**Research Program**

**1. Scientific Background**

Eating disorders (EDs) are a group of psychiatric conditions in which disordered eating leads to severe impairments in psychological and physical functioning (American Psychiatric Association, 2013). EDs are associated with the highest mortality rate of all psychiatric disorders and their prevalence among young adolescents has increased over the years (Smink, Van Hoeken, & Hoek, 2012). Current evidence-based treatments for adolescents with EDs have had limited success, with symptom remission occurring only in 30%-50% of patients (Kass, Kolko, & Wilfley, 2013).

Disordered eating can be characterized by a severe restriction of food intake that results in dangerous weight loss, as in the case of anorexia nervosa (AN), or episodes of disinhibited binge eating that can lead to compensatory behaviors (e.g., vomiting), as in the case of bulimia nervosa (BN). Disordered eating in AN and BN is typically motivated by a desire to control one’s body weight due to a disturbance in body image (American Psychiatric Association, 2013). However, **the mechanisms underlying the ability of individuals with AN to endure long periods of starvation, on the one hand, and those responsible for disinhibited eating in BN are poorly understood**. A better understanding of these mechanisms is important for identifying and developing novel and effective treatments.

When searching for the potential mechanisms that contribute to disordered eating, it is important to consider if the same underlying mental process can account for different types of disordered eating. Given that binge eating and restrictive eating represent two opposite extremes in the ability to exert **control over one’s behavior** (i.e., loss of control vs. excessive control over eating, respectively), one of the most relevant mental processes to examine is the ability to control and inhibit undesired actions and behaviors, namely, inhibitory control (IC).

**Inhibitory Control and Disordered Eating**

IC allows us to deliberately inhibit dominant, automatic, or prepotent actions when necessary (Miyake et al., 2000). Thus, researchers have suggested that deficient IC may lead to disinhibited eating in individuals with EDs that are characterized by recurrent binge eating or purging behaviors (Bartholdy, Dalton, O’Daly, Campbell, & Schmidt, 2016; Hirst et al., 2017; Wu, Hartmann, Skunde, Herzog, & Friederich, 2013). To test this hypothesis, studies have used behavioral tasks (e.g., stop-signal task, go/no-go task) to measure the ability of inhibiting prepotent responses in patients with binge eating/purging EDs. A meta-analysis supported the notion that IC deficits exist in these patients, especially in tasks that include presentation of high-calorie food stimuli (compared to non-food stimuli; Wu et al., 2013). This suggests that triggering environmental cues, such as the presence of high-calorie foods, lead to IC failures in individuals with binge eating/purging EDs and thus, may account for their disinhibited eating episodes.

In contrast to poor IC in individuals with binge eating/purging EDs, excessive use of IC has been suggested to subserve dietary restraint in individuals with restrictive EDs. Restrictive EDs are characterized by severe food restriction, which occurs in the absence of binge eating or purging behaviors, such as in the restrictive subtype of AN (AN-R; Bartholdy et al., 2016; Hill, Peck, Wierenga, & Kaye, 2016; Kaye, Fudge, & Paulus, 2009). Only a few studies have assessed IC in AN, with two neuroimaging studies showing aberrant brain activation related to IC in the absence of conclusive behavioral effects (Lock, Garrett, Beenhakker, & Reiss, 2011; Wierenga et al., 2014). However, these studies did not expose participants to triggering stimuli such as high-calorie foods. In our recent work using the stop-signal task, we demonstrated that adolescents with AN-R are better able to inhibit a response following exposure to high-calorie food images compared to healthy adolescents (Weinbach, Lock, & Bohon, 2019). We also observed excessive IC in adolescents with AN using other IC tasks (Weinbach, Bohon, & Lock, 2019; Weinbach, Sher, Lock, & Henik, 2018). Overall, it appears that exposure to food stimuli is a critical situational factor that modulates IC in opposite ways among patients with binge eating/purging EDs and restrictive EDs. However, in order to achieve a more holistic understanding of how IC contributes to disordered eating, it is important to assess if IC interacts with other situational factors that are known to influence disordered eating.

**Emotion, Inhibitory Control and Disordered Eating**

In addition to the presence or absence of food stimuli, another situational factor that is extremely relevant in modulating disordered eating is individuals’ affective state. Patients with eating disorders suffer from elevated negative emotionality (Engel et al., 2013). In order to regulate negative emotions, one needs to have some level of control over which emotions are experienced and how intensely they are felt (i.e., emotion regulation; Gross, 1998). Numerous studies have reported difficulties in emotion regulation among adults and adolescents with EDs (e.g., Lavender et al., 2015; Prefit, Cândea, & Szentagotai-Tătar, 2019; Segal & Golan, 2016; Weinbach, Sher, & Bohon, 2018). Difficulty in regulating negative affect leads to experiencing intense emotions, which can act as a trigger for disordered eating behaviors (Lavender et al., 2015). For example, using ecological momentary assessment (EMA), studies have shown that negative affect increases prior to binge eating episodes in patients with binge eating/purging EDs and that higher daily ratings of negative affect are associated with a greater likelihood of dietary restriction on subsequent days in patients with restrictive EDs (Engel et al., 2016, 2013). **However, an important question remains unanswered: What is the mechanism through which negative emotions trigger disordered eating in patients with EDs?**

**There are reasons to believe that IC is the missing link between emotional experiences and disordered eating. The current research proposal aims to examine three main reasons.** First, triggering negative emotions experimentally can impair healthy participants’ performance on IC tasks (Kalanthroff, Cohen, & Henik, 2013; Okon-Singer, Hendler, Pessoa, & Shackman, 2015; Verbruggen & De Houwer, 2007), indicating that emotions modulate IC, irrespective of psychopathology. If negative emotional states impair the ability to exert efficient IC, and IC is required for regulating eating behaviors, it follows that negative emotions may exacerbate abnormalities in the ability to exert control (i.e., deficient or excessive control) over one’s eating behaviors. However, the literature on EDs seriously lacks studies that attempt to link affective states and IC, as indicated by a recent systematic review (Smith, Mason, Johnson, Lavender, & Wonderlich, 2018). Nevertheless, using EMA, we have recently shown that among adults with binge eating/purging EDs, the relationship between momentary negative affect and subsequent binge eating is stronger on days characterized by reduced IC to food stimuli (Smith et al., 2019). This finding implies that negative affect impairs these patients’ ability to exert a control response after being exposed to food stimuli, which subsequently leads to binge eating. **However, in order to determine if a causal relationship exists between negative affect and deficient/excessive control in response to food, it is vital to manipulate affective states experimentally (as opposed to correlational designs).**

