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Study protocol for a randomized, placebo-controlled, double-masked mechanistic clinical trial of transdermal estrogen replacement in hypoestrogenic eating disorders to explore the role of estrogen on cognitive flexibility and reward processing

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ABSTRACT

Background: Restrictive eating disorders (EDs) are associated with cognitive inflexibility, reduced reward responsiveness, and tendency to favor delayed rewards, which contribute to illness maintenance and poor outcomes. Low estrogen is common in EDs and has been linked to poor cognitive flexibility and reward processing in other conditions. We describe a randomized controlled double-masked trial of short-term (12 weeks) transdermal estrogen (100 μg 17-β) replacement versus placebo to test estrogen-effects on cognitive flexibility, reward responsiveness, delay discounting, and ED pathology in females with EDs and low estrogen (ED-LE).
Methods: Participants will include $N = 120$ females with ED-LE (14–35 years) with clinical, neuropsychological, and neural assessments occurring at baseline, eight weeks, and 12 weeks.
Results: Primary outcomes will include between-group differences in 8-week change in cognitive flexibility, reward responsiveness, and delay discounting, and between-group differences in 12-week change in ED pathology. Secondary outcomes will include between-group differences in 8-week change in neural activation during cognitive flexibility and reward-related functional magnetic resonance imaging paradigms and mediation

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effects of 8-week change in cognitive flexibility, reward responsiveness, and delay discounting on 12-week change in ED pathology.
Conclusion: We hypothesize that estrogen replacement will (1) increase cognitive flexibility, reward responsiveness, and delay discounting, and (2) reduce ED pathology; and (3) 8-week changes in cognitive flexibility, reward responsiveness, and delay discounting will mediate 12-week changes in ED pathology. These data will systematically probe the role of estrogen in key neurocognitive features associated with poor ED outcomes to guide development of novel interventions for this population.

1. Introduction

Restrictive eating disorders (EDs) typically onset in adolescence, a period of hormonal changes and brain development, affecting ~10 % of youth [1,2]. These disorders are chronic, highly treatment-resistant, and have among the highest premature psychiatric mortality rates [3–6]. Neurocognitive traits, including cognitive inflexibility, diminished reward responsiveness, and delay discounting, contribute to illness persistence [7,8]. Estrogen, a critical neuromodulator, influences these processes [9–15] via ERα and ERβ, which are highly expressed in the ventral striatum, prefrontal cortex (PFC), and amygdala [16]. Low estrogen states are associated with blunted reward sensitivity, decreased approach behaviors, and increased cognitive rigidity, which may reinforce restrictive eating disorder behaviors [17–19].

Low estrogen is transdiagnostic feature common across restrictive EDs [20–22], yet the relationship between low estrogen and cognitive and reward traits remains understudied in this population. Neuroimaging research shows altered reward processing in EDs, particularly within the ventral striatum, medial PFC, and amygdala [17,23]. Individuals with anorexia nervosa (AN) show blunted ventral striatal responses to food and monetary rewards, suggesting reduced reward salience [24]. Concurrently, hyperactivation of the dorsolateral (DL) PFC and anterior cingulate cortex (ACC) in AN may reflect increased cognitive control over reward-driven behavior [25], reinforcing rigidity. Additionally, altered medial OFC activity has been linked to dysregulated reward valuation, and may further drive maladaptive decision-making in restrictive EDs [26]. Given these findings, it is critical to explore whether estrogen replacement can help normalize reward processing and cognitive flexibility, thereby serving as a potential therapeutic intervention for restrictive EDs.

Cognitive inflexibility and altered decision making are linked to restrictive EDs and hypoestrogenic states. Cognitive flexibility, the ability to adapt changing environmental demands [27,28], is impaired in individuals with restrictive EDs [29] and hypoestrogenic conditions [9,10]. It involves skills such as set shifting– that is, switching between tasks or responding flexibly to a changing set of rules– which is often impaired among these individuals. Reward responsiveness, the capacity to experience and respond to rewarding stimuli, is often blunted in restrictive EDs, leading to reduced motivation to consume palatable foods and engage in pleasurable activities [24,30,31]. Likewise, individuals with restrictive EDs are characterized by shallow delay discounting, meaning individuals overvalue long-term rewards (e.g., weight loss) at the expense of immediate gratification (e.g., food intake) [32,33]. By reinforcing rigid behavioral patterns and diminished responsiveness to positive reinforcement from food, impaired cognitive flexibility, reward responsiveness, and delay discounting may perpetuate restrictive eating behaviors [32,34]. Conversely, improving cognitive flexibility could help patients adapt to changing dietary and emotional demands, while enhancing reward responsiveness and delay discounting may increase motivation to engage in non-restrictive eating. These neurocognitive and motivational dysfunctions represent targets to enhance treatment effectiveness.

