TITLE: Lower cognitive functioning as a predictor of weight gain in bipolar disorder: A 12-month study

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ABSTRACT: Objective: In cross-sectional studies, elevated body mass index (BMI) is associated with cognitive impairment in bipolar disorder (BD). We investigated the direction of this association – ie. whether weight gain negatively impacts cognition, or lower cognitive functioning predisposes patients to weight gain – by prospectively examining changes in BMI and cognition.

Method: We measured BMI and performance in six cognitive domains over 12 months in 80 early-stage BD patients and 46 healthy comparison subjects (HS). We investigated whether 1) higher BMI and increasing BMI over time predicted lower cognitive functioning, and 2) lower cognitive functioning and changes in cognition predicted increasing BMI.

Results: Neither baseline BMI nor BMI change predicted worsening cognition. Lower baseline scores in attention, verbal memory, working memory, and a composite measure of global cognition predicted increasing BMI in patients and HS. In patients, cognitive impairment remained associated with increasing BMI when clinical and treatment variables were adjusted for. Improvement in working memory predicted a smaller subsequent BMI increase in patients.

Conclusion: Lower cognitive functioning in specific domains predicts increasing BMI in BD patients and healthy young adults. Targeting cognition may be important for minimizing weight gain in BD.

Intriguing rationale and findings that will undoubtedly make a contribution to knowledge in this research field. I have a few suggestions and queries regarding methods and interpretation of the results that should be easily addressed by the authors.

-in the introduction please discuss etiology of obesity as part of BD. For instance the authors could at least mention the link between medication, metabolic disorder and weight gain.

-are there other lifestyle changes associated with the disease that may lead to weight increase? This could be addressed too.

-I am surprised that the authors did not address current knowledge of the link between eating disorders (bulimia, binge eating) and cognition. Could the authors comment on this or address this in the introduction.

-also please address how the authors think that weight fluctuations/increase differ between HS and psychiatric populations e.g. mood, hormones. For instance are there studies between low IQ and BMI?

-please provide references for the “North American Adult reading test full scale”. Is this the NART?

-although tests of the MATRICS are described in other papers it would be helpful to have a summary table either in the supplementary material or within the manuscript describing what kind of tests were used and what they measure. Equally helpful would be to know how the authors calculated the total (raw) score for each cognitive domain e.g. was there just one score for memory including immediate, delayed, recognition)? And what kind of “attention” are they referring to? Was processing speed taken into account?. This is important and should be well defined especially since the authors mention that cognitive remediation could be helpful to protect against weight gain in BD. A specific description of what each cognitive score means could help to apply these findings to a clinical setting

-did the authors conduct separate regression analyses for BD and HC? I am asking this because on page 10 the authors mention that …patients experience greater improvement…”. If this is the case how did the authors compare models between HC and BD? (by the way the authors should conclude the sentence and add “than HS” on page 10). Please clarify this in the manuscript.

-Would HS be expected to display cognitive fluctuations over time? What does the literature say?

-the authors refer to a mediation analysis on page 12 but this was not mentioned in the methods. Please address this in the methods, and please provide a mediation path graph for further clarification.

-did the authors compare results of the weight increase observed in the current sample of BD and HS to that reported in other studies? Also how do the percentages of underweight/average/overweight in the current sample compare to that reported in other studies? I would like to know how representative the current sample is in terms of weight, weight increase etc.

-could the authors please provide effect sizes, power analyses (estimates) and betas/R2 for regressions and correlations.

-could the authors explain why they conducted both both repeated-measures and longitudinal mixed models. What not just longitudinal if they were concerned with the effects of time on the results? I would recommend that they add 1 sentence prior to describing each model to facilitate the understanding of the results.

-Discussion: some mention of affective processing and reactivity to food cues could be helpful. Also the authors record the occurrence of stressful events during the study period? If not this could be addressed as a potential future direction.

Tables. Please mention onset of the disease, how many did the patients take medications for, how many euthymic-depressed-manic did you have in your sample (based on SCID or else). Did you have rapid cyclers too?

Figure legends. I would recommend to rewrite the your captions to try to convey as much information as possible. A good rule of thumb is that captions of tables or figures should be sufficiently clear, well labeled, and described by the legend to be understood without reading the results. For instance please mention what kind of coefficient of correlation you are showing (Pearson?)(please mention this in the methods too), add a text box mentioning r and p value for the correlation you are showing, and consider reducing the number of figures to 1-2 (just the most relevant ones).

Minor details

-add a ref to the initial sentence in the introduction

-in the abstract please mention that the sample included adult patients, whether patients were medicated and whether they were euthymic/remitted. Add 1 sentence about the statistical analyses you used.

-in Significant outcomes: please correct “of of bipolar disorder”

-page 8. Correct mdcitions, repated

Page 15: type ‘predcited”

Page 10 please make sure to explain the acronym BL before talking of BL on its own (I am referring to the sentence “at BL…”)