Author's response to reviews

**Title:** Poor ability to resist tempting calorie rich food is linked to altered balance between neural systems involved in urge and self-control

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**Author's response to reviews:** see over
Response to reviewers' comments

We thank the reviewers for their constructive comments, which we hope we have addressed satisfactorily in the revised manuscript (see point-by-point responses below). Briefly, we addressed the concern on gender differences by providing additional results, as well as a paragraph in the Discussion section. Several potential confounding factors to the results are now acknowledged in the limitations section. Procedural details on scanning time, hunger rating, etc. are now provided. The detailed responses to the reviewers’ concerns are the following:

Major compulsory revisions:

Methods:

Participants:

1. Paragraph 4: Did the authors investigate whether or not the participants were following any specific diets, were taking medication, were smokers and/or were physically active? All of these factors can impact on dietary habits and food choice.

As a part of our screening procedure for subjects to rule out certain neuropsychiatric disorders, medications, or health issues that could impact the neuroimaging results, we do collect this information using (1) the Structured Clinical Interview for DSM-IV (the SCID) to exclude individuals who meet the criteria for current psychoses, anxiety, or bipolar disorders, as well as the criteria for substance abuse; (2) a 41-item questionnaire that asks for the presence of diabetes, hypertension, lungs,
heart, kidney, or liver disease. The same questionnaire also asks for a history of head trauma, or other neurological disease, and also records the use of current medications, smoking (nicotine), alcohol, and caffeine, and whether they are currently receiving clinical treatment for obesity or following a certain diet. Subjects who meet a psychiatric diagnosis, or report a history of head injury or neurological disease, or currently using medications that impact the central nervous system, including nicotine, or currently in clinical treatment for obesity and following a certain diet are excluded. Therefore none of the participants were taking medications that cross the blood-brain-barrier and impact the nervous system, and none of them were being clinically treated for obesity or following a specific diet. This information is now added and provided in the Methods section of the manuscript.

As for physical activity, we asked each participant to refrain from any intense physical activity prior to scanning for 24 hours. This information is now added to the Methods section. However, we did not use any standardized instrument to collect detailed information on the level of the physical activity of each participant in her or his daily life. We now acknowledge this shortcoming as a limitation in the Discussion section.

Procedures:

2. Paragraph 5: There is a potentially major flaw in the procedure, which is related to the time of day that the participants completed their fMRI assessments and the dietary control prior to their scans. How many of the volunteers completed their scans in the morning and how many in the afternoon? Were there enough participants in the morning and evening groups to examine potential differences in neural responses due to time of
day? Furthermore, the type and possibly volume of food consumed prior to the fMRI scans would have most likely been different between the morning and evening participants, i.e. breakfast vs lunch. Why was diet not controlled more strictly prior to the fMRI scans? Why did the authors choose not to provide standardised meals to the participants that could have been consumed prior to the scans? I don’t think the authors can state with any certainty that meals would have been equivalent across participants.

Was the time between the pre-fMRI scan meal and the start of the fMRI scan standardized? Were volunteers asked not to exercise prior to their scans? Food consumed pre-scan, timing of the pre-scan meal and physical activity may have impacted substantially on the results of the study. Details regarding these controls are important.

We agree with the reviewer on all these points, and here we try to clarify some of them, but also acknowledge certain limitations and potential remedies in future studies: Twenty six subjects completed their scan in the morning between the hour of 10am and 11am, and only 4 subjects were scanned in the afternoon. We now add this information to the Methods section. As such, it is not feasible to run an analysis comparing the morning and afternoon groups. However, the idea of examining potential differences in neural responses due to time of day, that could be related to the volume of food consumed prior to scanning (i.e., breakfast versus lunch), is very intriguing, and it should be evaluated in future studies. Therefore, we added this point as a limitation of the current study, and we suggest that it should be addressed in the future.

We also agree that a more controlled diet (i.e., providing standardized meal) prior to fMRI scanning is important, but the reason we did not do it is simply economic in
nature, since a standardized meal would incur additional costs, and it would require the availability of additional resources. However, at the same time one could argue that there is an advantage to allowing participants consume their normal meal, as opposed to imposing on them a standardized meal that would be considered perfect in terms of ingredients and basic nutrients, but perhaps problematic in terms of “likes” and “dislikes” of that particular meal by a given subject that are also influential on brain mechanisms of choice. But nonetheless, the idea is intriguing, and examining potential differences in neural responses due to eating standardized versus normal meals prior to scanning should be conducted in future studies. Therefore, in the revised manuscript we acknowledge this point as a limitation of the current study, but also suggest that these comparisons should be made in the future.

