

Characterizing Acute Exercise Response in Restrictive Eating Disorders

12/5/2024

NCT06213883

Title: Characterizing Acute Exercise Response in Restrictive Eating Disorders
PI: Katherine Schaumberg, Ph.D.

Protocol Title: Characterizing Acute Exercise Response in Restrictive Eating Disorders

Principal Investigator Katherine Schaumberg, Ph.D.
Department: Department of Psychiatry
Address: 6001 Research Park Blvd, Madison WI 53719
Telephone: 608-263-6109
E-mail: kschaumberg@wisc.edu

Point of Contact Katherine Schaumberg, Ph.D.
Department of Psychiatry
6001 Research Park Blvd, Madison WI 53719

A. Project summary

Eating disorders (EDs) are the deadliest of all psychiatric disorders. However, first-line treatments for EDs are effective for only an average of 40% of patients. One barrier to treatment efficacy is the persistence of driven exercise (DEX; exercising in a compulsive manner to control weight and/or regulate affect), a hallmark symptom reported among many of those diagnosed with EDs (37- 80%). Among other negative sequela, DEX is associated with suicidal behavior, poorer treatment outcome, increased comorbid psychopathology, and risk for relapse. As DEX is a poorly understood symptom that plays a key role in ED maintenance, investigating its biobehavioral underpinnings is of critical importance. Existing research points towards both reward (positive valence system) and anxiety reduction (negative valence system) functions of exercise, and the engagement of these systems may vary across individuals. Evaluation of both rewarding and negative reinforcement functions of exercise among those with EDs will improve mechanistic understanding of this ED feature. Elucidating factors that contribute to risk for DEX in EDs is vital to improving ED treatment and will aid in clarifying activity recommendations throughout ED treatment. Further, idiographic assessment of DEX risk and mapping of multiple potential risk pathways (e.g., via negative and/or positive valence systems) could point towards individually tailored intervention targets. The proposed project will recruit adolescent and young adult females (16-25y) with Eds and healthy controls without Eds from two sites (control n = 35, non-control n = 35) to participate in a comprehensive evaluation of physical activity risk and response, with the aim of defining positive valence (reward), and negative valence (avoidance/escape) factors associated with DEX. The current project will (1) examine biobehavioral response to in-lab exposure to PA, (2) develop and validate exercise-based tasks that capture the reward and negative reinforcement value of PA and (3) define variability in positive and negative valence factors associated with exercise among those with EDs. We will comprehensively examine how ED severity, biological and affective markers of PA response, and both exercise-specific and general positive (reward) and negative (avoidance/escape) valence sensitivities associate with PA. Based on task and measure performance, we will refine an assessment battery to identify factors associated with PA. Detailed explication of potential functions of DEX in this study will directly aid in future studies that aim to stratify DEX risk and evaluate whether individual difference factors could moderate DEX risk and response. Data from this study will provide the foundation for exercise prescriptions to be used through the process of ED recovery, and assessment methods validated in this study will be used in future studies (R01s) that examine varying PA prescriptions for individuals at risk for and diagnosed with EDs.

B. Significance & Background

Physical activity (PA) can engage both negative (Asmundson et al., 2013; Matthew P. Herring et al., 2010; Ströhle, 2009) and positive (Greenwood et al., 2011; Guarda et al., 2015; Ströhle, 2009) valence systems identified within the NIMH Research Domain Criteria (RDoC), and the recent addition of the Sensorimotor domain underscores both the importance and underrepresentation of research on PA dysregulation in psychiatric disorders. PA can relate to positive mental health outcomes (Chekroud et al., 2018; Deslandes et al., 2009; VanKim & Nelson, 2013) and is increasingly prescribed as a component of mental health treatment (Carek et al., 2011; Matthew P. Herring et al., 2010). However, among individuals with eating disorders (EDs), a considerable number of patients present with hyperactivity and the symptom of driven exercise (DEx) (Cook et al., 2014; C. Davis et al., 1997; Caroline Davis & Kaptein, 2006; Shroff et al., 2006). DEx is a serious, concerning, and understudied symptom in EDs and is associated with: risk for suicidal behavior (Smith et al., 2013) poor treatment outcome (Dalle Grave et al., 2008), disorder prognosis, and quality of life; obsessive-compulsive traits and symptoms (Caroline Davis & Kaptein, 2006; Shroff et al., 2006); anxiety (K. Holtkamp et al., 2003; Shroff et al., 2006); perfectionism (Shroff et al., 2006); body dissatisfaction (Brewerton et al., 1995); reward dependence (Dalle Grave et al., 2008); dietary restraint (Dalle Grave et al., 2008; K. Holtkamp et al., 2003); anhedonia (Caroline Davis & Woodside, 2002); and hypoleptinemia. (K. Holtkamp et al., 2003; Kristian Holtkamp et al., 2006) At present, we know relatively little about the etiology of DEx or how to manage this symptom in the context of ED treatment and recovery. In addition, we do not understand factors that contribute to the substantial variability in PA among those with EDs, and why only a portion of individuals present with the symptom of DEx. Given the critical need to improve prognosis for those who engage in DEx,¹⁸ enhancing our understanding of risk for and function of DEx is paramount.

Psychological factors associated with exercise behavior. PA levels vary across individuals, and both automatic, affective processes as well as higher order self-control influence PA engagement in the general population (Brand & Ekkekakis, 2018; Ekkekakis et al., 2005; Zenko & Ekkekakis, 2019). In EDs, exercise can become habitual and compulsive (i.e., DEx) (Cook et al., 2014; C. Davis et al., 1997; Caroline Davis & Kaptein, 2006; Shroff et al., 2006) and theories contend that DEx is reinforced by reductions in negative affect and/or by rewarding experiences (Adams & Kirkby, 2002; Bamber et al., 2003; Bratland-Sanda et al., 2011; Cook et al., 2014; C. Davis & Claridge, 1998; Caroline Davis & Kaptein, 2006; Guarda et al., 2015; M. P. Herring et al., 2014; J, 2009; Lichtenstein et al., 2017). Conceptualizing DEx as

a compulsive behavior implies that the anxiety-reduction functions of exercise reinforce PA (i.e., engaging the negative valence system). In contrast, defining DEx through the lens of behavioral addiction or dependence holds that the rewarding properties of PA drive the symptom (i.e., positive valence). In clinically-oriented studies, both obsessive-compulsive and addictive traits associate with DEx, (C. Davis & Claridge, 1998; Shroff et al., 2006) with two studies specifically linking symptoms of obsessive-compulsive disorder (OCD) with DEx in anorexia nervosa (AN) (Caroline Davis & Kaptein, 2006; Shroff et al., 2006).

Biological factors associated with exercise behavior. Understanding biological mechanisms associated with PA can inform how and for whom this behavior may be reinforcing. In the general population, propensity for PA is variable and heritable, (Aaltonen et al., 2017; de Geus et al., 2014; M. P. Herring et al., 2014; Kelly & Pomp, 2013; Klimentidis et al., 2018) and variability in risk for DEx in EDs may mirror this finding. Recent analyses demonstrate a genetic correlation between broad spectrum AN and propensity for engaging in PA (Anorexia Nervosa Genetics Initiative, 2019). Further, an OCD polygenic risk score has predicted DEx in an epidemiological sample of adolescents, (Yilmaz et al., 2019) highlighting variability in DEx-related risk and association between this risk and vulnerability for compulsive behavior.

