if the task is too constraining or if they know that they will have to eat foods at the end of the task [2, 23]. The experiment had three runs: two valuation runs and a decision run involving 50 food items (Fig. 1A). These foods were selected to elicit

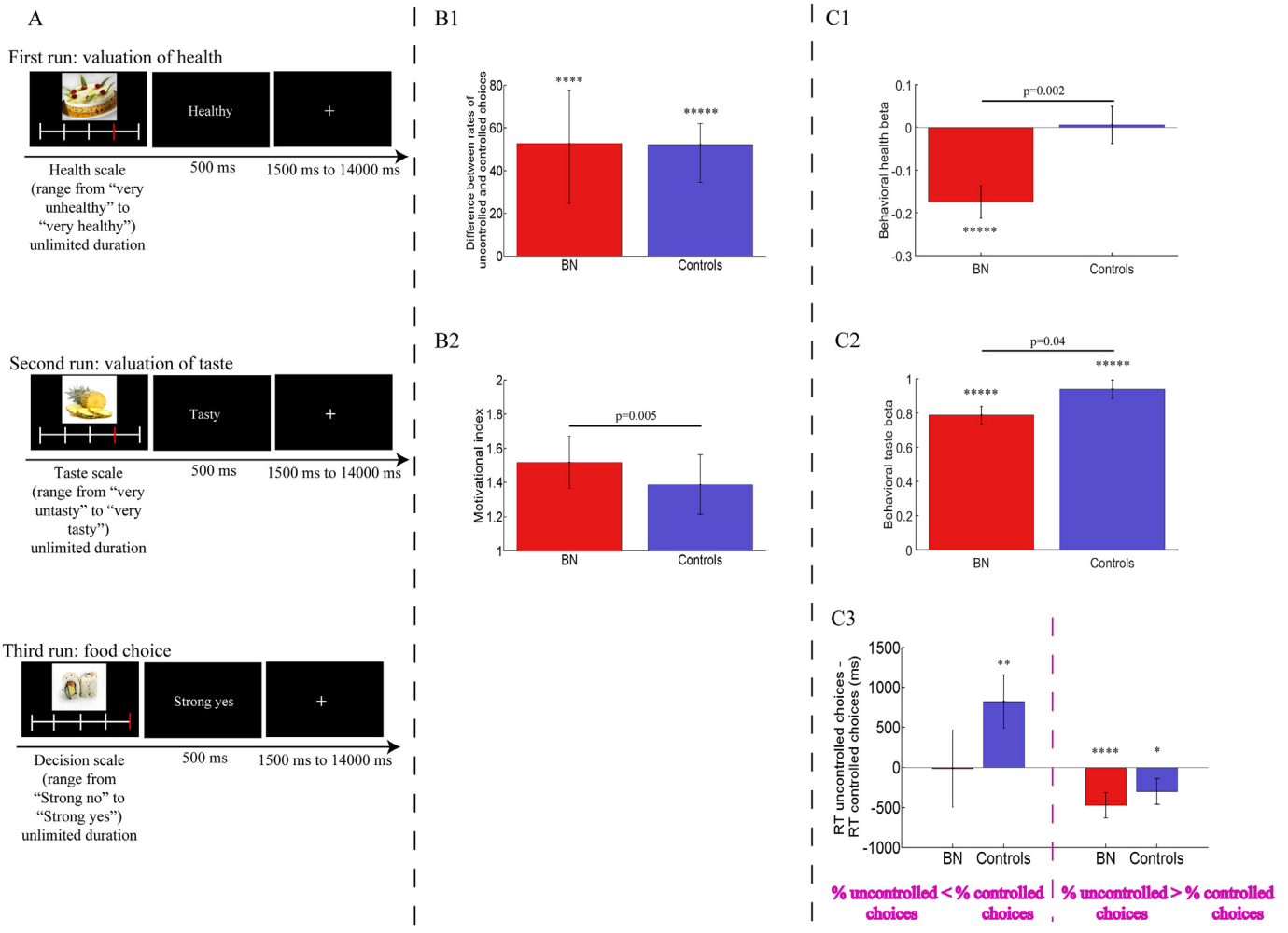

Fig. 1. (A) Trial design in each run of the experiment. Participants had to answer on a 5 points Likert scale. The red cursor shows the choice of the participant. In the third run, decisions were made between a reference food selected among foods rated as neutral after the first two runs and an alternative food. The reference food was displayed at the beginning of the run and only the alternative food was displayed in each trial of the run. These binary forced choices were built to elicit cognitive conflict when the reference food was tastier than the alternative food and the alternative food was healthier than the reference food and vice versa; (B) median (interquartile) of the difference between percentages of uncontrolled and controlled choices (B1) and mean motivational index when making choices in the third run (B2) in BN (Bulimia Nervosa) patients (red) and healthy participants (blue); (C) Beta estimates of the association between health ratings and choice ratings (C1) and taste ratings and choice ratings (C2) and difference in reaction times between controlled and uncontrolled trials (C3) within each group split based on the highest proportion of uncontrolled or controlled choices.

BN = Bulimia Nervosa

different levels of binge craving (supplementary method 1). Participants rated, on a five points Likert scale, the 50 foods, displayed randomly, for their healthiness during the first run and tastiness during the second run of the task (Fig. 1A) without randomization of the run order contrary to Hare & al. Then, for each participant, the first food rated by the participant as neutral for both characteristics was selected as the reference food. In the third run, for each of the 49 remaining foods, participants had to choose between eating the proposed food or the reference food. There were thus 49 two-item forced choices tailored to each participant, some of them eliciting a cognitive conflict as explained in the introduction and checked in supplementary result 1. Contrary to Hare & al, we neither asked participants to eat one of the foods they chose at the end of the experiment nor provided food at the end of the experiment. Instead, participants were instructed to imagine that they could eat the food they chose ad libitum at the end of the scan and we assessed the degree to which they imagined the situation, a proxy of the participant's involvement. Note that patients had access to vending machines with food in the hospital and could get a substantial panel of food they had selected during the task.*: $p < .1$; **: $p < .05$; ***: $p < .01$; ****: $p < .005$; *****: $p < .001$. These p-values are for comparisons of bars against zero (paired t-test).