The concern about the timing of the pre-scan meal is also valid. We did not ask participants to have their meal consumed at a specific time prior to scanning. However, we did rate their hunger level (from 1 to 10) 15 minutes before the scan, and this could be used as a proxy for the last time they consumed a meal (i.e., higher hunger levels reflect longer time for pre-scan meals). Again, at the level of brain responses and potential influence on food choice, one could argue that “hunger” level is a better control measure than the precise time of pre-scan meals. From this viewpoint, hunger levels were controlled for, and participants rated their hunger $\leq 4$, with a mean score of 2.6. Nonetheless, the fact that the precise time for pre-scan meals was not uniform across all subjects represents a limitation in the current study. We acknowledge this limitation in the revised manuscript, and we suggest that future studies should examine differences in
brain responses to food choices when variables such as the timing of pre-scan meals versus variables such as hunger level are controlled.

Regarding the concern about physical activity, we addressed this issue earlier in our response.

Overall, we do agree with the reviewer that we cannot state with certainty that meals were equivalent across participants, and we have deleted statements reflecting this assertion. We also agree that all the variables discussed earlier (i.e., type of food consumed prior to scanning, time of the pre-scan meal, and physical activity) are key variables that could impact brain responses related to food choices. However an explicit understanding of the specific effects of each of these variables on food decision-making would require a substantial amount of future research that it is not reasonable to include in one study.

Discussion:

3. Paragraph 27: The limitations section of the discussion needs attention. The authors state that the study participants were not attempting to diet. What evidence is there for this? Did the authors assess the participants habitual dietary habits prior to participation?

We have clarified the limitations section of the discussion to include only the most pertinent limitations. Further, we have clarified the potential influence that dieting may have had on our findings despite not assessing weight control status explicitly.
4. Paragraph 27: Can the authors please explain how allowing the volunteers to consume a typical meal prior to their fMRI assessment minimized cognitive restraint? Cognitive restraint is regarded as a habitual behaviour, and so it is not clear how consuming a meal a short time prior to the fMRI assessment would have minimized the impact of cognitive restraint on food choice. Also, how can the authors be sure that the participants consumed a typical meal, when the authors do not know what a typical meal was for each participant?

We agree that cognitive restraint is a habitual behavior and that we misstated the influence of consuming a typical meal prior to their fMRI assessment on cognitive restraint. Additionally, we now have clarified that compliance with pre-test day eating instructions was not assessed. Rather, we assessed perceived hunger status to confirm that participants were fed (not hungry).

5. Paragraph 27: As previously mentioned, there is no reference to dietary control prior to the fMRI scans, i.e. what the participants ate and when. Also, there is no mention of physical activity control prior to the fMRI scans. In addition, the time that the participants completed their fMRI scans was different. All of these points should be raised in the limitations.

We agree. These concerns are now a collection of individual concerns that were raised earlier, and we hope that we have addressed each one satisfactorily.
6. Paragraph 27: There was no measurement of appetite hormones in the present study. This should be stated in the limitations.

We agree. This is now included in the discussion of the limitations of the study.

Minor essential revisions (list 7-13):

All of the minor points indicated by the reviewers listed under comments 7 to 13 have been addressed and corrected one by one. The relevant changes in the text are now included in the revised manuscript.

14. Paragraph 18: I would suggest stating the fMRI task results in a new section, under a different heading, i.e. fMRI Tasks or fMRI Go/Nogo Tasks.

We followed the reviewer’s suggestion, and it is now under the heading:

“Behavioral Results in fMRI Tasks”

fMRI Results:

15. Paragraph 19: The high-calorie food neural response data are stated. What did the low-calorie food neural response data show?

We realize the confusion raised by reporting on the results of “high” calorie food only (and not mentioning “low” calorie food). However this is unfortunately related to
the fMRI methodology itself, which relies on a subtraction approach, and stating a
difference in neural responses between one condition and another condition. In this
particular case, we reported that the striatum is more active in the “high” calorie food go
trials than in the “low” calorie food go trials. This means that the striatum is more
responsive to “high” calorie food. The reverse comparison (low – high calorie foods)
revealed no brain area activation for low calorie foods compared to high calorie foods.

*Minor essential revisions list 16-25:*

All of the minor points indicated by the reviewer listed under comments 16 to 25
have been addressed and corrected one by one. The relevant changes in the text are now
included in the revised manuscript.