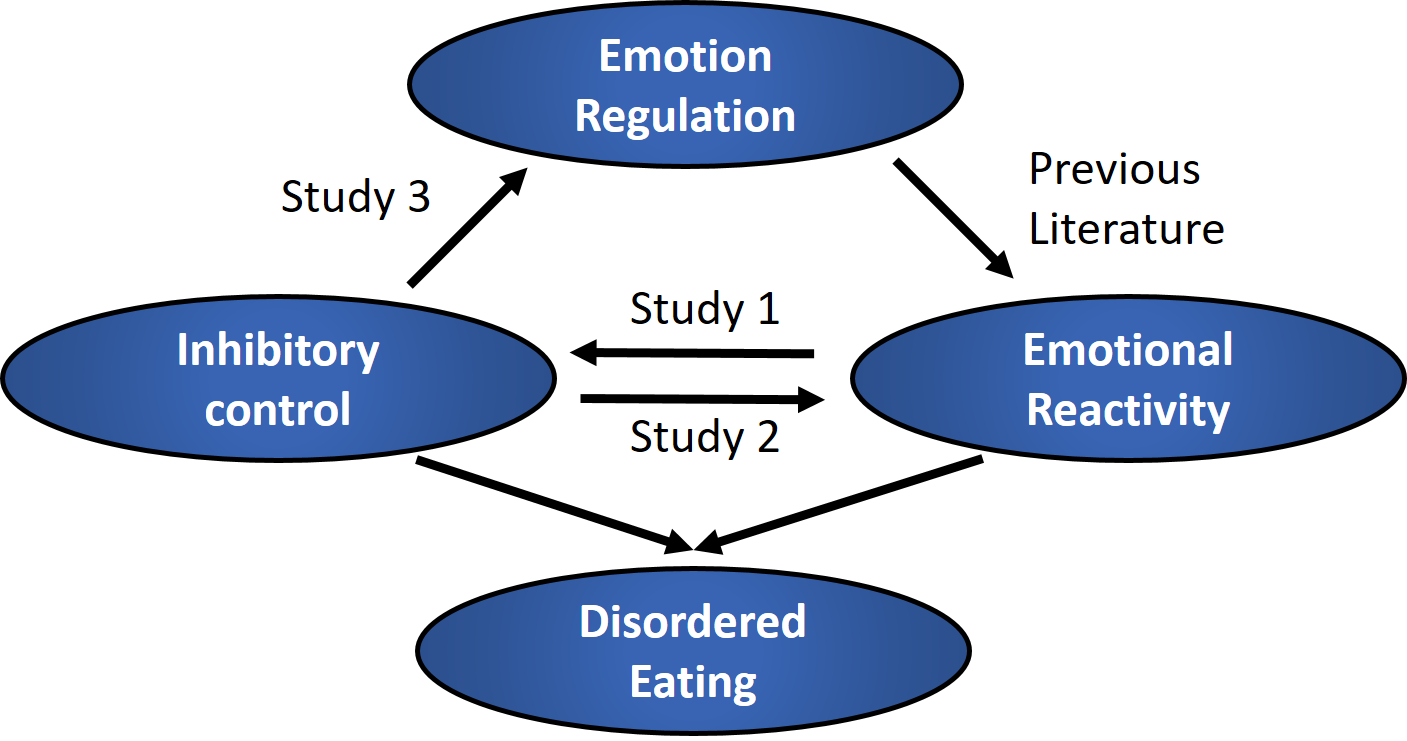
A second reason for examining IC is because of possible bidirectional effects. While emotions may influence IC in a way that could lead to disordered eating (emotion 🡪 IC), IC may also influence emotional experiences (IC 🡪 emotion) in a way that would contribute to disordered eating. At the physiological level, emotions activate an increased sympathetic response of the autonomic nervous system (ANS). For example, pupil dilation is considered a proxy for emotional arousal because studies repeatedly show that the pupil’s diameter increases to a greater extent (a sympathetic response of the ANS) in response to emotional stimuli as compared to neutral stimuli (e.g., Bradley, Miccoli, Escrig, & Lang, 2008; Bradley, Sapigao, & Lang, 2017; Cohen, Moyal, & Henik, 2015; Granholm & Steinhauer, 2004). Importantly, a study by Cohen and colleagues (2015) revealed that when IC is triggered experimentally (after trials that require IC resources to resolve a cognitive conflict), the increase in pupil diameter in response to negative emotional stimuli is attenuated. In other words, IC can suppress negative emotional reactivity (Cohen et al., 2015). In the context of EDs, food stimuli represent emotionally arousing stimuli, as indicated by the increased pupil dilation in response to high vs. low calorie food images in adults with AN (Godier, Scaife, Braeutigam, & Park, 2016). **It could be that a failure to use IC to suppress emotional reactivity in response to high-calorie foods may increase the risk of patients with binge eating/purging EDs to lose control over their eating behavior. In contrast, among patients with restrictive EDs, excessive IC may suppress emotional responses to food stimuli and lead to a greater ability to control one’s behavior in the presence of food.**

Lastly, difficulty in applying effective emotion regulation strategies has been shown to lead to increased negative affect, which in turn exacerbates disordered eating (Lavender et al., 2015). For example, cognitive reappraisal is an effective emotion regulation strategy that involves the ability to reinterpret a negative event with the goal of reducing its emotional impact (Gross, 1998). Limited use of cognitive reappraisal predicts higher levels of eating pathology in individuals with binge eating/purging EDs, but not in individuals with restrictive EDs (Danner, Evers, Stok, Van Elburg, & De Ridder, 2012). Interestingly, tight links exist between cognitive reappraisal and IC, as both are involved in regulating thoughts and behaviors. For example, one study found correlations between performance in a cognitive reappraisal task and an IC task (e.g., stop-signal task) at the brain and behavioral level (Tabibnia et al., 2011). Another study demonstrated that transcranial direct current stimulation (tDSC) above the right dorsolateral prefrontal cortex (dLPF), an area highly implemented in IC, resulted in decreased emotional arousal ratings in a reappraisal task (Feeser, Prehn, Kazzer, Mungee, & Bajbouj, 2014). Lastly, a recent study trained healthy adults to employ IC (via the flanker task) while watching negative images. Participants in the training group exhibited a higher propensity to reappraise a negative personal event after the IC training compared to those in the sham training group (Cohen & Mor, 2018). **Thus, it is important to extend research conducted on healthy populations to examine whether priming IC can improve cognitive reappraisal in clinical populations as well. Specifically, whether priming IC in patients with EDs may help improve cognitive reappraisal**, especially in individuals with binge eating/purging EDs wherein limited use of reappraisal predicts eating pathology (Danner et al., 2012).