While estrogen replacement therapy is widely used to optimize bone health [35], emerging evidence suggests it may also enhance neurocognitive and motivational dysfunctions [36–38]. Our prior work shows that long-term estrogen replacement improves cognitive flexibility in female athletes with amenorrhea [36] and reduces ED psychopathology in athletes and in adolescents with AN [39,40]. Likewise, published work in other hypoestrogenic states shows that short-term estrogen/estrogen agonist administration positively impacts cognitive flexibility and reward processing [37,38]. However, whether estrogen deficiency contributes to dysfunction across cognitive flexibility, reward responsiveness, and delay discounting among individuals with restrictive EDs and low estrogen (ED-LE), and whether correcting this deficiency improves ED pathology via its impact on these neurocognitive and motivational domains has not been studied.

This study investigates the impact of estrogen replacement on key neural circuits implicated in reward processing [41] and cognitive control, including the ventral striatum, medial PFC, amygdala, and DLPFC. The ventral striatum, a key region for reward anticipation and motivation, has been found to show reduced activation in restrictive EDs [42], while the medial PFC and orbitofrontal cortex, critical for reward valuation and decision-making, demonstrate altered function that is modulated by estrogen levels. Additionally, the amygdala, which regulates emotional salience and reward learning, has been found to be dysregulated in restrictive EDs and is highly sensitive to estrogen fluctuations [26]. Finally, the DLPFC appears to be hyperactive in AN, potentially as a compensatory response to reduced reward sensitivity. By examining the mechanistic effects of estrogen, we aim to determine whether correcting estrogen deficiency can normalize neurocognitive dysfunction and improve ED-LE pathology.

In this paper, we describe the rationale, design, method, and analytic plan for a randomized, double-masked, placebo-controlled, mechanistic clinical trial of physiologic estrogen in individuals with ED-LE to study the impact of estrogen deficiency (and replacement) on cognitive flexibility, reward responsiveness, delay discounting, and restrictive ED pathology, specifically drive for thinness, dietary restraint, and restrictive eating behavior (Fig. 1). We are currently randomizing 120 females with ED-LE (ages 14–35 years) to 12 weeks of physiologic estrogen replacement (17-β E2) or placebo to evaluate changes in cognitive flexibility, reward responsiveness, and delay discounting at 8 weeks (Aim 1), ED pathology at 12 weeks (Aim 2); and to determine whether 8-week improvements in these domains mediate the 12-week improvement in ED pathology (Aim 3). We hypothesize that in those with ED-LE, correcting estrogen deficiency will improve cognitive flexibility, reward responsiveness, delay discounting, and ED pathology; and improvement in ED pathology will be mediated by changes in neurocognitive and motivational dysfunction.

2. Methods

2.1. Trial design

This study is a single-site, two-arm randomized controlled clinical trial of physiologic estrogen versus placebo for females ages 14–35 years old with ED-LE. Females with ED-LE are randomized (double-masked design) for 12 weeks to i) 100 μg 17-β estradiol transdermal patches, used continuously with cyclic progesterone pills (200 mg daily in two 10-day courses), or ii) placebo patches and cyclic placebo pills (Fig. 2). This dosage mimics physiological estrogen levels similar to those found in healthy adolescents and adults [43]. We focus on young adulthood (14–35) because this is a window when ED-LE onset is common [44];

when most women have attained menarche and puberty is mostly complete with stable menstrual cycling in a healthy population [45,46].