26. *Table 3: Why are p values not included in this table? Consider separating this table
into two tables if possible; perhaps present the Go/Nogo task results separately. Add the
sub-title “Hemisphere” in the column that states on which side of the brain activation
was observed. Why are the low-calorie food fMRI results not included in this table? Why
did the authors not distinguish between DLPFC and insula activation, and insula and
OFC activation?*

The report of fMRI results was according to the standards of the neuroimaging
literature. The fMRI results only listed the clusters above the threshold, which was set as
$Z > 2.3$ corrected for whole-brain multiple comparisons (GRFT correction). And for each
cluster, we listed the maximum Z value, which could be transformed into p values. The table has been separated into two tables as suggested. The “Hemisphere” information has been moved to a separate column. As we mentioned above, fMRI data analyses employ subtraction approaches (i.e., the low calorie data are included, but their response condition is contrasted to the high calorie condition). As such, activations for a single condition are not reported because they are difficult to interpret. Some of the activations in the table showed a large cluster extending from the insula to the DLPFC and OFC, since both regions (DLPFC and OFC) are anatomically adjacent to the insula. With the threshold we used (which is standard in the field), we cannot distinguish the anatomical borderline between these regions because the statistical maps would clump them together as one cluster. However, these statistical maps are ultimately pasted on a clear structural scan with defined anatomical regions. While the statistics do not allow us to separate these anatomical regions (and they are included as one cluster), our naming of the different brain regions is simply to give the reader a sense of where these activations were located anatomically (without having to present additional figures that show the anatomical locations of these activations).

*Figure captions and discretionary revisions (list of comments 27-34):*

All of the comments made by the reviewer and listed from 17 to 34 have been addressed and corrected according to the reviewer’s suggestion. The relevant changes in the text are now included in the revised manuscript.
Reviewer #2

1) RESULTS

Table 1 (last paragraph)

“However, there was a significant gender difference in consumption of low calorie food per 1000 kcal ($t(28) = 2.76, p < .01$), with females reporting more consumption of low calorie food per 1000 kcal (3.0 ± 1.6) than males (1.6 ± 1.1).” If this is the case, this either means that the females practice the “cognitive restraint” more than males or simply female’s energy needs are significantly lower than males. In any case, this possesses a problem for the interpretation of your data if we combine these two intrinsically two groups together in the analysis. They should control for gender. Controlling for age, and explaining why they controlled for age, is not any more important than controlling for gender and explaining it. If anything, it could be more important factor regarding the brain activation, and energy metabolism and eating habits. In fact it does not even necessary for any protocol to explain why they controlled for gender regarding energy homeostasis related neural activation.

We agree with the reviewer’s concern. In the revised manuscript, we report on sex related differences in neural responses (using ROI analysis) as suggested by the reviewer. As expected, we found a trend of a significant increase in activation within the ACC region in females relative to males. This is consistent with our behavioral results showing females ate more low-calorie foods than males. A paragraph discussing the potential implications of these results is now added to the Discussion section.
MINOR REVISIONS

1) If the authors are planning to make a whole story regarding the gender differences from their data base and make it a separate manuscript, that is understandable, however then they must mention not controlling for or analyzing for gender albeit reporting a behavioral difference (and known established sexually dimorphic aspects of the brain) as a limitation and also insert their planned future directions.

As indicated earlier, we added the main results related to sex related differences in the ROI analysis. We also clarified that we controlled for gender and age in the fMRI analysis.

2) Abstract:
“(right striatum) was more activated in response to high calorie foods during the “go” trials than low calorie food “go” trials, and its activity…” In here they should rephrase the term “high calorie foods” and “low calorie foods” to “high calorie food cues (or pictures or visual cues)” and “low calorie food cues (or pictures or visual cues), or something they can come up with to make it clear that subjects did not actually responded to the “foods” but cues of food. Thus, their neural activation in response to cues versus actual food would be different. This should be modified throughout the manuscript if there are more.

We agree with the reviewer. We carefully checked the whole manuscript and changed all instances related to this issue.
3) Methods

It would be better if they spell out that this was a fMRI BOLD study at some point in the manuscript.

It was added to the methods section which reads “Blood oxygen level dependent (BOLD) functional scanning used a z-shim gradient echo EPI (Echo Planer Imaging) sequence with PACE (Prospective Acquisition Correction)”.

4) Results

Page 15- 1st paragraph

Further, of particular interest to us, the activation in the ACC region (Figure 3A, MNI = 4, 44, 4) was negatively correlated with BMI (Figure 3B; r = -.71, p < .01) and high calorie food consumption as measured by the 24-hour recall/NDSR (Figure 3C; r = -.69, p < .01). In this paragraph, the authors should spell out in response to what exactly that “the activation in the ACC region” negatively correlated with BMI. In response to no-go versus go tasks or other way around? I can infer it from the first sentence of that paragraph but it would be better that it is spelled out in that sentence also.

This has been fixed.

DISCRETIONARY REVISION

1) It would be really informative to in fact to look at the gender differences in these fMRI paradigms either gender as a main factor or at least they should control for it. It would
be specifically making it a stronger work, if they also look at the ROI for the reflective system for gender differences. I understand to make it more than 2 contrast is difficult. High vs low calorie, go versus no go and females versus males. However, if they solely pick the no-go trials, since we are interested in the restraint system here specifically, they can compare the genders in terms of their fMRI responses in the reflective system (or whole brain) to the high vs low calorie food cues on the no-go trials.

As mentioned earlier, we now report the gender difference results.