**Research Objectives & Expected Significance**

The overarching aims of the current research project are to **(1) examine causal relationships between IC and emotion processing in adolescents with binge eating/purging EDs and restrictive EDs and (2) assess how these constructs may contribute to disordered eating (see Figure 1).**

Figure 1. Hypothesized links between IC, emotion regulation, emotion reactivity, and disordered eating.



**More specifically, the current study includes four measurable objectives, each with a distinct significance. Objective 1 is to examine if the experience of emotion (negative, positive, or neutral) influences the ability to inhibit a response following an exposure either to food or non-food stimuli in adolescents with EDs (Study 1).** Results from the study are expected to shed light on a potential mechanism by which negative affect exacerbates different disordered eating patterns. **Objective 2 is to assess if experimentally triggering IC can modulate the physiological response (assessed via pupil dilation) to high- and low-calorie food stimuli among adolescents with EDs (Study 2).** Findings from this study are expected to elucidate whether the ability to exert control over an automatic emotional response to food differs as a function of the ED type. **Objective 3 is to determine whether priming IC can improve reappraisal in adolescents with EDs (Study 3).** Results of this study are expected to clarify whether activating IC in emotional contexts can improve the ability to reappraise negative emotional content in adolescents with EDs. Our prior work has shown promising preliminary results for Study 3, as will be detailed below. Lastly, **Objective 4 is to assess whether the primary measures from each of the three studies described above can prospectively predict disordered eating patterns.** This predictive relationship will be assessed by conducting a comprehensive assessment of disordered eating at baseline and at a 3-month follow-up.

**The proposed studies are expected to greatly advance basic and clinical understandings of EDs.** First and foremost, IC abnormalities have been suggested to be a mechanism that contribute to disordered eating. In addition, negative affect is known to trigger disordered eating. **At present, the literature on EDs seriously lacks studies that investigate the relationship between emotion and IC** (Smith et al., 2018). **Thus, the studies suggested in the current proposal will help to better understand how interactions between IC and emotion contribute to and maintain the primary clinical symptom in EDs, namely, disordered eating.**

Moreover, focusing on adolescents with EDs is important because the onset of EDs commonly occurs during this developmental stage, which is also a critical period for the development of both IC and emotion regulation (Ahmed, Bittencourt-Hewitt, & Sebastian, 2015; Silvers et al., 2012; Steinberg, 2005). As such, it is possible that abnormalities in cognitive and emotional systems during adolescence will have lasting effects into adulthood among individuals with EDs (Hirst et al., 2017). An additional advantage of studying adolescents with EDs is that this population is less subjected to potential effects of enduring illness or diagnostic crossovers, which mitigates the potential confounding influences of these variables.

The proposed project is also expected to have clinical implications. If we uncover abnormalities in cognition-emotion interactions among adolescents with EDs, it will emphasize the need to target cognitive functioning and emotion regulation in therapy during early stages of the disorder. Various cognitive trainings are currently offered for patients with EDs. Much research has been conducted on Cognitive Remediation Therapy (CRT) for adolescents and adults with EDs (for a review, see Dahlgren & Rø, 2014; Tchanturia, Giombini, Leppanen, & Kinnaird, 2017); however, although CRT leads to some improvements in cognitive functioning, evidence regarding the ability of CRT to alleviate clinical symptoms is sparse (Smith et al., 2018). **A potential reason for that is a poor understanding of the mechanisms by which neurocognitive processes contribute to the clinical symptoms involved in EDs. In order to increase the precision of cognitive training procedures, it is important to identify which neurocognitive processes are affected, determine how to best influence them, and specify what clinical outcome is expected.** Findings from the proposed studies are expected to help achieve these goals. For example, the proposed studies may shed light on how negative emotions contribute to abnormalities in food-related IC, as well as how IC can be used to promote adaptive emotion regulation skills in adolescents with EDs. Such results may highlight the importance of prioritizing emotion-focused treatments (Sala, Heard, & Black, 2016) that target better management and expression of emotion among individuals with EDs, instead of solely focusing on training neurocognitive processes.

**Detailed Description of the Proposed Research**

Participants: The experimental tasks included in each studies will be administered to 180 female adolescents (see power analysis below) aged 12-18. We will recruit 60 adolescents with restrictive EDs (30 AN-R and 30 Atypical AN, which include all the symptoms of AN-R except for low body weight), 60 adolescents with binge eating/purging EDs (30 BN and 30 AN-binge eating/purging type; AN-BP includes episodes of binge eating and purging behaviors but, unlike those with BN, the individuals are underweight) and 60 healthy controls (HC). In light of the potential variability across age in IC, half of the participants in each group will be between the ages of 12-14 and half will be between 15-18 years old. This will increase our ability to interpret the results while considering developmental stage. Inclusion criteria for the patient groups are: (a) a diagnosis of AN-R, Atypical AN, AN-BP or BN, and (b) a body mass index (BMI) > 12 in the AN group. Inclusion criteria for HC include: (a) the absence of a first-degree relative with a lifetime eating disorder, (b) the absence of a currently diagnosed major psychiatric disorder, and c) percentage of expected body weight > 85%. Exclusion criteria for both groups include the presence of a condition that may interfere with cognitive abilities such as acute psychosis, traumatic brain injury, epilepsy, or attention deficit disorder. Clinical details regarding illness duration, use of psychotropic medications, details on current/past treatments, and history of hospitalizations, if any, will be collected from the patients’ medical files. Demographic data regarding years of education, parental income, parental marital status, country of origin, and ethnicity will also be collected.

General procedure and recruitment strategy: Adolescents with EDs will be recruited via collaborations with three of the largest eating disorder clinics in Israel: Soroka Medical Center, Be’er Sheva; Sheba Academic Medical Hospital, Ramat Gan; and Rambam Health Care Campus, Haifa (see letters of collaboration attached). Upon the identification of eligible participants, a research coordinator in each site will contact the patient and her parents to provide information regarding the study. Short eligibility phone screenings based on the inclusion and exclusion criteria will be carried out. Healthy adolescents will be recruited via advertisements through social networks and local schools. Consent and assent forms will be signed by the adolescents and their parents prior to participation in the study. After the consent process, a website link for a Qualtrics survey containing the clinical questionnaires will be sent to the adolescent. Following completion of the questionnaires, a research coordinator will schedule two in-person meetings (separated by at least one week, but no more than one month) with the adolescent either in the PI’s lab at the University of Haifa or at the local EDs clinic. Participants will be asked to refrain from eating for two hours before the session in order to control for effects of hunger. The first session will include administration of the SCID-5, a short IQ assessment, and the experimental task for Study 1. The second session will include the experimental tasks for Studies 2 and 3. After the completion of all three studies, the adolescents will be debriefed. Three months after the last session, adolescents will be contacted again to complete a follow-up assessment of disordered eating. Ethical approvals from the University of Haifa’s IRB committee and the Helsinki committee at each eating disorder clinic will be obtained prior to the study.