Participants are enrolled at an academic medical center (Massachusetts General Hospital). We will recruit 120 participants who will complete a screening evaluation (see Table 1), and main study assessments at baseline, 8-weeks, and 12-weeks follow-up (See Table 2). Data are gathered and stored using REDCap electronic data capture tools hosted at Massachusetts General Hospital [47,48], LabArchives, and cloud-based storage, all of which are HIPAA-compliant and Institutional Review Board (IRB)-approved.

2.2. Participants

Participants must be females, aged 14–35 years, with clinically significant restrictive eating disorders (e.g., AN, atypical AN, OSFED-restricting type) and hypoestrogenism (oligo-amenorrhea or low estradiol levels <50 pg/mL). Bone age > 13.5 years is required for participants under 16 to ensure statural growth is nearing completion.

Exclusion criteria include psychiatric conditions affecting neural circuitry (e.g., psychotic disorders, active substance use disorder), alternative causes of oligo-amenorrhea (e.g., PCOS, thyroid dysfunction unless euthyroid for ≥3 months), current estrogen-containing medications, seizure disorders, MRI contraindications, pregnancy, and contraindications to estrogen therapy.

See Table 1 for detailed measures completed for inclusion/exclusion criteria and Online Supplement for Detailed Definitions of Eligibility and Exclusion Criteria and diagnostic classification.

2.3. Recruitment

Participants are recruited through the MGH EDs Clinical and Research Program (EDCRP), Klarman EDs Center at McLean Hospital, and other ED treatment centers in and around New England; mailings to pediatricians, nutritionists, therapists, sports medicine specialists, high schools, and colleges in New England; and through advertisements in local newspapers and online postings.

2.3.1. Sample size calculation

We determined the sample size needed to target the minimum detectable statistically significant effect size of between-group differences for endpoints related to Aims 1 and 2 of ≤65 % of the clinically meaningful effect size shown by pilot or preliminary studies as Cohen's $d \geq 0.92$ [30,68]. We thus targeted a detectable effect size of $d \geq 0.56$ ($p < 0.05$) or $d \geq 0.62$ ($p < 0.025$) depending on relatedness of endpoints (Table 3). Adjustment for multiple comparisons of co-primary endpoints was not performed, as these endpoints are included to generate hypotheses for future randomized clinical trials. One hundred and two completers (51 in each treatment arm) are required to detect these effect sizes using a 2-sided test at a 2.5–5 % type-1 error rate and with 80 % power. Assuming attrition of up to 15 %, we determined a target enrollment of 120 subjects for the 1:1 randomization. The study is adequately powered to detect a conservative target effect size for the primary analysis and for the Sobel test for mediation. Our data from an RCT showed Cohen's $d = 1.2$ ($p = 0.0009$) for a 12-month estrogen effect on body dissatisfaction score change and its Pearson's correlation of 0.6,