3. Data Acquisition

A 1.5 T Sonata MRI scanner (Siemens, Erlangen, Germany) was used to acquire three runs of fMRI images, that assessed blood oxygen level dependent (BOLD) activity. With a standard T2* echo planar imaging sequence. Functional scans involved a single shot gradient echo T2* echo planar imaging sequence (matrix size = 64*64, 37 slices, in plane voxel size = 3.44*3.44 mm, slice thickness = 3.4 mm, TR = 3.5 s, TE = 50 ms, bandwidth = 2790 Hz/voxel, field of view = 220*220 mm, slice acquisition order = interleaved) and an 8 channel head coil. The flip angle α of slices was 60° (i.e. 90° minus a tilt of 30° along anterior-posterior axis) and a z-shimming over the frontal lobe was performed before functional runs as recommended to minimize artifacts [28, 29]. A standard T1 high resolution sequence provided anatomical images at the end of the functional scans (176 slices, in plane voxel size = 1*1 mm, field of view = 256*256 mm, TE = 3.93 ms, TR = 1.97 s, flip angle α = 15°, bandwidth = 130 Hz/voxel, slice thickness = 1 mm).

Contrary to previous studies which used stronger magnetic fields but without any optimization [22, 23], we optimized the T2* parameters and the timings of the sequence of stimuli to get the minimal artifacts and the highest signal detectability (see supplementary methods 1 and 2).

Physiological, psychopathological and clinical measurements complemented the assessment (supplementary method 3, Table 1).

4. Statistical Considerations

4.1. Analyzed Population

We removed the data for participants who had head movements larger than 2 mm translation or 2° rotation that would bias fMRI statistical analyses (two BN and one control) and participants who did not comply with the instructions of run three (two BN and one control).

Patients and healthy participants had similar socio-demographic profiles and time elapsed since the last meal. Patients had a lower level of education and BMI and higher scores for all psychopathological scales (Table 1), but neither the educational level nor BMI had any impact on the brain activity results (supplementary results 2 and 3).

4.2. Statistical Analyses

Analyses were performed with R 3.1.3 (lmerTest package) and MATLAB R2012b (Mathworks inc.) with SPM 8 (http://www.fil.ion.ucl.ac.uk/spm/software/). *P*-values of brain maps were corrected for multiple comparisons using the Family Wise Error (FWE) correction.