Measures:

*Structured Clinical Interview for DSM-5 (SCID-5;* First, Williams, Karg, & Spitzer, 2015)*:* Presence/absence of EDs, including specific subtype and comorbid diagnoses, will be assessed using the SCID-5-Research Version. The assessment will be administered by trained clinicians in each of the participating EDs centers and by clinical graduate students in the PI’s lab.

*Percentage of Expected Body Weight (%EBW):* Height and weight will be measured on the day of the assessment (either at the EDs clinics or during the first lab visit). Percent EBW will be calculated based on the 50th percentile of body mass index (BMI), corrected for age and gender, as specified by the Centers for Disease Control and Prevention growth charts.

*Wechsler Adult Intelligence Scale and Wechsler Intelligence Scale for Children:* Potential differences in IQ between the groups will be assessed using the vocabulary and matrices subsets of the Wechsler Adult Intelligence Scale (WAIS; for participants aged 16 or above) and Wechsler Intelligence Scale for Children (WISC; for participants under the age of 16).

*Eating Disorder Examination Questionnaire (EDE-Q; Fairburn & Beglin, 1994):* The EDE-Q is a reliable and validated self-report questionnaire aimed to assess eating disorder severity and disordered eating patterns. The EDE-Q assesses the severity of the eating pathology based on four subscales: restrained eating, eating concerns, shape concerns and weight concerns. The EDE-Q also assesses the frequency of binge eating and purging behaviors (i.e., vomiting and the use of laxatives to control weight) over the past month. The EDE-Q will be administered at baseline (first assessment session) and at the three-month follow-up.

*Other self-report questionnaires:* Symptoms of depression will be assessed using the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996), anxiety levels will be measured using the State-Trait Anxiety Questionnaire (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), and emotion regulation skills will be assessed using the Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004) and the Emotion Regulation Questionnaire (ERQ; Gross & John, 2003). These questionnaires will be used to validate that the participants’ characteristics are similar to those found in previous studies and to assess associations between these measures and performance on the study tasks.

**Experimental Design - Study 1**

*Objective:* Study 1 will examine how emotions (negative, positive, or neutral) can impair or improve the ability to inhibit a response following exposure to food and non-food stimuli in adolescents with EDs.

*Working hypothesis:* It is hypothesized that emotional stimuli (negative, neutral, positive) will modulate the ability to inhibit an already initiated response during exposure to high-calorie food stimuli. Specifically, it is expected that negative emotion will trigger greater disinhibition (i.e., difficulty in stopping a response) in the presence of food stimuli in the binge eating/purging group, and excessive inhibition (i.e., a superior ability to stop a response) in the restrictive ED group, compared to neutral emotion. In light of evidence suggesting that positive emotion can improve cognitive control (Xue et al., 2013), all groups are expected to perform similarly to the HC group under the positive emotion condition.

*Emotion-Food-Stop-Signal Task (E-F-SST):* The stop-signal task is considered to be a hallmark measure of response inhibition (Verbruggen & Logan, 2008). In a Food-SST (Ganor-Moscovitz, Weinbach, Canetti, & Kalanthroff, 2018; Weinbach, Lock, et al., 2019), participants will be presented with a fixation cross (1,000 ms) that will be replaced by a target image. Participants will decide, as quickly as they can, if an image in the center of the screen is of a food (e.g., by pressing the ‘z’ key) or non-food item (e.g., by pressing the ‘m’ key). In 25% of the trials, a stop signal (e.g., an auditory beep of 100 ms) will be delivered via headphones after the presentation of the target image (with an equal proportion of stop signals occurring after food and non-food images). The stop-signal instructs participants to withhold their response. The time between the target appearance and the stop signal (i.e., stop-signal delay; SSD) will initially be set at 250 ms and then adjusted in each subsequent trial based on performance. Specifically, following a successful stop, the SSD will increase by 50 ms in the next trial, increasing stopping difficulty. In the case of a failure to stop, the SSD will decrease by 50 ms in the next stop signal trial, making it easier to stop. This procedure results in ~50% accuracy in stop signal trials. After the stop signal, a response window will appear for a maximum of 1,500 ms, but will disappear earlier if a response is made. The stop-signal reaction time (SSRT) is the main measure of response inhibition, such that a longer SSRT indicates a greater difficulty to stop the already initiated response. SSRT is calculated by subtracting the mean SSD from the mean reaction time (RT) in trials without a stop signal (for more details on this calculation, see Verbruggen & Logan, 2009). In the current task, the SSD will be evaluated separately for food and non-food items, allowing us to calculate a different SSRT for food and non-food items. Forty-eight high-calorie food images (with an equal proportion of sweet and savory foods) and 48 images of non-food items will be selected from a food picture database (Blechert, Meule, Busch, & Ohla, 2014). In order to manipulate emotional states, the task will include three emotional blocks. In each block, an emotional image (negative, positive, or neutral) will be presented prior to the target for 2,000 ms (for examples of typical trials, see Figure 2). The order of the blocks will be counterbalanced. Each block will include 48 images (144 emotional images overall). Negative, positive and neutral images that are appropriate for adolescents to view will be selected from the International Affective Picture System (IAPS) based on normative data (Lang, Bradley, & Cuthbert, 1997). Overall, the task will consist of 10 practice trials with feedback and three experimental blocks (96 trials per block), resulting in 288 experimental trials (72 of which will include a stop-signal).

