No. Rejected Application: 1072/19 No. Current Application: 1313/20

I would like to thank the reviewers for their time and insightful comments on the grant application. Based on the reviewers’ suggestions, I have made a number of revisions that have made the proposal more focused, direct, and theory-driven. The primary changes are (1) the emphasis on causal relationships between inhibitory control and emotion and (2) the inclusion of both behavioral and physiological measurements.

**Reviewer 1**

“With a higher level of funding it might be of interest to include a longitudinal design”.

Response: I thank the reviewer for this suggestion. A 3-month follow-up has been added.

**Reviewer 2**

*\*\*\* Please note that I did not include responses to comments regarding missing literature and methodological aspects that are no longer relevant in the revised proposal. This includes comments regarding task-switching and N-back tasks. \*\*\**

“…clarity is needed that the coordination of the multiple sites, particularly if quite a distance apart, will be well managed to avoid missing/corrupted data entry etc.”

Response: All of the data will be collected on the laboratory-owned laptops, which will be located in each site throughout the study. The laptops are connected to the lab’s HIPAA-certified google drive. The research team will have immediate access to the data, regardless of the location in which it was collected. The leading research coordinator will be responsible for coordinating between the sites on all other aspects of the study (see details in the budget justification section under personnel).

 “...is there any way the personnel can be based at the various sites as recruitment is underway? … How will the PI ensure that the students, especially the less experienced BA and MA students, will collect the data effectively with all the travel as well?”

Response: As the reviewer suggested, we will make efforts to recruit and train personnel that will be based in each site (see more details under personnel in the budget justification section). Additionally, we would like to note that there is little room for human error because the computerized tasks require minimum interaction with the experimenter, and all of the data will be automatically stored on the lab’s HIPAA drive.

“Based on the above point, can the PI provide a little more information on the following “A PhD student will … oversee recruitment aspects of eating disorder patients and supervise the work of the research coordinators, ensure that the study procedures, data collection and storage run smoothly according to protocol.” Can the authors suggest any foreseeable pitfalls and how these will be specifically addressed, with regard to recruitment and data collection specifically?”

Response: An experienced PhD student will travel once every three months to each recruitment site and meet with the sites’ research coordinators to make sure that the protocol is being implemented according to the instructions. The head research coordinator will write a weekly report, indicating recruitment rates in each site. The report will be discussed with the PI and research team in a weekly meeting. In this meeting, we will address potential issues with recruitment, equipment, and data storage and organization. In the case that recruitment falls short in a specific site, we will work to understand potential causes and assess solutions with the research coordinator and clinical team located in the relevant site.

“The methods are sound, however, perhaps the authors could be more specific in their working hypotheses (page 6) about the nuances of each EF and the link to abnormalities in EDs” … “Please make the working hypotheses more specific to rise above what is already being done in the field.”

Response: I thank the reviewer for this important comment. The revised proposal includes more specific, theory-driven hypotheses. In the Research Objectives & Expected Significance section (pages 4-5) you will find details on how the objectives extend beyond what has already been done in the field.

 “How are the ED patients to be diagnosed? With DSM-5? Please specify.”

Response: We added the SCID-5-RV for diagnosing EDs and comorbid disorders (page 6).

“Please explain in more detail about the secure system: “an online link with the clinical questionnaires will be sent to the adolescent via a secure system”.”

Response: ‘Qualtrics’ will be used to deliver the questionnaires to the participants (page 6).

“Why are the investigators not performing MANCOVA analyses? It would be interesting to also examine the potential interactions between the EF tasks. One could also examine the incidence of risk in HC (at risk for ED, no risk for ED based on EDEQ), given the high incidence of restrained/avoidant eaters in the adolescent population that might influence the effects.”

Response: In the revised proposal, a MANOVA is less relevant because each study is qualitatively different from the other. With respect to adolescents at risk for EDs, it is true that some adolescents may not receive a diagnosis of an eating disorder using the SCID, but may still show high levels of eating pathology in the EDE-Q. The analyses reported in the “Contribution of IC-emotion interactions to disordered eating” section (page 13) will allow us to assess if high levels of restricted eating (assessed via the EDE-Q) in the HC group is associated with the primary measures in each task.

“The authors should also consider duration of illness …”

Response: I thank the reviewer for this suggestion. Duration of illness is now included as a variable of interest in the correlational analysis section (page 13).

“The abstract is quite detailed for the background, but quite vague in terms of the hypotheses”.

Response: I agree with the reviewer. The abstract now includes all theory-driven hypotheses.

In several comments, the reviewer suggested that adding a neurobiological assessment could greatly strengthen the project: “It would be excellent if the proposal had additional neurocognitive or psychophysiological measures as well, such as fMRI, fNIRS (less expensive than MRI) or SCR, eye-tracking, heart rate variability, EEG”.

Response: A physiological measurement (pupil dilation) has been added to the project to assess whether inhibitory control can suppress pupil dilation in response to high-calorie foods in adolescents with EDs. I agree that adding an fMRI component could also strengthen the proposal. However, I believe that due to the complexity and costs of running an fMRI study on a population of minors with psychiatric disorders, it is important to first establish a strong theoretical justification for such procedures by demonstrating causal relationships between emotion and inhibitory control at the behavioral and physiological levels. In the future, I hope to be able to run these studies using additional neuroimaging techniques.