4.3. Behavior

Choices were transformed into numeric values ranging from −2 for a “strong no” to +2 for a “strong yes” answer. For each individual, we computed the difference between the rates of uncontrolled and controlled choices. This index ranged from −100% corresponding to making exclusively controlled choices to +100% corresponding to making

Table 1
Socio-demographic, clinical, psychological and psychopathological characteristics of patients and healthy participants included in the analysis. Mean (standard deviation) are reported except when specified.

	Bulimia nervosa ($n = 31$)	Controls ($n = 23$)	p-value
Socio-demographic:			
Age (year)	24 (3.87)	23 (2.7)	0.5
Brothers (nb)	0.935 (0.801)	0.739 (0.792)	0.33
Sisters (nb)	0.935 (1.05)	0.826 (0.867)	0.89
Educational level (years)	13.3 (2.43)	15.2 (1.61)	0.0029
Body Mass Index (kg/m*m)	19.9 (2.15)	21.3 (2.36)	0.025
Duration since last meal (min)	137 (53.3)	124 (55.1)	0.45
With hormonal contraceptive (n (%))	11 (35)	14 (61)	0.14
With amenorrhea (n (%))	3 (10)	0 (0)	0.25
Number of binges over the past 28 days at admission	56 (50)	–	–
Duration of cares between admission and assessment (days, median (interquartile))	24 [12–47]	–	–
Any comorbities (n (%))	6 (19)	–	–
Undergoing antidepressant medication (n (%))	8 (26)	–	–
Duration between last menses and assessment (days)	26 (22)	14 (8.4)	0.014
Psychological			
Degree of implication at run 3 of the task (range 0 to 10)	7.4 (2.3)	7.4 (1.33)	0.96
Psychopathological:			
Dieting score (EAT 26)	18 (9.9)	1.8 (1.6)	4.2e-10
Bulimia and food preoccupation score (EAT 26)	12 (4.8)	0.13 (0.45)	5.3e-15
Bulimia (EDI 2)	9.9 (4.8)	0.21 (0.51)	6.8e-13

Co-morbities: obsessive compulsive disorder (one patient), scholar phobia (one patient), major depressive disorder (5 patients); EAT 26: Eating Attitude Test 26 items; EDI 2: Eating Disorder Inventory 2; INSEE #: socio-professional category according to the “Institut National de la Statistique et des Etudes Economiques”: 1,2: Farmer, craftsman, shopkeeper and large retailer, chairman and managing director; 3:senior executive, manager; 4,5,6: intermediate jobs, employees and workers; 7,8: retired, no job.

exclusively uncontrolled choices and 0% to an undecided state. Because motivation is a key process in goal directed behaviors [8, 30], we also computed a motivational index defined as the absolute value of the choice rating [30]. This index ranged from 0 (no motivation) when making a neutral choice to +2 (strong motivation when making a "strong yes" or "strong no" choice).

Comparisons between groups of quantitative variables were performed with two-sampled or paired-sample *t*-tests whenever appropriate or Mann-Whitney or Wilcoxon test whenever applicable, and qualitative variables with Fisher exact tests or chi square tests whenever applicable. Correlations were quantified with Pearson or Spearman coefficient whenever appropriate.

We used two linear mixed models (LMM) to investigate [1] the associations of health and taste ratings with choice ratings (first hypothesis) and [2] the association between the type of choice (controlled/uncontrolled) and reaction time (second hypothesis). Per se, the associations of health and taste ratings with choice ratings capture value-based decision processes and the association between the type of choice and reaction time of the recruitment of control processes. The first model included choice ratings of all controlled and uncontrolled choices and the following regressors: health ratings, taste ratings and the group (BN/Healthy participants) with appropriate interactions (LMM 1, supplementary method 4). Trials with neutral choices and trials without cognitive conflict were removed because they provide no information about participants' preference for taste over health or vice versa when making a choice. The second model included reaction times on the third run and the following regressors: the type of choice (controlled/uncontrolled), the difference between rates of uncontrolled and controlled choices and the group with appropriate interactions (LMM 2, supplementary method 4). The rationale for adding the difference between rates of uncontrolled and controlled choices is that control processes are recruited in accordance with the goal which can be indirectly captured by the dominant pattern of choices [8, 9, 22]. Choices opposite to the participant's dominant pattern of choices should be more demanding with longer reaction times [31, 32].

4.4. Brain Activity

We first preprocessed the brain images. Realignment, slice timing, normalization and smoothing were applied to the fMRI volumes (supplementary method 2).