With regards to physiological functions of exercise, PA promotes changes in the brain via increases in metabolism, oxygenation and blood flow. Basic animal and human research supports that PA is influenced by neurochemical pathways related to both reward (Greenwood et al., 2011; Heyman et al., 2012) and anxiety reduction (Anderson & Shivakumar, 2013; Asmundson et al., 2013; Greenwood et al., 2011; Matthew P. Herring et al., 2010). The majority of current understanding of the neurobiology of PA derives from animal studies, which indicate that PA modulates major neurotransmitters associated with an state of alertness (norepinephrine), the pleasure and reward system (dopamine; DA) and level of anxiety (serotonin; 5-HT) (Matta Mello Portugal et al., 2013). Other neurochemical factors altered by PA include endocannabinoids (eCB), which promote a sense of euphoria and well-being, anxiolytic effects, and decreased sensitivity to pain in humans (Dietrich, 2004). Further, the activity-based anorexia model, a key animal-based model of AN, identifies changes in leptin, a hormone that modulates brain reward circuitry, as predictive of hyperactivity (K. Holtkamp et al., 2003, 2006). As with other psychopharmacological agents, response to PA may differ based on baseline levels of these neurotransmitters, neurochemical factors, and hormones (Hill & Gorzalka, 2009) For some individuals with EDs, elevated biological responsiveness to PA may translate to improvements in affect that are supported by cognitive processes, eventually leading to DEx.

C. Specific Aims

Aim 1: Investigate biobehavioral response to in-lab exposure to PA. **H1:** PA will induce changes in body image, affect, and biological markers among those with EDs; biobehavioral PA response will associate with DEx risk.

Aim 2: Develop and validate exercise-based tasks that capture the reward and negative reinforcement value of PA. **H2:** Measured by task features, reward and negative reinforcement values of PA will exhibit idiographic variability. Performance on these exercise tasks will exhibit both shared and unique variance.

Aim 3: Examine how ED severity, biological and affective markers of PA response, and positive (reward) and negative (avoidance/escape) valence sensitivities associate with PA. Refine assessment battery to identify broad factors associated with DEx. **H3:** Positive and negative valence sensitivities and more marked biobehavioral response to PA will positively relate to DEx, controlling for fitness. **H4:** Multiple measures and domains will inform DEx risk and PA behavior at an idiographic level among individuals with EDs.

D. Study Design

Overview. There are 3 stages to this experimental protocol: 1) Screening Day with screening assessments, 2) take-home questionnaires, 3) Day A, Day B and Day C will consist of computational and exercise tasks, questionnaires, and blood draw. Participants would complete these stages (excluding the take-home questionnaires) across 4 separate days. The take-home questionnaires will be completed at any point between the screening assessment and the first visit day. Day A, Day B and Day C will occur randomly, spaced 6-8 days apart. A diagram outlining tasks on each day is presented in **Figure 1**.

During the Assessment stage, participants will undergo a structured clinical interview to assess current eating disorder symptoms, psychological symptoms, cognitive function assessment, physical status (all measurements and weight will also be collected at the first in-person visit), and demographics. If participants are under 18 years old parents will also be asked to complete a demographics form. This intake will also be conducted with the study #2023-0719, so if the participant decides to participate in both studies within a 3 month period, then the intake data will be shared between studies to diminish participant fatigue and not require participants to complete the same intake twice. The assessment stage lasts 3-4 hours.

During the time between the intake and the first study visit (at least 7 days to allow for activity tracking), participants will also be asked to complete a collection of online self-report measures at their convenience on REDCap. If the participant fails to complete these questionnaires at home, they will be completed on Day B.

During Day A, participants will complete two different task, Task 1: Reward task (rest condition), will include self-report measures, two blood draws immediately before and after completing 30 minutes of rest to examine changes in key neurotransmitters over time, and a post-rest behavioral task. Task 2: Threat task (active condition) will include self-report of state affect, body image, behavioral urges, and cravings, a food challenge task of drinking a milkshake, and 30 minutes of exercise.

During Day B, participants will complete task 1: Reward (active condition), that includes a behavioral task in which participants will work to earn 'points' for exercise and two blood draws, including one immediately before and one immediately after completing the 30 minutes of exercise to examine changes in key neurotransmitters.

On Day C, participants will complete Task 2: Threat (rest condition) , which will include completion of self-report questionnaires, a food challenge task, and 30 minutes of rest. They will also complete the Approach Avoidance Conflict task.

Participants will provide four blood samples total. In order to ensure that blood monoamine and hormone levels are controlled, participants will be asked to refrain from eating after 1:00pm, only eating a provided nutritional supplement (nutrition bar) as a snack before attending Day A and Day B study visit at 4pm. Additionally, task day B will be scheduled during the follicular phase to control for possible menstrual phase effects on the biological response to exercise. Menstrual phase will be further clarified and controlled by the collection of blood samples on Task Day B to quantify estradiol levels. Participants would also complete a reinforcement learning task following Day A and Day B to examine the acute impact of exercise on reinforcement learning mechanisms. Day A, Day B, and Day C will each last ~2 hours.

Lastly, participants will be provided with an accelerometer to wear for 7 days between the screening visit and their second visit to objectively determine average levels of physical activity.

Study Population

Participant recruitment. Participants will include 100 (50 controls and 50 non-controls) female adolescents and young adults aged 16-25. In order to achieve these enrollment goals, up to 300 individuals could be recruited and screened for eligibility. Participants will be recruited

to UW primarily through the UCSF Eating Disorder Program (EDP) and UW-Madison EMBARK Lab. Also, from general community-based advertising (e.g., flyers, postcards, brochures, campus-wide emails, social media platforms, etc.). Recruitment will include the use of social media platforms to post study information in relevant groups or communities, with administrator approval, to broaden participant outreach. We would also have focused networking with local mental health providers, including providers within Wisconsin Psychiatric Institute and Clinic (WisPIC), as well as outside of the UW settings (e.g., at Community Mental Health Centers, private practices, etc.) to notify them of the study and provide materials (e.g., study brochures and postcards) to them that they would post in their facility. UCSF will include flyers for the study in their recruitment packets, and any family/patient who presents to the EDP clinic and is interested in research opportunities can request the packet to take a look at the ongoing studies. Interested participants would then contact us to learn more about the study.

Inclusion/Exclusion Criteria. Inclusion criteria will be 1) females age 16 - 25 years of age, 2) Either healthy controls with no eating disorder, psychological pathology, and meets all health related criteria or meeting mild to moderate; or in partial remission criteria for DSM-5 restrictive-spectrum eating disorders (Anorexia Nervosa, Atypical Anorexia Nervosa, Other Specified Eating Disorder, Purging Disorder), 3) English speaking, 4) medically healthy and stable for outpatient treatment, and 5) Been cleared by a medical personally to participant in an exercise study. Medical clearance will be via signed waiver from a Physician or Advanced Practice Provider (i.e. nurse practitioner). As part of medical clearance, each ED participant will need to have a basic metabolic panel in the last year with no levels indicating concern and no major deterioration in ED psychopathology. Additional clearance is needed for ED participants with BMI <17 and/or purging >2x per week. See attached Medical Clearance form for all clearance criteria.