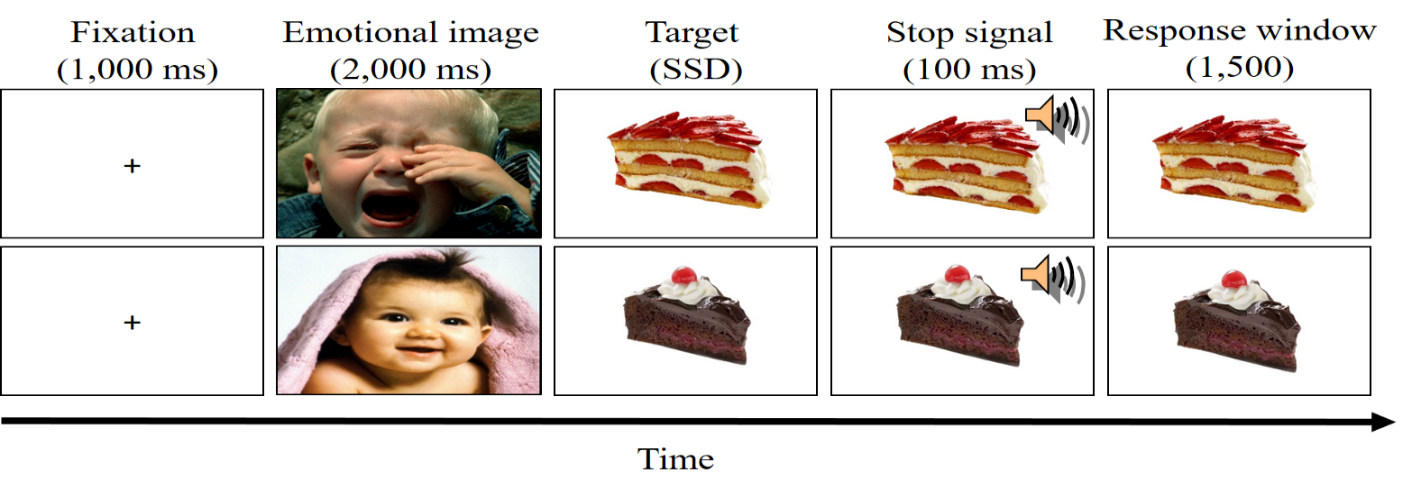


Figure 2. Example of two typical trials in which participants need to stop their response following exposure to high-calorie foods. The top row displays a trial from the negative emotional block and the bottom row shows a trial from the positive emotional block.

*Mood and hunger assessment:* Before each experimental block and at the end of the experiment, participants’ moods will be assessed using questions from the positive and negative affective schedule (Watson, Clark, & Tellegen, 1988) and participants’ hunger levels will be measured via a visual analogue scale. These assessments will allow us to examine carry-over effects in hunger and mood between the blocks.

*Preliminary results:* We have recently shown that exposure to high-calorie food images leads to superior response inhibition in adolescents with AN-R compared to HC in the Food-SST (Weinbach, Lock, et al., 2019). As such, the proposed task should be sufficiently sensitive to detect changes in food-related IC in adolescents with EDs. Additionally, we have recently found that deficient food-related IC moderates the relationship between negative affect and binge eating in individuals with BN and AN-BP (Smith et al., 2019). Thus, it is likely that emotions will modulate food-related IC in the task proposed here.

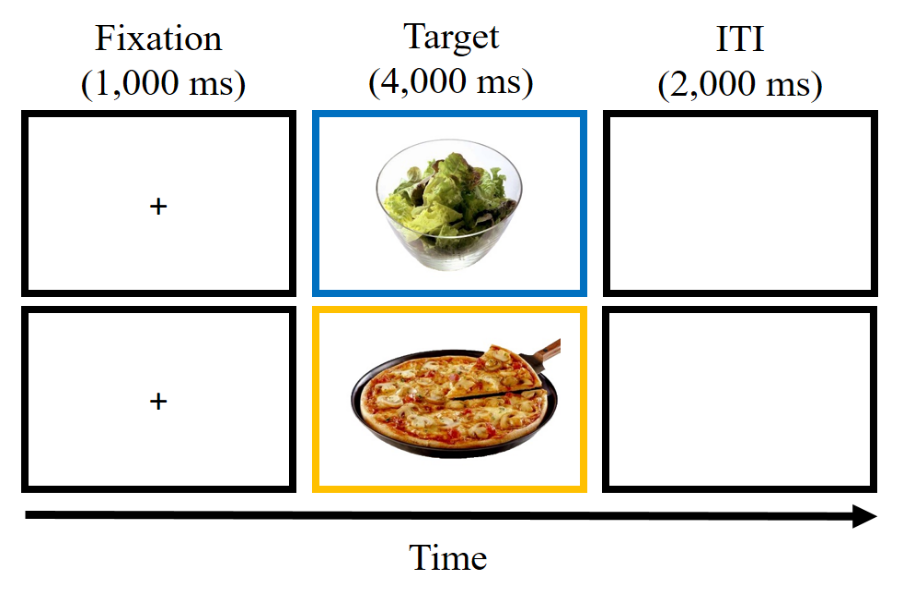
**Experimental Design - Study 2**

*Objective:* Study 2 will examine whether experimentally triggering IC will modulate the physiological response (assessed via pupil dilation) to high- and low-calorie food stimuli among adolescents with EDs.

*Working hypothesis:* High-calorie food images elicit an emotional response in patients with EDs (Horndasch et al., 2018; Zhu et al., 2012) and increase pupil dilation (Godier et al., 2016), an indicator of an increased sympathetic reaction of the ANS. We expect to replicate these findings and show that adolescents with restrictive and binge eating/purging EDs will exhibit increased pupil diameter when viewing high vs. low calorie food images. **However**, when IC will be experimentally triggered (in trials wherein participants are instructed to inhibit a response during exposure to high-calorie food images), the effect of increased pupil diameter for high-calorie foods will be suppressed. The suppression effect is expected to occur in patients with restrictive EDs (who are characterized by excessive food-related IC), but not in those with binge eating/purging EDs (who are characterized by deficient food-related IC). This pattern will confirm that patients with restrictive EDs can use IC resources to suppress an automatic physiological response to high-calorie foods.

*Food Go/No Go task (Food-GNG):* In the Food-GNG task, participants will be presented with a fixation cross for 1,000 ms that will be replaced by a colored frame. Participants will be asked to respond by pressing the space bar when a blue frame is presented (go-trials; 75% of the trials) and withhold their response when an orange frame is shown (no-go trials; 25% of the trials). Figure 3 depicts an example of two typical trials. The colors for go and no-go trials will be equal in luminance level, and the assignment of blue and orange to go vs. no-go signals will be counterbalanced across participants. Inside the frames, images of high- and low-calorie foods (64 of each, and different from those in Study 1) will be presented. Scrambled versions of the food images will also be included in order to control for luminance, color, and other visual characteristics that can influence pupil dilation. The target frame with the image inside will be presented for 4,000 ms and will not disappear upon response. This will ensure that the image remains visible for an equal amount of time in all conditions so that there will be sufficient time for pupil dilation without a change in luminance. The task will include 16 practice trials and 480 experimental trials (120 no-go trials) distributed equally across five blocks.