We then used standard general linear models (GLM) to analyze BOLD activity and we followed the framework of analysis implemented by Hare & al. in their paper [22]. This framework aims first at identifying the neural correlates of goal-directed processes (GLM1 described below) and at assessing how these brain regions integrate health and taste ratings into a decision value (GLM2). Then the framework aims at identifying the neural correlates of control processes when making controlled and uncontrolled choices (GLM3). Finally, the framework aims at investigating how the neural correlates of brain control processes identified with GLM 3 influence the neural correlates of goal-directed processes (GLM4). Details of analyses controlling for medication and menstrual cycle effects are provided in supplementary method 4.

GLM 1: using a whole brain parametric GLM including the decision run only, we identified, in all participants, the brain regions whose BOLD activity was associated with the choice ratings and a goal relevance index. This index was computed as the product of the absolute value of the choice ratings with the trial type (i.e. -1 for controlled choices, 0 for trials without cognitive conflict and + 1 for uncontrolled choices). The rationale of adding this index is that the choice ratings alone cannot capture the fact that the same type of choice (e.g. choosing the tastier food) can be associated with opposite decision ratings: choosing the reference food (e.g. bread) rather than the proposed food (e.g. an apple) when the bread is rated more tasty than the apple leads to a "strong no" or a "no" answer while choosing the proposed food (e.g. a candy bar) rather than the reference food (e.g. bread) when the candy bar is rated more tasty than the bread leads to a "strong yes" or a "yes" answer. To capture goal-directed processes, a brain activity correlating with choice rating is not specific enough [30]; likewise for a brain activity correlating with the goal relevance index, because this index captures also control processes per se. Therefore, a brain region encoding goal-directed processes should correlate with both choice rating and the goal relevance index. Previous work let us hypothesize that vmPFC activity will correlate both with choice ratings and the goal relevance index in all participants [22]. To identify the regions whose activity correlates both with choice ratings and the goal relevance index, we identified first, at the whole brain level, the brain regions for which the sum of the beta capturing the brain activity associated with choice rating and the beta capturing the brain activity associated with the individual goal index was significantly different from 0. We refer to these regions as the output GLM 1 regions in the result section. Then at the peak of activity within each of these brain regions, we tested separately whether each beta (choice rating and goal relevance index parametric modulators) was significantly different from 0. Only the brain regions for which the two betas were significantly different from 0 could be associated with goal-directed processes.

GLM 2: we ran a region-of-interest parametric GLM over the decision run to investigate how health and taste ratings were mapped, at the time of choice, into the brain regions identified in GLM 1 [8, 9, 22]. A regressor included controlled and uncontrolled choices only, and another regressor the remaining choices (neutral choices and choices without cognitive conflict). Health and taste ratings were set as parametric modulators. We tested whether the individual betas of the health and taste parametric modulators, averaged over the cluster of activity identified with GLM 1, differed between BN and healthy participants.

GLM 3: to investigate the role of control processes at the brain level when making choices, we ran a whole brain GLM including the decision run only and four regressors, one for each type of choice: controlled, uncontrolled, neutral and trials without any cognitive conflict. We then tested whether the difference between rates of uncontrolled and controlled choices was associated with the difference in brain activity between controlled and uncontrolled choices in all participants.

GLM 4: using a region-of-interest standard psycho-physiological interaction analysis of SPM 8, we compared the modulation of vmPFC activity identified by GLM 1 by left dlPFC activity identified by GLM 3 between uncontrolled and controlled choices in all participants. This analysis investigated the role of control processes upon the goal-directed process in vmPFC.

5. Results

5.1. Behavior

Compared to healthy participants, BN rated foods as tasty but less healthy (supplementary fig. 1). BN and healthy controls made similarly more uncontrolled than controlled choices (Figure 1B1). The motivational index was greater in BN than in healthy participants (Figure 1B2).

Choice ratings were negatively associated with health ratings in BN participants but there was no association in healthy participants and the difference between BN and healthy participants was significant (LMM 1, Figure 1C1). Choice ratings were positively associated with taste ratings in BN and healthy participants but with a stronger association in healthy participants than in BN (LMM 1, Figure 1C2).

In all participants, the difference in reaction times between controlled and uncontrolled choices correlated negatively with the difference between rates of uncontrolled and controlled choices: in those participants who made more uncontrolled choices than controlled choices, reaction time was higher for making controlled choices than uncontrolled choices (LMM 2, figure 1C3, supplementary table 1).