Exclusionary criteria include: 1) Severe ED: BMI <15; reported intake on Eating Disorder Examination <1000kcal daily; purging >1 per day; participants under the age of 18 with less than a 75% expected body weight determined by BMI <18 2) ED related hospitalization in the past 1 month 3) Any endorsed medical concerns related to physical activity (as probed in the phone screening questions) regarding cardiovascular, pulmonary, or metabolic disease. Participants would not be excluded if they report this condition being "controlled" or "addressed" through medication or lifestyle change, such as regular exercise. 4) major medical disorders (such as cancer, AIDS), 5) physical discomfort or difficulty with blood draws, 6) psychotic

disorders, 7) intellectual disabilities, 8) developmental disorders, 9) active substance use disorders, and 10) pregnancy. Psychiatric medications will not be exclusionary, as long as the medication has been stable for at least 4 weeks. Acute sedatives / pain killers (e.g., benzodiazepines, opioids) and prescription stimulants (e.g., methylphenidate, amphetamines) would not be permitted for the full day prior to the laboratory session. The noted short-term medication holds would only apply to subjects taking the noted medications in cases used to treat ADHD or other psychiatric conditions. Medication prescription use will be modeled as a covariate. See below for detailed exclusion criteria.

Due to safety concerns, participants with these conditions will be ineligible to participate:

- Resting heart rate <60 beats per minute (assessed at screening visit)
- Low blood pressure (<90/60), (assessed at screening visit)
- Major medical disorders (e.g., HIV, cancer)
- Daily cannabis use
- History of light headedness or fainting during blood draws or physical activity
- History of chest pain during physical activity
- Bone, joint, cardiac, pulmonary, metabolic, or other medical conditions that may be worsened by physical activity (e.g., COPD, diabetes, hypertension) that is not currently addressed via medication or lifestyle change.
- Physical disabilities that prohibit task performance (such as blindness or deafness)
- Any other condition that the investigator believes might put the participant at risk

Online survey screening.

Initial screening for eligibility will occur in two phases. First, an online survey screening will be conducted to ensure a high probability that participants are eligible for the study. The online survey begins with a description of the study. This online survey screening will assess the presence of an eating disorder symptoms, and transportation capability to WISPIC. The online survey screening will also assess other possible exclusionary criteria such as medical disorders and difficulty with physical activity. If the participant meets probable inclusion criteria, the research coordinator will call the participant to schedule them for phase-two of the screening process.

For WisPIC patients who see a flyer or hear about the study from a WisPIC clinician, this online screening might be done in person. That is, providers in WisPIC may tell a patient about the study. If the patient indicates a preference for meeting with the research staff to talk about

the study while the patient is already in the clinic, we would accommodate this request by telling the patient about the study, and if she is interested, we would do the screening at that time.

Informed Consent Process. The participant will first be given a written and verbal description of the study and informed consent. The PI or designated staff will discuss the informed consent form with the subject volunteer. The consent process will take place in a quiet and private room. Subjects may take as much time as needed to decide about their participation and may take the document home if desired. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and follow-up requirements of the study. Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. No research related procedures will be performed prior to obtaining informed consent. All signatures and dates will be obtained. A copy of the consent will be given to the participant. The informed consent process will be documented in each subject's research record. If participants are under 18 years old parents will sign the informed consent along with the participant.

Use of email and phone number to communicate. We will ask participant's permission to use their email address and phone number so we can schedule and confirm research appointments for this study. We include language in the phone screen and the consent document consistent with UW IRB policy for use of emails and phone number. Use of either form of communication is optional.

screening assessment. Participants who meet eligibility based on the online screening assessment will complete several interviews, questionnaires, neurocognitive tests, and biobehavioral tests to determine psychological and medical history, current life functioning, stress experiences, individual traits, and demographic variables. The purpose of the assessment is to 1) establish inclusion / exclusion criteria, 2) thoroughly clinically characterize the samples for the purposes of generalization, 3) collect quantitative clinical characteristics that could be used as covariates if necessary. The first visit will be ~3 hours, during which they will complete the bulk of these measures and all interviews. The assessments will be completed by research staff trained by the PI to administer the assessments. UW participants who also enroll in 2023-0719 POWERED will have their screening assessment data shared between studies to reduce participant fatigue and minimize attendance to one intake. Only the data collected in the

assessments under “Structured clinical interviews” will be shared between studies. The data will not only be shared from this study to POWERED, but from POWERED to the current study. Data will be shared securely by being retained on REDCap and will be labeled separately with individual studies IDs. Furthermore, the current study will be protected by a Certificate of Confidentiality from the National Institutes of Health (NIH). This means that even if the police or courts ask to look at the data we have collected, we will not share any information that would identify you as a participant in the study. Once issued, the Certificate will retroactively cover information collected since the beginning of the study. Data will not be shared if the participant only enrolls in one of the two studies or if the enrollment gap between the two studies is greater than three months.

Structured clinical interviews:

Eating Disorder Examination: Provides a measure of the range and severity of eating disorder features (White, Haycraft, Goodwin, & Meyer, 2014)

Columbia Suicide Severity Rating Scale (CSSRS): measures the severity of current suicidal ideation (Posner et al., 2011)

Diagnostic Interview for Anxiety, Mood, and OCD and Related Neuropsychiatric Disorders (DIAMOND): measures current psychological functioning and drug use history (Tolin et al., 2018).

Data Collection Form: Internal form used to collect study specific information such as handedness, age, race/ethnicity, medications, exercise activity, menstruation history, medical status and conditions, Tanner staging for participants under 18 years old, etc.

Mini-Mental State Exam (MMSE): widely used test of cognitive function; it includes tests of orientation, attention, memory, language, and visual-spatial skills (Khanfer et al., 2013).

The structured clinical interview diagnostic assessments would be delivered by trained research staff.

Objective Assessment:

Measures of weight and height will be obtained by research coordinators at the time of screening visit. Weight and height will be measured in light street clothes (participants will be asked to bring shorts and a light t-shirt for weight measurements) without shoes.

Self-Report Measures: (*marks the take-home questionnaires)

These measures will be administered via an iPad linked to UW's secure REDCAP database system.

Mini Menstrual Questionnaire (MMQ): Form generated in-lab to assess current and history of menstruation and artificial hormone use.

MMQ-Shortened (MMQ-S): 2-item measure derived from the MMQ to address current menstruation.