“There is a distinct lack of discussion of the roles impulsivity (e.g. binge eating) versus compulsivity (e.g. cognitive ruminations in AN) play in the phenotypes being tested”.

Response: The revised proposal no longer includes studies on working memory updating and its relation to rumination. However, I extended the discussion on theoretical aspects that address how inefficient vs. excessive use of inhibitory control could translate into disordered eating (pages 1-2).

The reviewer suggested to include a Visual Analogue Scale to assess mood during the task.

Response: A measurement of mood and hunger on the visual analogue scale has been added (page 8).

“If needed, the number of trials in each task will be reduced, and the time gap between the tasks increased” – how will it be determined if this is needed?

Response: I believe that participant burden is not a pressing issue in the revised proposal because the number of tasks was reduced and they will be administered across two separate sessions.

“Finally, besides Stanford, does the PI have any other international experts in the field of eating disorders that he would count as collaborators?

Response: Yes, during the past year, I have initiated a collaboration with Prof. Ross Crosby from the University of North Dakota, Fargo. We currently have a manuscript that has been accepted for publication in the *Journal of Psychiatric Research* and another manuscript which is in preparation. In addition, Prof. Eric Stice from Stanford University is a new collaborator on the current project (a letter of collaboration is attached).

**Reviewer 3**

The two main concerns raised by reviewer were that: 1) the proposal did not sufficiently address the fact that low weight in the AN group could explain variability in cognitive functioning and 2) the proposal did not address comorbidity like depression and anxiety which could lead to cognitive impairments.

Response: I thank the reviewer for these important comments. Weight status will be addressed in two ways. First, I now include a group of patients with Atypical AN, a diagnosis which has all of the same symptoms of AN-R, except for being underweight. If no differences are found between Atypical AN and AN-R patients, but are found between AN-R and AN-BP patients, this will provide strong evidence that differences between the groups are likely due to disordered eating patterns (restrictive vs. binge eating/purging) rather than weight status. In addition, we will assess correlations between the primary results from each task and participants’ weight status (%EBW). With respect to comorbidity, in the revised proposal I added a section regarding how comorbid symptoms of anxiety and depression, as well as comorbid DSM-5 diagnoses, will be addressed (page 14).

**Reviewer 4**

*\*\*\* Please note that I did not address several comments regarding set-shifting (proactive vs. reactive) because these are no longer relevant in the revised proposal \*\*\**

“Numerous studies have assessed EF, particularly set-shifting and response inhibition, in individuals with eating disorders. This body of work diminishes the originality of Study 1, which aims to compare individuals with AN-R, AN-BP, and BN on EF in a non-emotional context. The hypothesized differences among adolescents with AN-R, AN-BP, BN, and healthy controls on task performance largely replicate the findings of previous research.”

Response: After considering the reviewer’s comment, I have decided to exclude Study 1 and focus on causal relationships between emotion and inhibitory control. While some studies have assessed food-related inhibitory control in eating disorders, none, to the best of my knowledge, have systematically examined the role of **emotions** in modulating food-related inhibition (Study 1), assessed whether food-related inhibition can attenuate emotional arousal at the physiological level (Study 2), or examined whether priming inhibitory control can improve emotion regulation (Study 3) in adolescents with EDs. Hence, the revised proposal includes a set of novel studies, all addressing potential interactions between inhibitory control and emotion from different angles.

“Figure 1 hypothesizes that EFs are associated with different aspects of the eating disorder clinical phenotype (i.e., set-shifting 🡪 inflexible thinking; response inhibition 🡪 impulse control difficulties; updating 🡪 rumination). Yet, measures of these clinical phenotypes are not included in the assessment battery. This is a missed opportunity to test a central component of the PI’s theoretical model.”

Response: I agree with the reviewer that measurements of clinical phenotypes were missing. The revised proposal focuses on the interaction between inhibitory control and emotion as a potential mechanism contributing to **disordered eating**. Thus, on page 13, under *“Contribution of IC-emotion interactions to disordered eating”* you will find details on how we plan to assess the contribution of inhibitory control-emotion interactions on restricted eating, binge eating, and purging behaviors.

“Potential confounds that could influence performance on EF tasks in emotion and non-emotion contexts (e.g., pubertal status, comorbid psychiatric disorders, personality traits, duration of eating disorder symptoms, emotion regulation difficulties, etc.) are not considered in the analyses”.

Response: The reviewer is correct. In the revised proposal, I have addressed these potential confounds (see the correlational analyses section and the dealing with comorbidity section on pages 13-14).

“BMI percentile is preferable to BMI as an index of adiposity in adolescents”.

Response: The reviewer is correct. I now discuss percentage of expected body weight (%EBW) as I have done in my previous work studying adolescents with EDs (Weinbach, Bohon, & Lock, 2019; Weinbach, Lock, & Bohon, 2019; Weinbach, Perry, Sher, Lock, & Henik, 2017; Weinbach, Sher, & Bohon, 2018; Weinbach, Sher, Lock, & Henik, 2018).

“Documenting within-person changes in EF following exposure to emotional stimuli (in addition to between-group differences on these measures) would be a much stronger test of the PI’s theoretical model…”

Response: I thank the reviewer for this suggestion. In the revised proposal, all of the analyses are separated to examine both within- and between-subject effects.