Binge craving increased in BN after, compared to before the scan (supplementary result 4) and the increase in binge craving correlated

with the degree to which the patients imagined that they were facing real foods when making food choices ($r_{Spearman} = 0.35, p = .04$). The absolute value of the difference between rates of uncontrolled and controlled choices correlated with the increase of binge craving during the scan ($r_{Pearson} = 0.36, p = .04$). Food tastiness ratings were positively associated with the binge craving elicited by each food while food healthiness ratings were negatively associated with binge craving elicited by each food (supplementary results 5).

5.2. Brain Activity

The analysis of BOLD activity aimed first at identifying the neural correlates of goal-directed processes and how the identified brain regions integrate health and taste ratings. In all participants, the sum of brain activity correlating with choice ratings and of brain activity correlating with the goal relevance index was the largest in calcarine (highest peak at X = 10 mm; Y = −78 mm; Z = 8 mm, cluster size = 3223 mm^3, pFWE = 0.002) and vmPFC (highest peak at X = −10 mm; Y = 51 mm; Z = 1 mm, cluster size = 2083 mm^3, pFWE = 0.02); but only vmPFC activity was associated with both choice ratings and the individual goal index when considered independently (GLM 1, Figs. 2A and supplementary fig. 2, supplementary table 2). The correlation between vmPFC activity and health rating at the time of choice was more negative in BN than in healthy participants (Fig. 2B, GLM 2). There was no difference between BN and healthy participants regarding the correlation between vmPFC and taste rating (Fig. 2B, GLM 2). These results mirrored the behavioral results reported in figures 1C1 and 1C2.

BN = Bulimia Nervosa.

*: p < .1; **: p < .05; ***: p < .01; ****: p < .005; *****: p < .001. These p-values are for comparisons of bars against zero (paired t-test).

Second, the analysis of BOLD activity aimed at identifying the neural correlates of control processes during food choices. In all participants, the difference in brain activity between controlled and uncontrolled choices correlated negatively with the difference between rates of uncontrolled and controlled choices in the left dlPFC (highest peak at X = −47 mm; Y = 10 mm; Z = 35 mm, cluster size = 1415 mm^3, pFWE = 0.05, GLM 3, Fig. 3A, supplementary table 3): participants who were making more uncontrolled choices than controlled choices had a higher activity when making controlled choices than when making uncontrolled choices and vice versa. These results mirrored the ones of LMM 2.

Third, the analysis of BOLD activity aimed at investigating the link between the neural correlates of control processes and the neural correlates of goal-directed processes. Using the peak of activity of the left