**Eating Pathology Symptom Inventory:* a self-report questionnaire that includes 45 items covering 8 subscales: Body Dissatisfaction, Binge Eating, Cognitive Restraint, Purging, Restricting, Excessive Exercise, Negative Attitudes toward Obesity, and Muscle Building (Forbush et al., 2013)

**Obsessive-Compulsive Inventory – 12 (OCI-12):* self-report measure of obsessive-compulsive disorder symptoms (Abramovitch et al., 2021)

**The Drive for muscularity scale:* A measure of people's drive to be muscular. (McCreary & Sasse, 2000)

Compulsive Exercise Test: Assesses 5 different subscales, avoidance and rule-driven behavior, Weight control exercise, Mood improvement, Lack of exercise enjoyment, and Exercise rigidity (Meyer et al., 2011)

Exercise Dependence Scale: Assesses exercise dependence following the DSM-IV criteria for substance dependence (Hausenblas & Downs, 2017)

Analogue Exercise Decisions: Presents options to have exercise only when paired with eating (e.g. 10 mins of exercise if eating 100 kcal snack) or exercise vs. another reward (e.g. exercise for 30 mins vs. earn \$5) to determine drive for exercise

Athlete's Relationship with Training Scale (ART): Assesses unhealthy training practices which could be associated with an eating disorder (Chapa et al., 2018)

Function of Exercise (adapted from Wedig & Nock, 2010): Assesses different functions of exercise that individual may endorse.

**STAI:* measures an individual's trait and state anxiety (Spielberger, 2012)

**Behavioral avoidance/inhibition (BIS/BAS) scales:* measure two motivational systems: the behavioral inhibition system (BIS), which corresponds to motivation to avoid aversive outcomes, and the behavioral activation system (BAS), which corresponds to motivation to approach goal-oriented outcomes. (Carver & White, 1994)

**Habit Index:* measures self-reported perceptions of habit strength for an identified behavior. (Verplanken & Orbell, 2003)

**Sensitivity to Punishment and Reward:* assess reinforcement sensitivity according to very specific cues and situations in individual with eating disorders (Torrubia et al., 2001)

**Intolerance of Uncertainty Scale:* terms relating to the idea that uncertainty is unacceptable, reflects badly on a person, and leads to frustration, stress, and the inability to take action (Carleton et al., 2010)

**Fear of Negative Evaluation Scale:* self-rated scale used to measure social anxiety (Leary, 2011)

**Frost Multidimensional Perfectionism Scale (FMPS):* multidimensional assessment of perfectionism: concern over mistakes, personal standards, parental expectations, parental criticism, doubts about actions, and organization. (Stöber, 1998)

**Anxiety Sensitivity Index:* measure 'fear of fear,' that is, the degree to which a person believes that physical symptoms of anxiety have negative consequences (Taylor et al., 2007)

**SUPPS-P:* measure impulsivity across dimensions of the four factor model of personality: premeditation (lack of), urgency, sensation seeking, perseverance (lack of). (Cyders et al., 2014; Whiteside & Lynam, 2001)

**Beck Depression Inventory (BDI):* measures the severity of current depression (Beck et al., 1996)

**Difficulty in Emotion Regulation Scale (DERS):* assesses multiple aspects of emotion dysregulation (Gratz & Roemer, 2004)

**ED100k-Plus:* Assesses both current and eating disorder (ED) history using measures including ED100k (Thornton et al., 2018), Eating Disorder Diagnostic Scale (EDDS; Stice et al., 2004), and the Eating Disorder Examination Questionnaire (EDE-Q; Mond et al., 2004).

EMA 1 & 2: lab-generated measures to assess eating disorder behaviors and cognitions both immediately before and after attending study visits.

**Eating Disorder Fear Questionnaire (EFQ):* Scale used to assess fear of weight gain, social consequences, personal consequences, physical sensations, and social eating (Levinson et al., 2019)

**Personal Health Questionnaire- 9 (PHQ-9):* Scale used to assess levels and severity of depression (Kroenke, K., Spitzer, R. L., & Williams, J. B., 2001)

**GAD-7:* screens for General Anxiety Disorder and assess severity of the disorder (Spritzer et al., 2006)

**DSM-5 Level 1 Cross-Cutting Symptom Measure- Adult Report:* assesses mental health symptomology across psychiatric diagnosis in adults (Narrow et. al, 2013)

**DSM-5 Level 1 Cross-Cutting Symptom Measure- Child Report:* assesses mental health symptomology across psychiatric diagnosis in children and adolescents (Narrow et. al, 2013)

**World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0):* assesses difficulties due to physical/mental health conditions (Ustün et. al, 2010)

**Revised Child Anxiety and Depression Scale – 25 Youth Self-Assessment (RCADS-25 Youth Self-Assessment):* measures levels of anxiety and low mood (Ebesutani et. al, 2002)

**Research Subject:* collects participant demographic data (NIMH Data Archive)

**Genomics Subject:* collects participant demographic data (NIMH Data Archive)

Biobehavioral Task

Two-Step Decision Task: Two choice options A1 and A2 are available, which lead to two intermediate outcomes B1 and B2 at different probabilities. Intermediate outcomes B1 and B2 lead to rewards with different probabilities. Participants are instructed to try to earn as much treasure as they can.

Work for Exercise: The participant selected a computer screen icon that represented the reinforcer of her choice, opportunity to exercise, or cash. Once this was selected, the participant was required to continue to work for that reinforcer until that trial was completed (or until she stopped working for the session). After completion of a trial, the participant had 8 s to decide which reinforcer she would work for at the next trial. She could change her selection at the beginning of a trial but not within a trial (i.e., after she had pressed the keypad multiple times). The work required in the first trial for each reinforcer was 50 presses; however, the work requirement increased each subsequent trial that reinforcer was selected. At the first trial, a given reinforcer was chosen, 50 presses were required. The second time it was selected, 250 presses were required, and then 450; 650; 850; 1,050; 1,250; 1,450; 1,650; and 1,850 presses were required to complete the trial. If the participant selected the alternative reinforcer, it would require 50 button presses, then 250, 450, etc. Thus, the work requirement for each reinforcer increased independently during the session. To earn the maximum amount of exercise or cash,

the participant had to perform 9,500 keyboard finger presses within the 40-min period. Fewer presses were required if choices were distributed between the two reinforcers. Patients were informed before beginning the experiment about these procedures. At the end of each trial, an icon representing the earned reinforcer was displayed on the right side of the computer screen. At the end of the 40-min session, total earnings were displayed (Klein et al., 2010)

Physical Activity Assessment

Objective physical activity assessment will occur for a one-week period using an accelerometer (a small matchbox size device). Participants will be provided with an accelerometer (Actigraphy GT3X+, Actigraphy, Pensacola, FL), which they will be required to wear as a watch for one week. Participants will be given instructions on the proper use of the accelerometer and will also be given a physical activity log to complete during the week.

Task Procedures

Effort Expenditure for Rewards Task. Participants have to select between an Easy and a Hard task. Both tasks involve pressing the Spacebar for a predetermined amount of time. The Hard task offers more money (in this script: 8 variable amounts) but is harder and takes twice as long. Participants make their selection knowingly under 3 different win probabilities (aka they might not win money even if they are successful; particularly not if the win probabilities are low). By default, E selects the Easy task and I selects the Hard task. The task would last approximately 22 minutes and will be completed on Day C study visit.

Aim 2 procedures.