Figure 3. Example of two typical trials. In the upper row, participants respond (blue frame) and an image of a low-calorie food is presented. In the lower row, participants withhold their response (orange frame) and a picture of a high-calorie food is presented.



*Apparatus and procedure:* Pupillometry will be measured via a portable eye-tracker (EyeLink Portable Duo, SR Research) with a sampling rate of 1000 Hz (1 ms inter-sampling time). To ensure that the luminance level in the experimental room is similar between the sites, the room will be darkened and the same lamps (with a 40v light bulb) will be placed in each site. Portable chin rests will also be purchased and used in each site.

**Experimental Design - Study 3**

*Objective:* Study 3 will assess whether priming IC can improve reappraisal in adolescents with EDs.

*Working hypothesis:* It is expected that priming IC will improve reappraisal of a negative emotional image on a trial-by-trial basis in adolescents with EDs. Because adolescents with binge eating/purging EDs have greater difficulties using reappraisal strategies compared to those with restrictive EDs (Danner et al., 2012), it is expected that adolescents with binge eating/purging EDs will show the greatest IC priming effects; that is, they will show the greatest improvement in the ability to reappraise negative emotional content.

*GNG-reappraisal task:* In the cognitive reappraisal task, participants will view negative images and be requested to rate how negative they feel after each image (on a scale from 1-5, 5 being most negative). Before the images appear, a cue will instruct participants to either “watch” the image without trying to change their emotional experience or to “rethink”, that is, to think about the picture in a way that would make it less negative (i.e., reappraisal condition); for example, “*This is just a scene from a movie...*”. Additional examples will be given to the participants before the task to ensure that they understand the “rethink” condition. Lower negativity ratings after the “rethink” instruction compared to the “watch” instruction will represent successful reappraisal. Numerous behavioral and neuroimaging studies have used this task to assess reappraisal (for a review, see Buhle et al., 2014). In the current study, we will modify the original task so that participants perform a GNG task between the task cue and the presentation of the target image (see Figure 4). In the GNG task, participants will see different letters and will be instructed to respond as quickly as they can to each letter (go-trials; 75% of the trials), but withhold their response when seeing the letters ‘C’, ‘F’, or ‘T’ (no-go trials; 25% of the trials). Immediately after they either respond or withhold a response, a negative image will appear and participants will “watch” or “rethink” based on the cue that was presented before the GNG task. The task will include 240 trials (60 no-go trials and 180 go trials) spread out over three blocks. In each no-go and go condition, the proportion of “watch” and “rethink” cues will be equal. The images will be taken from the IAPS (different from those in Study 1) and will be different across the “watch” and “rethink” conditions; however, the mean valence and arousal ratings (based on norms) will be kept equal between the two conditions.

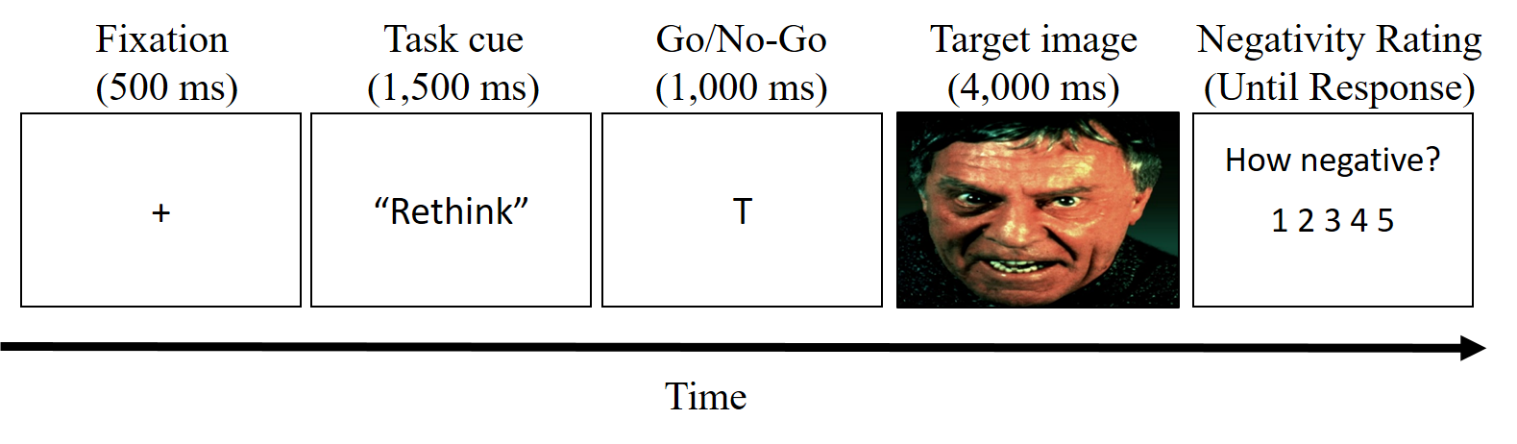


Figure 4. An example of a typical trial in the GNG Reappraisal task. In this example, participants see a “Rethink” cue (meaning they will need to reappraise the upcoming picture). However, before the image appears, they will need to withhold their response (because the letter ‘T’ is a no-go signal). After the image is presented, participants will rate how negative they currently feel. The task will allow for comparing participants’ ability to reappraise negative images following go vs. no-go trials.

*Preliminary results:* We have obtained promising preliminary results in a nearly identical version of this task, with the only difference being that an interference control task (the flanker task) was used to prime IC (instead of a GNG task). The task was administered to 14 adolescents with binge eating/purging EDs (10 with BN and 4 with AN-BP). In the flanker task, participants indicated whether an arrow in the center of the screen pointed left or right. Flanking arrows next to the target were either congruent (i.e., pointing in the same direction; 🡪🡪🡪🡪🡪) or incongruent (i.e., pointing in different directions; 🡪🡪🡨🡪🡪). Incongruent arrows thus created a conflict that required IC resources to resolve. **The results showed that, following “rethink” cues, participants had lower negativity ratings when incongruent flankers preceded the image compared to congruent flankers**, indicating that participants reappraised better after IC was primed. This effect did not reach statistical significance [(*F*(1,13) = 2.67, *p* = .12] but had a robust effect size of η2 = .17; thus, this effect will likely reach significance with 60 participants in each group. Because the current proposal focuses on behavioral inhibition (using GNG and SST) and not interference control, we would like to pilot a version of this task using the GNG task. However, if the results do not prove as promising as those with the flanker task, we will carry on using the flanker task to prime IC in the current study as well.