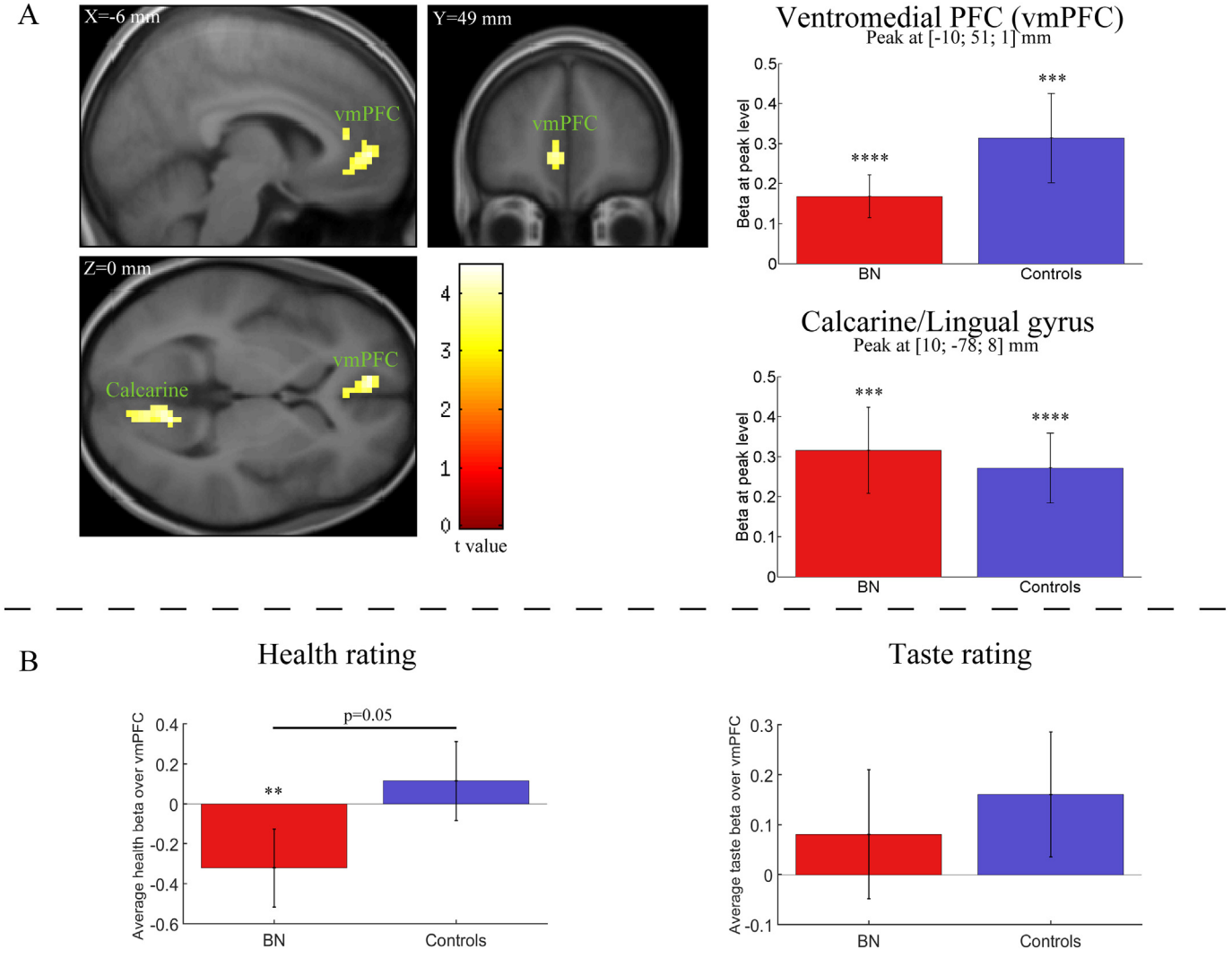

Fig. 2. (A) Sum of the brain activities associated with the magnitude of the choice ratings and associated with a goal index in BN patients and healthy participants; (B) Association of ventromedial prefrontal cortex (vmPFC) activity reported in Fig. 2A with health (left) and taste ratings (right). All coordinates are in Montreal Neurologic Institute space. Brain maps are thresholded at $p = .001$.