Negative Valence System (NVS) Exercise Task (Figure 1) This task will capture PA to avoid/escape from ED cognitions and associated distressing emotions; it is designed to be ecologically-valid and relevant to an ED population. Individuals will report baseline state body image, affect and urges to engage in compensatory behaviors. Participants will be asked to ingest a calorically-dense milkshake, a common task component in ED research, (Jansen, 2016) to elicit moderate levels of anxiety and distress and examine negative reinforcement processes. After finishing the milkshake, individuals will again report state affect, urges to engage in a range of compensatory behaviors (e.g., fasting, purging, exercise), and associated expectancies. Participants will then either 30 min quiet rest (day c) or will have the opportunity

to exercise for up to 30 min (day a) on a stationary bike at a self-paced rate (>80% maximum heart rate). We will evaluate self-reported affect and state body image at 5-min intervals. We will also capture variability in exercise intensity (e.g., heart rate, distance covered, time spent exercising) over the exercise session. After participants are done exercising they will be asked how many calories of the milkshake they believe they burned during the exercise phase.

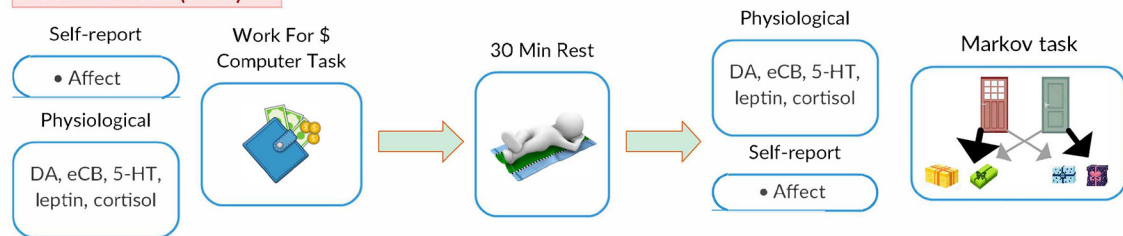
Figure 1. Positive and Negative Valence System (PVS) Exercise Task

Participant Flow through Study Screening Day

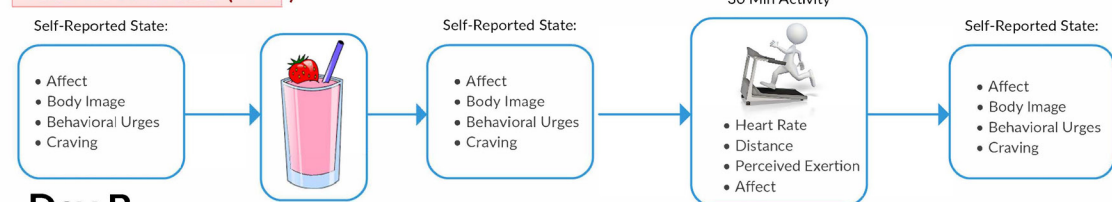


Day A

Task 1: Rest (PVS)



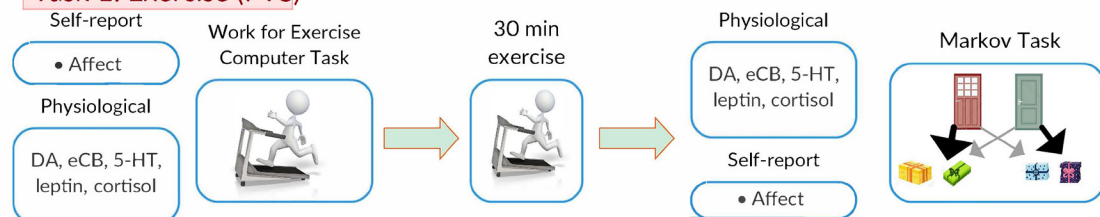
Task 2: Exercise (NVS)



Day B

Self-report measures part 1

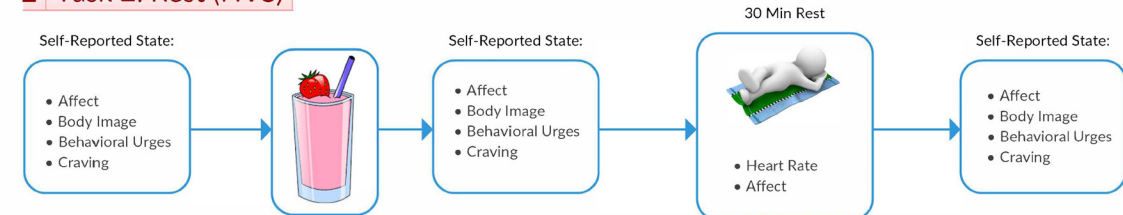
Task 1: Exercise (PVS)



Day C

Self-report measures part 2

2 Task 2: Rest (NVS)



*Day A-C order will be randomized across participants

Positive Valence System (PVS) Exercise Task (Figure 1) This task will capture rewarding aspects of exercise and biomarker engagement during structured exercise. Participants will complete the two-stage Markov task, an probabilistic learning task that requires individuals to use either model based or model free learning to maximize wins and minimize losses. Participants will complete an exercise session (day b) vs. distraction control (day a) which are counterbalanced across study days with the negative valence system task. In the positive valence task exercise (day b) condition, participants will complete a behavioral economic reward task capturing willingness to work for exercise.(Klein et al., 2010). Participants will then be asked to ride a stationary bike for 30 min (regardless of points ‘earned’) at a brisk pace (70% maximum heart rate). Participants will provide blood samples pre- and post-task during the exercise and rest condition to evaluate engagement of key neurotransmitters (DA, eCB). Participants will self-report state measures of drive to exercise, exercise expectancies, craving, and affect throughout both the exercise and ‘rest’ conditions (baseline, 5-minute intervals during the task, post-session). After the exercise and rest conditions, participants will repeat the Markov task with novel stimuli to assess task-induced changes in reward responsivity. Reward responsivity in probabilistic learning tasks has previously been associated with affective disorders (e.g., major depression) as well as acute dopaminergic agents, (Pizzagalli et al., 2008) thus, we expect that shifts in reward learning after exercise will compliment self-reported affective changes and changes in state biomarkers in identifying the degree to which exercise engages a reward system across individuals. We also expect individual differences in the degree to which the probabilistic learning task (i.e., measure of non-specific reward responsiveness) and behavioral economic reward task (i.e., measure of PA-specific related reward) will positively correlate.

Blood/biological Analysis

Blood samples will be de-identified and coded with a study ID code. Coded blood samples will be processed and frozen until shipped by a certified biohazard shipper to labs to conduct assays. Any remaining blood samples will remain frozen and banked for future unspecified analyses.

Study Compensation

Participants will be compensated for their time and participation. They will receive \$30 for the assessment phase, and \$240 plus task bonus up to \$30 after completing procedures on Day 2 and Day 3. For a total compensation between \$270 to \$300. WISPIC will not be held

responsible for replacing lost electronic gift cards. Participants may elect to be picked up and transported to study visits at no cost to them.

E. Data and Safety Monitoring

Data Acquisition, Collection, Transmission, and Entry

Self-report, behavioral, biological, and assessor-report data will be collected using both standardized paper forms, forms presented on a computer, blood draw, tasks on computer (for behavioral data), and real-time wearables (heart-rate and accelerometry) that all will be identified with the participant's study ID. The codes that link the name of the participant and study ID will be kept confidential in secured cabinets. Paper data will be entered into the computer independently by two different research staff trained to perform data entry, and the Data Manager will employ a verification program to determine and correct any discrepancies based on source data. The computer data, behavioral data, biological data, and data from wearables will be stored on a secure server and downloaded by the Data Manager, who will then transfer the data to SPSS and JMP files and check for missing data. The computer(s) used to collect data will be kept in a locked office or locked cabinet when not in use. Biological and behavioral task data are only identified via subject ID. Data identified by subject's study ID are entered into the computer independently by two different research staff trained to perform data entry, and the Data Manager will employ a verification program to determine and correct any discrepancies based on source data. REDCap will be used to transfer data between the current study and 2023-0719 by saving the completed survey and reuploading the completed survey to the other project.