Pilot testing using an analogue sample: In order to assess the feasibility of the procedure and the sensitivity of the tasks, we will first run all of the tasks described in the three studies using an analogue sample of healthy students who score high (N=35) or low (N=35) on a restricted eating scale (assessed via the restricted eating subscale of the Dutch Eating Behavior Questionnaire; DEBQ; van Strien, Frijters, Bergers, & Defares, 1986). We feel confident that this sample is best suited to assess the tasks given that a recent meta-analysis revealed converging evidence indicating that people who are high on restricted eating eat more in response to negative emotions (Evers, Dingemans, Junghans, & Boevé, 2018). Further, in our previous work, we have observed aberrant food-related IC in restricted eaters (Ganor-Moscovitz et al., 2018). These findings suggest that abnormal interactions between IC and emotion are present in restricted eaters. Administering the tasks to a sample of restricted eaters before conducting the study on clinical samples will allow for assessing potential carry-over effects between the tasks and conditions, which will help us to decide on the ideal approach for collecting data with clinical samples. Although referred to here as pilot testing, we note that the results obtained from this analogue sample may lead to three stand-alone publications on IC and emotion processing among restricted eaters and thus provide more deliverables from the current project.

**Statistical Analyses and Expected Results:**

**Study 1**

*Approach:* A mixed-model analysis of variance (ANOVA) with SSRT as the dependent measure, group (restrictive EDs / binge eating/purging EDs / HC) as the between-subject independent variable, emotional block (positive / negative / neutral) and target type (food / non-food image) as the within-subject independent variables will be carried out.

*Within-group effects:* In the restrictive EDs group, SSRT is expected to be **shorter** for food as compared to non-food items (indicating better inhibition following exposure to food images). Importantly, this effect is predicted to be larger in the negative emotional block compared to the neutral and positive emotional blocks. It is further expected that in the positive emotional block, there will be no difference in SSRT following food and non-food image exposure. In the binge eating/purging EDs group, we expect SSRT to be **longer** for food as compared to non-food items (indicating a poorer ability to stop a response following exposure to food images). Importantly, this effect is expected to be larger in the negative emotional block compared to the other two blocks. In addition, no difference between food and non-food SSRT is expected in the positive emotional block. In the HC group, no interaction between emotional block and target type is expected.

*Between-group effects:* We expect that SSRT in response to food images will be longer in the binge eating/purging group compared to the restrictive EDs group and the HC group. We also expect that food image SSRT will be shorter in the restrictive EDs group compared to the HC group. Furthermore, these group differences are expected to be largest in the negative emotional block and absent in the positive emotional block.

**Study 2**

*Data processing:* Pupillometry will be processed and analyzed using CHAP, an open source software for processing pupillometry (Hershman, Henik, & Cohen, 2019). Eye-blinks will be detected and replaced using linear interpolation. In each trial, the mean pupil size will be calculated during the 200 ms prior to the target and will be used as baseline. For each participant, pupil size during the target image time window will be subtracted from the baseline measurement in order to account for individual differences in pupil size.

*Approach:* A mixed-model ANOVA with mean pupil diameter for the target image (after baseline correction) as the dependent variable, group (restrictive EDs / binge eating/purging EDs / HC) as the between-subject independent variable and food type (high / low-calorie food) and trial type (go / no-go trial) as the within-subject variables will be conducted. Only accurate responses will be included. Pupillometry for erroneous responses (commission and omission errors) will be assessed if there will be enough trials to perform such analysis.

*Within-group effects:* In the restrictive EDs group, larger pupil dilation is expected in go trials following the presentation of high vs. low calorie food images. However, we expect that this effect will be attenuated in the no-go condition due to a reduction in pupil size in the high-calorie food condition. In the binge eating/purging EDs group, we expect to find that participants will show an increase in pupil diameter for high vs. low-calorie foods in both the go and no-go conditions.

*Between-group effects:* We predict that the increase in pupil diameter will be larger in response to high-calorie food images among the binge eating/purging group compared to the restrictive EDs group, but only in the no-go condition. In go trials (i.e., when IC is not triggered), we expect to see a similar increase in pupil diameter across both ED groups in response to high-calorie foods, and that this increase will be larger than in the HC group.

**Study 3**

*Approach:* A mixed-model ANOVA with mean negativity rating as the dependent variable, group (binge eating/purging EDs / restrictive EDs / HC) as the between-subject independent variable, and cue type (“watch” / “rethink”) and trial type (go / no-go trial) as the within-subject independent variables will be conducted.

*Within-group effects:* In the “rethink” condition, negativity ratings are expected to be lower when a no-go trial precedes the image compared to a go trial (in all three groups). Negativity ratings after a “watch” condition are not expected to differ as a function of go vs. no-go condition.

*Between-group effects:* We will compare the IC benefit in the “rethink” condition (i.e., the gap in negativity ratings between “rethink”-go and “rethink” no-go conditions between the groups). It is expected that this benefit will be larger for the binge eating/purging EDs group compared to the restrictive EDs and HC groups.

**Power analysis:**

A previous meta-analysis indicated a medium-large effect size for deficits in food-related IC among individuals with binge eating/purging EDs (Hedge’s g = -0.67; Wu et al., 2013). Additionally, in our previous study we showed a medium-large effect size for superior food-related IC in AN-R (η2 = 0.11; Weinbach, Lock, et al., 2019). Further, a previous study reported a large effect size (η2 = .19) for IC suppression on pupil dilation to emotional stimuli in healthy participants (Cohen et al., 2015). Lastly, our preliminary results revealed a large effect size (η2 = 0.17) for the benefit of IC on reappraisal in adolescents with binge eating/purging EDs. Thus, for the power analysis, we used a medium-large effect size estimate of η2 = .09. A power analysis using G\*Power (Faul, Erdfelder, Lang, & Buchner, 2007) showed that for a power of > 80% with an a priori alpha set at 0.05 to study within-between variables interactions in ANOVAs, 30 participants are needed in each diagnostic group. We decided to recruit 60 participants in each group so that our specific EDs subtype analysis (see above) will be sufficiently powered.

**Additional Analyses:**

*Contribution of IC-emotion interactions to disordered eating:* The contribution of the primary measures in each task to disordered eating will be assessed. Primary measures refer to the difference in SSRT to food vs. non-food stimuli in a negative emotional block in Study 1, the average difference in pupil diameter in response to high vs. low calorie foods in the no-go condition in Study 2, and the difference in negativity ratings following a “rethink” cue in go vs. no-go conditions in Study 3. Three main measures of disordered eating will be taken from the EDE-Q: the restricted eating subscale, frequency of binge eating episodes over the past month, and number of purging behaviors to control weight (vomiting + use of laxatives) over the past month. In each study, a multilevel regression analysis will be performed, which will include the primary measure relevant for that study, group, and the primary measure\*group interaction as predictors of the three disordered eating measures. To analyze the follow-up data, the three measures of disordered eating at baseline will be added to the set of predictor variables and the follow-up disordered eating measures will serve as the dependent variables. It is expected that the primary measures will prospectively predict follow-up clinical measures of disordered eating, over and above baseline measurements of these variables.