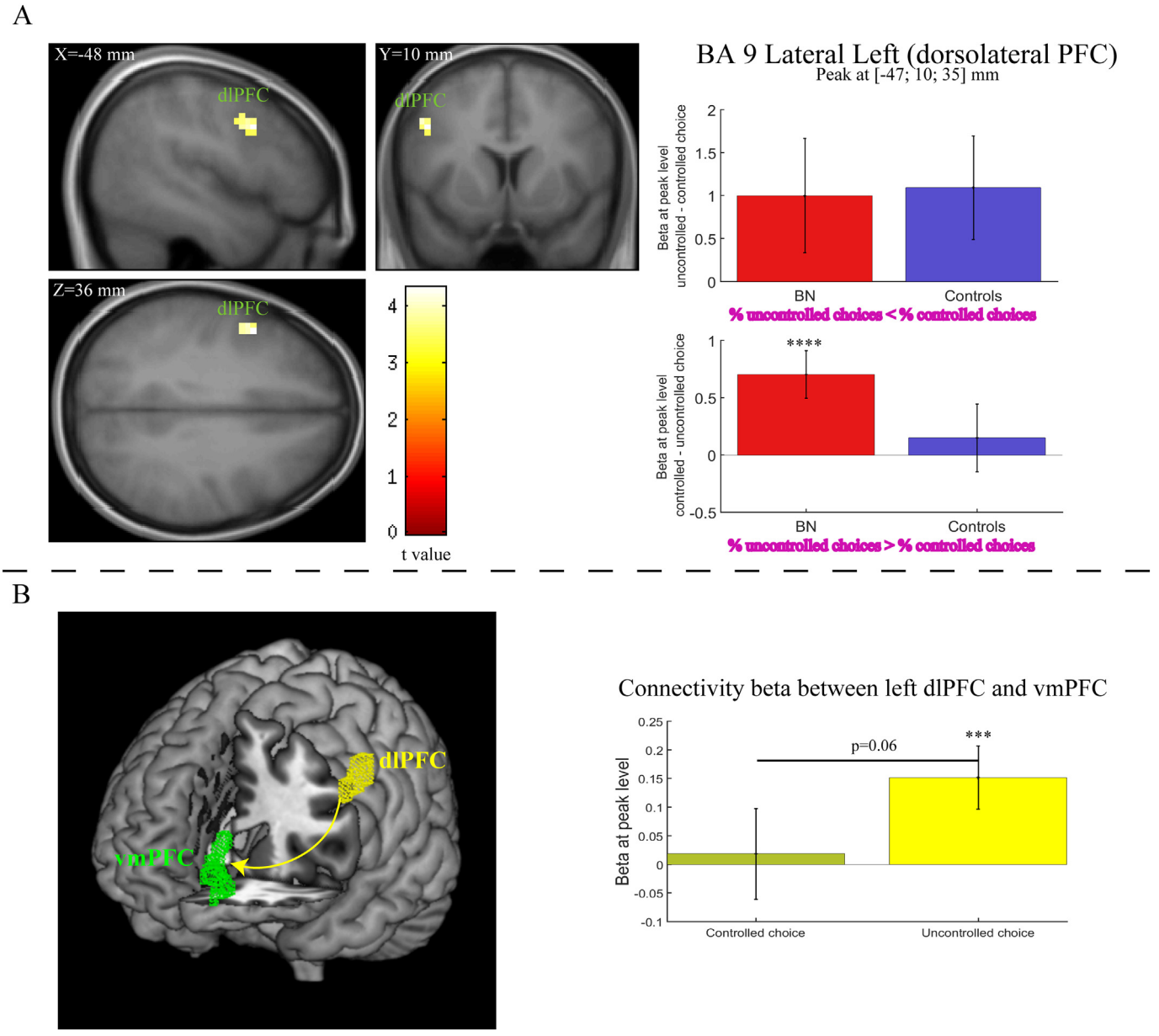

Fig. 3. (A) Difference in activity in the left dorsolateral prefrontal cortex (dlPFC) between uncontrolled and controlled choices that correlated with the difference in rates between uncontrolled and controlled choices in BN patients and healthy participants. All coordinates are in Montreal Neurologic Institute space. Brain maps are thresholded at $p = .001$. (B) Functional connectivity between left dlPFC and vmPFC in all participants. The beta reported in the bar graph are the regression betas between the seed time course of BOLD activity specific to controlled or uncontrolled trials extracted over a 5 mm radius sphere centered on the peak reported in 3A and the time course of BOLD activity specific to controlled or uncontrolled trials extracted over a 5 mm radius sphere centered on the connectivity peak (x = −10 mm, y = 55 mm, z = 1 mm).

dlPFC shown in Fig. 3A as a seed region, the functional connectivity analysis showed that in all participants, the dlPFC was more coupled to vmPFC when making uncontrolled choices than controlled choices (GLM 4, Fig. 3B, peak at x = −10 mm, y = 55 mm, z = 1 mm; Z = 3.08, $t = 3.27$, $p_{FWE} = 0.03$).

BN = Bulimia Nervosa.

*: p < .1; **: p < .05; ***: p <0; .01; ****: p <0; .005; *****: p <0; .001. These p-values are for comparisons of bars against zero (paired t-test).

6.;6. Discussion

This study shows for the first time how BN patients recruit goal directed processes when making more uncontrolled than controlled food choices. BN used food unhealthiness and tastiness to make food choices while healthy participants used only food tastiness; the vmPFC activity correlating with health and with taste ratings mirrored these findings and activity in the vmPFC, which is known to integrate food values into a food choice [8, 9, 22], correlated also with choice ratings. This suggests that the process that leads to uncontrolled and controlled choices differs between BN and healthy participants. Moreover, in BN patients, uncontrolled choices were linked with binge craving: the difference between the percentages of uncontrolled and controlled choices correlated with the increase in binge craving during the task, and food healthiness and food tastiness ratings correlated with binge craving elicited by each food. In the meantime, the higher the difference between the percentages of uncontrolled and controlled choices, the higher the difference in reaction times between controlled and uncontrolled choices. This suggests the recruitment of a control process to maintain uncontrolled choices [12–16]. Consistently, activity in the left