Study data will also be shared with the National Data Archive (NDA) as a part of the grant agreement. Data will be completely de-identified prior to submitting data to the NDA and each participant's data will have a Global Unique Identifier (GUID) created.

Data used to create the GUIDs include the participants full name (first, middle, and last), sex, date of birth, and place of birth. The NDA GUID tool used to input this data will create one-way hashes are securely transmitted to the NDA cloud database, which uses the same secure transmission protocol (via a secure web service) to return random alphanumeric strings called GUIDs. Data that is used to create the GUIDs are never stored by the NDA.

GUIDs and their matched hash codes are only ever stored in the secure database maintained by NDA's security team in the Amazon cloud.

Researchers with NDA data access who are not submitting data will not have access to the NDA GUID Tool. They are unable to use birth certificate data to generate GUIDs and identify themselves or others in the NDA database.

Storing Samples and Data for Future Research

We plan to keep study data and remaining samples for use in future research studies to promote tenants of open science, including rigor and reproducibility in our work. We will store data and samples indefinitely. Examples of “data” would be blood samples and assessment data. De-identified data will be added to a repository on OSF.IO at the end of this study. This study would represent the first study in the repository. Data will be coded with a unique subject ID and no identifying data. If data is added outside of the current study a protocol change will be submitted. Furthermore, data collected by the #2023-0719 study at the screening assessment will be shared with this study, as will this study’s screening assessment data be shared with study #2023-0719. We may collaborate with others outside of UW and UCSF involving other eating disorders studies. Individuals wishing to collaborate or access the repository would submit a query and analysis proposal, which will be reviewed by senior personnel at the EMBARK lab. We would require appropriate IRB approval, as necessary, for secondary data analysis via the repository. After review, we would provide access to de-identified data via the OSF repository. Any data shared with outside collaborators would be labeled with the unique study code only and no identifying information. The link between the code and identifying information will be kept at UW and UCSF sites and accessible only to the research team. We have no plans to at this time to submit blood samples to a larger repository, though we will follow genomic data sharing policies if and when genomic samples are processed.

Data will be stored in the NDA for indefinite period of time. Data is coded with a GUID, which is a de-identified ID.

Procedures in Place to Ensure the Validity and Integrity of the Data

The research coordinator has at least a bachelor's level education and experience as a coordinator for double-blind RCTs. Under the direct supervision of the PI/Co-I, the research coordinator’s conducting the blind assessments will receive 1 month of training on the study measures, clinical interview, and exercise tasks. Training includes viewing videotapes, observation of interviews, ratings and tasks, co-rating, and interviewing with the supervisor present. To conduct interviews for this study, it is required that the rater complete three consecutive conjoint interviews on which diagnoses are in complete agreement with those of more experienced raters. After training, reliability will be spot-checked on a quarterly basis. Further, all interviews would be audio recorded and 20% would be evaluated for reliability. These procedures have been shown to ensure reliability of diagnoses. As for training on the other scales and tasks, the PI first gives a training session on the background of the particular scale/task and how it is to be completed. Then the staff member observes the completion of the

assessment by an experienced rater on at least three occasions. Afterwards, the staff member completes the assessment in the presence of an experienced rater on at least three occasions, with feedback given each time until the supervisor is confident that the person understands the assessment and completes it properly. Thereafter, assessments are checked on a continuous basis for appropriate completion, and constructive criticism is given as necessary. Staff members also undergo a refresher on assessments every 3 months.

Each research staff member is instructed on the timing of assessments for each individual. Checklists are used to ensure that assessments are obtained at the time indicated. The Data Manager will also review assessments as they are completed in order to ensure their completion and following of the timeline.

The research assistant/coordinators running the task will have the same training on computerized tasks as described above. Task data (timing data, behavioral data from the task) will be stored on a secure server and downloaded by the Data Manager into R. The computer(s) used to collect data will be kept in a locked office when not in use. For paper assessments, the research assistant reviews the assessments for missing/out-of-range values and then brings them immediately to the Data Manager to review as well. If any missing or inaccurate values are found, the participant will be asked to complete those again at a later visit. Paper data will be entered into the computer independently by two different research staff trained to perform data entry, and the Data Manager will employ a verification program to determine and correct any discrepancies based on source data. If the Data Manager notices recurring data entry errors, he/she will inform the person(s) responsible and retrain them as necessary. Prior to statistical analyses, the Data Manager will check the data for mislabeling, missing data, out-of-range data, etc., and change/correct as appropriate based on source data. The Data Manager will also assign study condition per study ID for analysis purposes. A master data set will be created with at least two backups. One of these backup disks will be given to the statistician, with a data assessment dictionary, for analysis. The master key linking participant data to their identifying information would be destroyed after study completion and data analysis. However, we would retain informed consent sheets (which contain identifying information) for 6 years. Though in the absence of the master key, the identifying info on these sheets could not be linked to participant data.

Collection and Reporting of Adverse Events (AEs) and Serious Adverse Events (SAEs).

The initial AE report needs to be completed by the staff person who first received the information that an AE occurred. The study fellow, if necessary, will follow up with the participant and document this in the participant's clinical notes. The reports with supporting materials are then collected and reviewed weekly by the PI and research staff. The PI and co-investigators will determine whether an event meets the criteria for a SAE or unanticipated problem involving risks to subjects or others (UPIRSOs). The PI will report AEs to the IRB once a year at continuing review, and to VHH during the annual progress report, in compliance with institutional policy. SAEs or UPIRSOs will be reported to the IRB and VHH PO within 10 days of learning of the event. Institutional policy states that an AE should be considered an UPIRSO if it was unanticipated, related to the research, and involves some increased risk to the subject. If an event is reported as an SAE, the initial report will be followed by submission of a completed SAE report to all institutions. Outcome of SAEs, as they relate to participant safety and the safety of future participants, will be periodically reported to VHH. A summary of all AEs that occurred during the previous year will be included in the annual progress reports to VHH. The study investigators will follow all AEs to the point of a satisfactory resolution. A study participant may be withdrawn from the study if the investigative team determines it is the best decision in order to protect the safety of the participant. In the event that a participant either withdraws from the study or the investigator decides to discontinue a patient due to an SAE, the participant will have appropriate follow-up medical monitoring. Monitoring will continue until the problem requiring hospitalization has resolved or stabilized with no further change expected, is clearly unrelated to study interventions, or results in death. The IRB communicates recommendations and decisions to the PI in a timely manner. In the event that the IRB takes an action that impacts the day-to-day operations of the trial (e.g., suspends recruitment, halts the trial.), the PI will report those actions to the VHH officer both verbally and in writing.