*Analyses of specific EDs subtypes:*In the primary analyses, we will separate the groups based on disordered eating type (i.e., restrictive vs. binge eating/purging). However, we also plan to assess differences between the specific diagnoses. This is important because if the results of the AN-R group and Atypical AN group are similar to one another, but different from AN-BP and BN, this will provide strong evidence that any abnormalities found in the interaction between IC and emotion cannot be attributed to weight status. This is because while individuals with AN-R and Atypical AN share similar disordered eating patterns, they differ in weight (i.e., Atypical AN are not underweight). In addition, individuals with AN-R and AN-BP do not share the same disordered eating patterns, but both are characterized by being underweight.

*Exploratory correlational analyses:*Exploratory correlational analyses will be utilized to examine associations between the primary measures in each task and clinical/demographic variables, including age, %EBW, illness duration (only in the patient group), emotion regulation difficulties (DERS) and propensity for using reappraisal (assessed via the ERQ). This will allow for an assessment of the contribution of each of these variables to IC-emotion interactions.

*Dealing with comorbid symptoms and diagnoses:*In order to assess potential confounds, such as comorbid symptoms of depression and anxiety which are common in patients with EDs (Bulik, 2002), we will assess if the results change when BDI and STAI are entered as covariates. In addition, the proportion of patients with a comorbid DSM psychiatric diagnosis (e.g., major depression, obsessive-compulsive disorder, post-traumatic stress disorder, etc.) will be assessed using the SCID-5. We will assess if the primary effects remain unchanged when patients with comorbid diagnoses are excluded by using a similar approach to that we had taken in a previous study assessing emotion regulation in adolescents with restrictive vs. binge eating/purging EDs (Weinbach, Sher, & Bohon, 2018).

**Potential Pitfalls, Limitations, and Contingency Plans**

A recruitment rate of 3-4 patients per month is expected based on recruitment rates in previous studies conducted by the PI involving adolescents with EDs in Israel (Weinbach, Perry, Sher, Lock, & Henik, 2017; Weinbach, Sher, & Bohon, 2018; Weinbach, Sher, Lock, et al., 2018). To mitigate the risk of not reaching the target sample according to schedule, the study will be carried out in three independent EDs clinics (see letters of collaboration attached). If the recruitment rate will not be satisfactory, the PI will approach additional EDs centers across the country to offer collaboration on this project.

Limitations of the proposed study include an inability to determine if specific emotions (e.g., disgust, sadness, or anger) have specific influences on food-related IC. However, in light of previous research indicating that individuals with EDs have difficulties labeling and differentiating specific emotions (Nowakowski, McFarlane, & Cassin, 2013), it was decided that this research will consider negative emotions broadly. In addition, the study does not include a pure binge eating disorder group, which limits the ability to generalize conclusions to all ED types characterized by binge eating. However, we have recently found that the association between negative affect and food-related inhibition is stronger among individuals who have binge eating EDs with compensatory behaviors (e.g., BN, AN-BP) compared to those who have binge eating EDs without compensatory behaviors (Smith et al., 2019). In addition, diagnostic crossovers from restrictive EDs to binge eating/purging EDs may take place over time (Eddy et al., 2008). Cognition-emotion interactions may differ in patients who crossover compared to those who do not, and the current studies will have limited ability to detect such differences. However, such crossovers are less frequent among adolescents due to their short illness duration. In addition, we have recently suggested that a deterioration of IC over time may make patients with restrictive EDs more susceptible to engage in impulsive binge eating and/or purging behaviors (Weinbach, Lock, et al., 2019). If so, longer illness duration should be associated with a reduced ability to inhibit a response to food stimuli in the restricted EDs group, a prediction that we will be able to test. Lastly, to mitigate the risk of failed hypotheses, the three studies were designed to answer independent questions. Further, Bayesian statistics will be used to assess null results which can also be interesting in light of the unique research questions and population examined.

**Resources Available for the Proposed Study**

Dr. Noam Weinbach is starting his second year as a senior lecturer (assistant professor) in the Department of Psychology at the University of Haifa. Dr. Weinbach has extensive experience in studying IC and emotion regulation in healthy and clinical populations (particularly in adolescents with EDs). Dr. Weinbach is a certified clinical psychologist with over 8 years of clinical experience working in inpatient and outpatient eating disorder clinics. Dr. Weinbach completed a Fulbright post-doctoral fellowship at the world’s leading center for eating disorder research and treatment at Stanford University led by Prof. James Lock, where he gained hands-on training in integrating basic and clinical research on child and adolescent EDs. At the University of Haifa, Dr. Weinbach has established the Experimental Psychopathology Laboratory and is currently mentoring five graduate students, all of which are engaged in research on how cognitive and emotional functioning impacts eating behaviors and body image. Dr. Weinbach’s laboratory includes three experimental rooms with state-of-the-art equipment and facilities for conducting behavioral experiments in healthy and clinical populations. For the eye-tracking experiment in Study 2, two portable eye-tracking devices will be purchased using the ISF young faculty equipment grant. These will be used for running participants recruited from the sites located in Haifa and Tel Aviv. Another eye-tracking device will be used in the southern site (Beer-Sheva) through a collaboration with the Cognitive Neuropsychology Laboratory at Ben-Gurion University, led by Prof. Avishai Henik (Dr. Weinbach’s PhD mentor). We will make sure that the equipment is similar across all sites and that the experiments are being carried out in similar conditions. Dr. Noga Cohen, who is also a faculty member at the University of Haifa, will collaborate and consult on all technical aspects regarding the design, data collection, and analysis of the eye-tracking study (see letter of collaboration attached). Dr. Cohen is an expert in studying pupil dilation. She was the first to show how IC suppresses pupillary responses to emotional stimuli (Cohen et al., 2015) and is one of the developers of CHAP, a software for the processing and analysis of pupillary data (Hershman et al., 2019).

Additionally, Dr. Weinbach is currently engaged in international collaborations on studies of emotion and IC in EDs, which utilize behavioral, neuroimaging, and EMA methodologies. Prof. Eric Stice from Stanford University will collaborate on the current research project (see letter attached). These world-leading experts will be available to advise on the theoretical and practical aspects of the research project when needed.

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