dlPFC mirrored this result and the dlPFC was more coupled with the vmPFC during uncontrolled than controlled choices. The connectivity between the left dlPFC and the vmPFC is critical in the development of self-control [33] and in the improvement of anxiety and major depressive disorders [34]. We also showed that the vmPFC activity in BN correlated with a goal index capturing the preference for tastier foods than healthier foods. Therefore, BN food choices filled the main characteristics of goal-directed behavior: (i) motivation [8, 30] (as highlighted by the motivational index in BN), (ii) control processes [8, 30] (reaction times and dlPFC activity), (iii) the recruitment of vmPFC in line with a goal directed value [8, 9, 22], and (iv) goal maintenance (maintenance of uncontrolled choices as suggested by the reaction times and the connectivity between the dlPFC and the vmPFC). Altogether, our results suggest that the binge is a goal-directed behavior.

Our results should however be considered carefully. First, we enrolled inpatients. Results might be different with outpatients due to confounds rather than to mechanisms since an outpatient setting is a less experimentally controlled setting than an inpatient setting. Second, the uncontrolled choices of BN patients might have been driven by a therapeutic goal instead of being driven by the disorder as these patients were implementing cognitive behavioral therapy during care. However, making more often uncontrolled than controlled food choices as a therapeutic goal and not as a binge goal is more demanding in BN[2], which is in contradiction with the smaller reaction times in making uncontrolled rather than controlled choices. Additionally, the duration of cares between admission and the MRI scan was not associated with the behavioral results suggesting that food choices of BN participants at the time of assessment were unlikely the consequence of the beginning of the inpatient therapy; (supplementary result 6). Third, since we did not provide any real foods at the end of the experiment, BN choices could not reflect real choices and so be imaginary. However, this is unlikely because binge craving increased during the scan and this increase correlated with choices. Our setting also likely limited strongly the number of patients who declined to participate in the study to prevent themselves from having to eat the food at the end of the experiment, improving therefore the generalizability of our results. These data were not reported in previous studies [22, 23]. Fourth, the impact of medications over brain activities was likely limited because patients under medication and those free of medication had similar brain activities (supplementary result 7). Fifth, the impact of the level of hormones across menstrual cycle over brain activity [35] was also likely limited because the differences in brain activity between BN and healthy participants still remained after adjusting for the menstrual cycle (supplementary result 2).

Our results have possible theoretical and clinical implications. First, they support reconsidering the view of a cognitive control impairment in behaviors viewed as impulsive, like binge eating [36], relapses during therapy for drug or alcohol addictions [37, 38]. The differences observed between patients viewed as impulsive, like BN, and healthy individuals in tasks assessing cognitive control abilities may be due to a difference in the goals pursued at the time of assessment: BN may have two goals (one for managing binge craving present before the task and the other one to achieve the task), while healthy participants only have one goal (to achieve the task). Second, interventions might be more efficient if clinicians would tackle goal-oriented processes occurring specifically during binges as we have suggested [39]. Accordingly, the mixed results obtained in BN and in addictions with neurostimulation techniques targeting the left dlPFC [40, 41] only, might be explained by the fact that this region is also involved in the execution of maladaptive behavior and is a subpart of the dysfunctional network built at least of the vmPFC, the left dlPFC and the connectivity between these two brain regions, this later having been highlighted in other anxio-depressive disorders [34]. Third, classical and operant conditioning might not be the only main mechanism at the root of binge eating [2, 4]: goal directed processes should be considered as well. Among the goals of the binge, one may find: reducing the attractiveness of binge foods at the end of the binge in order to facilitate binge food restrictions thereafter [6] or avoiding tension or negative effects [42]. Fourth, that BN patients who make preferentially uncontrolled choices are using health ratings to make their choices while it is not the case in non-binging participants who also make preferentially uncontrolled choices [22] is intriguing as it suggests that binges, and potentially breaks of a diet in dieters, would be more deliberative than usually viewed: how BN patients appraise the healthiness of foods should be addressed. Fifth, binge eating in obese individuals may recruit the same mechanisms as in BN: similar brain activities during passive viewing of food cues have been reported in individuals with BN [17–20] and in binge eating disorder [43].

In conclusion, our neuroimaging study suggests the implementation of a neural substrate associated with goal-directed behavior in binge food choices in bulimia nervosa.

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Contributions: RN, GC, DN and AN designed the study; RN, AN and EC collected data; RN performed analyses; RN wrote the main draft and RN, GC, DN, AN, EC and AG critically reviewed the manuscript.

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Appendix A. Supplementary data

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