Data and Safety Monitoring (DSM) Plan

The PI will be ultimately responsible for monitoring the safety and efficacy of the trial, executing the DSM plan, and complying with reporting requirements. Any adverse events (AE) that occur will be monitored in an ongoing way, as well as being formally reviewed by the investigators and at each 6-month review meeting. Whether risks of participation remain acceptable under the present protocol or modifications to the protocol are necessary while still maintaining scientific integrity of the project will be determined. AEs will be documented and will be included in yearly progress reports submitted to VHH. Any data accrued will be summarized

and reviewed by the study investigators at each 6-month review meeting and after 50% of participants have been enrolled. Interim analyses will not be performed unless clinically indicated. All SAEs, such as death, hospitalization, will be reported to the IRB, FDA, and VHH under expedited reporting in accordance with VHH policy. The procedures for this reporting include written documentation using the clinical notes related to the adverse event and specific forms detailing the event with a sign-off by all appropriate supervisory personnel.

F. Risks and Benefits

Potential risks

Assessment of mental health and eating disorder. One potential psychological risk of the proposed study is the possibility that some participants might experience distress or become offended when asked questions pertaining to eating disorder and mental health history. Nevertheless, there is a specific protocol, should a participant become distressed as a result of participation in this study. This is discussed in detail below.

Distress related to eating. The act of eating may elicit anxiety/distress among participants. Participants are able to take up to 20 minutes to drink their milkshake and will be given breaks if needed. They will not be pressured to continue if they wish not to. Nevertheless, there is a specific protocol, should a participant become distressed as a result of participation in this study. This is discussed in detail below.

Procedures for suicidal participants. Individuals who are actively suicidal, defined as intending to hurt or kill themselves in the acute time frame, will receive immediate crisis counseling services by the 24-hour UCSF or UW nurse on call for such emergencies. An on-site licensed clinical psychologist involved with the study is also available to assist research staff during study visits. The treatment response may include hospitalization. These participants will be ineligible for the experimental sessions.

Transient distress in relation to conditioning task. Another potential risk is that the conditioning paradigm procedure will elicit anxiety/distress. Participants are able to quit the task at any time by indicating to the research staff that they wish to do so. They will not be pressured to continue or restart if they wish to quit the task or study.

Cardiac event related to exercise. Physical activity can acutely and transiently increase the risk of sudden cardiac death and acute myocardial infarction in susceptible persons. Although

this study recruits low-risk subjects, the plan to minimize risks and ameliorate an emergency situation is detailed below.

Personal health information/Loss of confidentiality. With all research participation, there is a risk that personal information obtained from research participants will be mishandled, and confidentiality may be compromised. Additionally, as mandated reporters, if we learn about a situation the participant is involved pertaining to child abuse or elderly abuse, we may have to break confidentiality.

GUIDs utilized by the NDA are also linked to other studies who have submitted their data to the data archive. Although GUIDs are deidentified ids, the link between different studies may increase the loss of confidentiality as the combination of information may lead to increased identifiability.

Blood draw. The risks associated with the blood draw itself include discomfort, bruising, redness, or bleeding at the needle puncture site.

Withholding Benzodiazepines and/or prescription stimulants. Possible withdrawal symptoms include increased anxiety, insomnia, fatigue, body aches, and a general feeling of unhappiness.

Adequacy of protection against risks: Procedures to minimize risks identified in the previous section are outlined below.

Assessment of eating disorder: Given the vulnerability of the sample, the participants will be told that they do not have to answer any questions they do not want to, and that they can withdraw their participation or take a break whenever they want to. Additionally, if in ascertaining a participant's current condition, the need for clinical intervention is determined, the appropriate mental health referral will be arranged.

Distress related to eating. Participants will be told they can withdraw their participation or take a break as needed when they are asked to ingest the milkshake. Additionally, if in ascertaining a participant's current condition, the need for clinical intervention is determined, the appropriate mental health referral will be arranged.

Transient distress in relation to conditioning task. With regard to potentials risks regarding anxiety/distress, as noted above, the participants are able to quit the tasks at any time. Participants who wish to terminate early due to distress will be assessed by a clinical psychologist

(the PI) and appropriate recommendations will be made (e.g., for individual therapy, instruction on coping and affect reduction skills, etc.).

Cardiac event related to exercise. Individuals at increased risk for cardiovascular events (ex. Prior experiences with chest pain during exercise, history of heart disease, etc. as evaluated by the PAR-Q during phone screening) are not eligible to participate in the study. Throughout the exercise intervention, physical risks will be minimized since research personnel will monitor heart rate through a heart rate monitor strapped to the chest prior to, during, and after each session. Subjects will be encouraged to communicate any discomfort, pain, exhaustion, dizziness, or light-headedness and they will also be informed that they can terminate the task at any time without penalty. If these alarming, non-emergency symptoms appear, research personnel will instruct the participant to immediately discontinue exercising and to sit or lie down while the staff member offers water and a snack. Blood pressure and heart rate will be monitored until normal, and the participant will be compensated and sent home, ineligible to continue participating in the study. UW sites are equipped with a telephone and an AED located in the same room as testing equipment. In the case of an emergency (fainting, unresponsive participant), research personnel will immediately call 911 to transport to a local hospital. Unanticipated problems will be evaluated by the PI, and reported to the UW IRB if deemed a reportable event.

Personal health information/Loss of confidentiality. Standard practices will be used to protect participant confidentiality and personal health information, including removing identifiers from all data collected, using only numbers to identify participant data, and keeping all data files when not in use in a locked filing cabinet behind a locked office. No names or other identifiers will be used in computerized data files. Participants would be notified in the informed consent that confidentiality might be breached in the case of suicidal ideation in order to protect the participant's safety. Regarding data submitted to the NDA, data which contains direct identifiers will never be stored by the data archive and data will only be linked to a de-identified id called the GUID. However, indirect identifiers like date of assessment will be shared with the NDA. The NDA will also not attempt to identify any of the participants. The NDA GUID Tool uses an SHA-512 hashing algorithm to generate a one-way hash. This hash algorithm has not been cracked and should not be reversible, meaning there is no way to identify a participant based on the hash created by the tool. GUIDs and their matched hash codes are only ever stored in the secure database maintained by NDA's security team in the Amazon cloud.

Blood draw. To minimize hazards during blood draw, only study staff trained to perform blood draws will be allowed to collect the sample from the participant. To lessen discomfort, blood

draws will occur in different arms before and after exercise. To protect the identity of research participants and prevent them from being re-identified, all samples will be coded upon collection.

Withholding Benzodiazepines and/or prescription stimulants. Possible withdrawal symptoms include increased anxiety, insomnia, fatigue, body aches, and a general feeling of unhappiness. Participants are advised to talk with their healthcare provider and determine if withholding medication is acceptable and safe before entering the study. Participants will be told of the possible withdrawal symptoms above and advised to contact their physician or 911 in the event of an emergency if any symptoms appear.

G. Benefits to Subjects

Potential benefits of the proposed research to the subjects and others. We do not expect participation in this study to benefit the individual participant directly. However, if the study is successful, the knowledge gained could lead to improvements in treatment efficacy, which would have a major beneficial impact on others. This information is conveyed to participants in the informed consent.

H. Statistical Plan

Power Analyses and Targeted Sample Size.

Power analyses were completed with the GLIMMPSE program (Kreidler et al., 2013), with primary power estimated on Time X Exercise interaction terms within the exercise tasks. To estimate moderate effect sizes in change in affect and biomarkers, we estimated models with 10 (affect and body image variables assessed every 3 minutes) and 2 (pre-post assessments) repeated measurements, controlling for a single, normally distributed covariate. We assumed within-participant covariance of 0.8 for repeated measures over time, with a decay rate of 0.1 and type 1 error of 0.05. We estimated changes assuming standardized normal distribution in outcome variables and a small-to-moderate interaction effect ($d = 0.3$). Power to detect effects over time with the proposed sample ($n = 60$ individuals with ED, $n = 30$ HC participants), was deemed adequate to detect effects of this nature. Due to the nature of repeated assessments, power was estimated to be very good (> 0.95) for detecting Time x Condition x Group interactions of even modest effect among variables assessed repeatedly (8x) across the exercise session (e.g., affect, state body image); Power detecting the estimated Time x Condition x Group interactions for pre-post biomarker measurements with a sample size of 90 participants (30 HC and 60 ED) was lower (0.88), but remained sufficient. There will be two

timepoints for analysis—any data collected prior to study improvements made due to initial NIH grant funding will be analyzed and interpreted in a registered report of the pilot study. The second round of analysis will be conducted with participants enrolled after the first NIH funded changes are made to the study.

Data analysis.

Analyses will culminate in identification and refinement of factors that associate with DEx (CET scores) along with general exercise engagement (accelerometer-assessed moderate-to-vigorous PA [MVPA]).

Aim 1: *Investigate biobehavioral response to in-lab exposure to PA.* We will determine change scores in self-report ratings of body image, and affect before, during, and immediately following PA, as well as pre/post change in DA, 5-HT and eCB biomarkers. Shifts in affect and biomarkers will be evaluated descriptively with measures of central tendency, skew, and variance. We will also employ paired-samples *t*-tests and reliable change indices to characterize the statistical and clinical significance of this pre-post change, at a group level. We will determine if ED characteristics (e.g., diagnosis/severity) moderate these shifts.

Aim 2: *Validate exercise-based tasks that capture the reward and negative reinforcement value of PA.* Validation of positive and negative valence exercise tasks will include participant acceptability and prediction of self-report DEx and accelerometer-measured MVPA. In the NVS exercise task, we will examine correlations among task-related variables (baseline urge to escape, biomarkers, exercise expectancies, state body image, attentional control, exercise intensity) along with mixed-effects regression models that will include baseline covariates, exercise intensity, and within-task change in physiological measures, as predictors of within-task anxiety reduction and body dissatisfaction. Overall, we expect swifter, greater reductions in anxiety and body dissatisfaction in the exercise condition, which will be moderated by individual difference variables. We hypothesize that high exercise expectancies, 5-HT levels, and greater increases in anxiety, body dissatisfaction, and urge to exercise resulting from milkshake ingestion will relate to higher levels of exercise intensity in the exercise condition, greater sustained anxiety in the non-exercise condition, and that exercise intensity will associate with slope of state body image and anxiety over the course of the exercise session. In the PVS exercise task, we will again examine correlations among task-related variables (baseline levels of DA, eCB, drive to exercise, positive exercise expectancies). Mixed-effects regression models will examine whether task-related changes in PVS variables (DA, reward learning) associate with within-task shifts in affective state, and whether changes in DA, reward learning, and

affective states across the task are predicted by baseline drive to exercise, positive exercise expectancies, and trait level reward orientation.

Aim 3: *Examine how ED severity, biological and affective markers of PA response, and positive (reward) and negative (avoidance/escape) valence sensitivities associate with PA. Refine assessment battery to identify broad factors associated with DEx.*

We will identify variables (e.g., cognitive, biological, disorder-specific) that relate to PA amount (accelerometer) and DEx (self-report; interview-based). This will first include univariate associations between each measure (see **Table 1**) and PA outcomes (accelerometer-based MVPA, compulsive exercise). We expect that multiple measures from the negative and positive valence domains will associate with PA frequency/intensity **and** DEx. We expect that measures of ED severity will relate to DEx but **not** PA frequency/intensity. This aim will include identification of assessments with maximum predictive and incremental validity and development of a weighted scoring method to capture 3 domains of risk (positive valence, negative valence, ED severity) in relation to both PA engagement and DEx. We will halve the sample and use lasso regression to identify a) relevant predictors and b) prediction weights for these variables. As a second step, to identify optimally efficient assessments for future clinical-research, we will assign a weight of participant burden based on a) average time for assessment and b) invasiveness, and multiply participant burden by effect sizes in the DEx models to identify the most *efficient* assessments that capture DEx risk. This will lead to refinement of a battery that will create a metric by which to stratify DEx risk and PA engagement, which will be used in future research examining whether these multivariate risk scores predict response to PA-based recommendations and interventions in the context of EDs.

Rigor, Transparency & Reproducibility. Rigor: We will apply the highest scientific standards in all aspects of this work. Transparency: We will record and annotate attempted analyses and share code with interested investigators Reproducibility: Project publications will provide full information about procedures and analyses to enable replication. We will share data and code on an institutional webpage for reproducibility.

Table 2. Project Timeline and Milestones			
	Pre-Award	Y1	Y2
Pilot tasks with healthy volunteers			

Potential problems, alternative strategies, & benchmarks for success. Potential problems:

(1) Although running is the most commonly endorsed exercise behavior among those with EDs (~50%),⁴⁶ not

Evaluate PA response & task feasibility: Aim 1				
Confirm PA response & task feasibility (Milestone 1)		X		
Recruitment & Data Collection: Aim 2				
Complete Data collection (Milestone 2)			X	
Data Analyses: Aim 3				
Complete analyses (Milestone 3)				X
Refine Assessment Battery for R01 (Milestone 4)				X
Grant writing for R01 submission				
Research Dissemination (Milestone 5)				X

all individuals who endorse DEx report walking or running as their typical PA. (2). As there is little existing research on lab-based exercise tasks among those with EDs, it is possible that some individuals may be unable to complete exercise tasks as described. Alternatives:

(1) individuals will self-report preferred modes of PA, included as a covariate in analyses. Future considerations may include alternate forms of PA. (2) We will evaluate the necessity of modulating exercise duration and intensity based on stage of ED treatment. Benchmarks: The success of the project in meeting study aims will be systematically evaluated according to the milestones detailed in **Table 2**. Recruitment plans are outlined in *Human Subjects and Clinical Trials Information*

Summary: This project will test the hypothesis that both positive and negative valence systems relate to DEx engagement among those with EDs, implicating multiple pathways by which DEx may develop and persist. We propose to develop tasks to capture both positive and negative valence features of PA and DEx among adolescents and young adults with EDs. We will refine an assessment battery that will yield a *parsimonious* and *idiographic* risk-profile for DEx. This project will provide essential information for mapping the multiple functions of exercise among patients with EDs and will lay the groundwork to explore precision exercise interventions for those at risk for or in recovery from EDs.

I. Dissemination of Data

All data will be coded. Publication of results will only include group level statistics: data will not be reported separately for any individual.

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