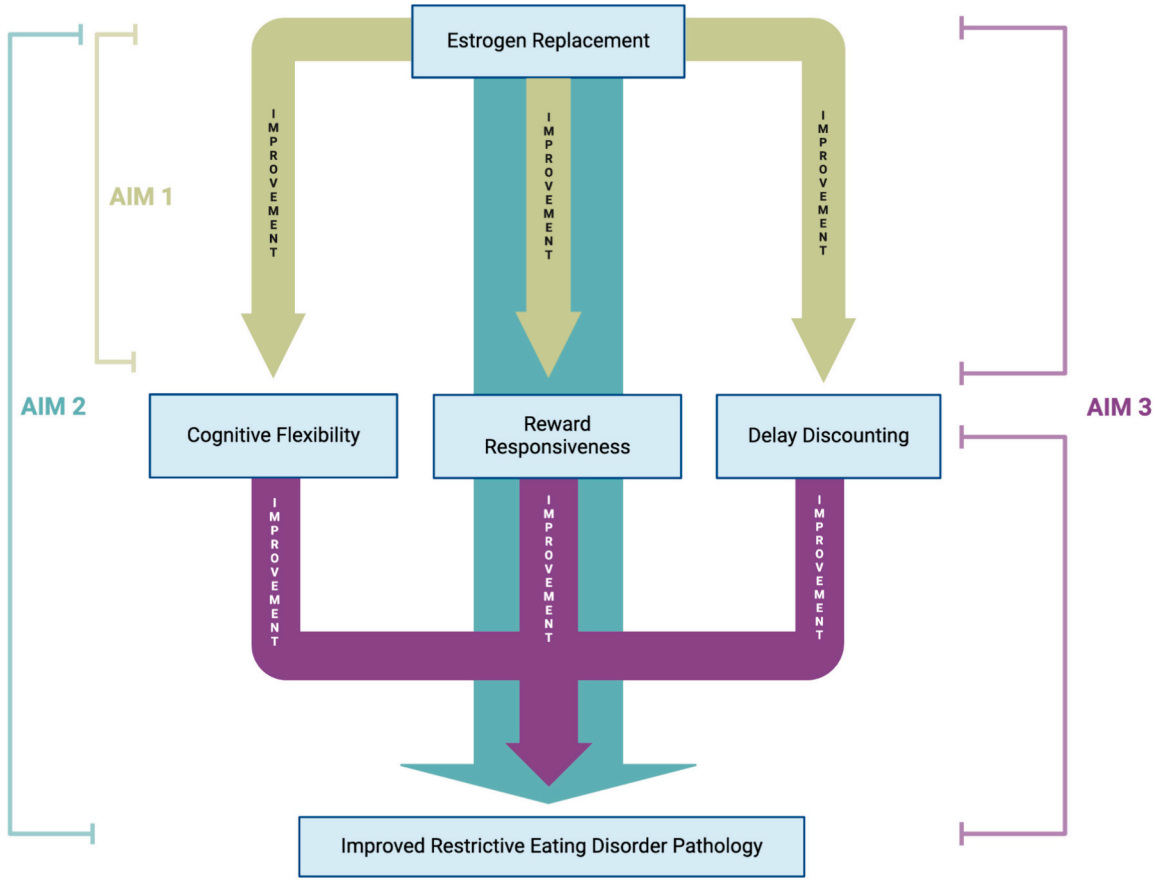

Fig. 1. Conceptual framework illustrating the hypothesized effects of estrogen replacement on cognitive flexibility, reward responsiveness, delay discounting, and restrictive eating disorder pathology in females with hypoestrogenic eating disorders (ED-LE). We will randomize 120 females with ED-LE (ages 14–35 years) to 12 weeks of physiologic estrogen replacement (17-β E2) or placebo to evaluate changes in cognitive flexibility, reward responsiveness, and delay discounting at 8 weeks (Aim 1), ED pathology at 12 weeks (Aim 2); and to determine whether 8-week improvements in neurocognitive and motivational dysfunction mediate the 12-week improvement in ED pathology (Aim 3).

equivalent to the total effect (τ) [35]. While the Sobel test will use the bootstrap sampling approach, we present detectable sizes of first- and second partial effects, α and β, for the parametric test at a 2-sided 5 % type-1 error rate with 80 % power. With 102 observations, the detectable size of α and β will be medium (>0.39) [69].

2.4. Main study visits and timeline

Following eligibility screens, participants were randomized to transdermal estrogen (17-β E2) or placebo arms.

2.4.1. Estrogen and progesterone administration & safety monitoring

Participants who are hypogonadal will receive transdermal 17-beta estradiol (100 μg) or placebo patches in physiologic replacement doses. Given the risk of endometrial hyperplasia with continuous estrogen, participants receiving active estrogen will also take micronized progesterone (200 mg daily) for two 10-day courses at least four weeks apart. Those randomized to placebo will receive matched placebo pills.

Participants are monitored at 8 and 12 weeks for adverse effects. A 24-h emergency contact will be provided for medical concerns, with study physicians available as needed.

To minimize risk, individuals with a history of complex migraines, estrogen-responsive breast cancer in a first-degree relative (without provider approval), or genetic hypercoagulability (confirmed through testing) will be excluded.

See online supplement for additional details.

2.4.2. Main study visits

Subjects complete main study visits at baseline (prior to start of intervention), eight weeks, and 12 weeks. In-person components of main study visits are completed at Massachusetts General Hospital, Boston, MA, USA, and McLean Hospital, Belmont, MA, USA.

2.4.3. MRI

2.4.3.1. Data acquisition and scan parameters. Data are acquired on a 3 T Prisma scanner with a 64-channel head-neck coil at the McLean Imaging Center. High-resolution anatomical data are acquired using a T1 magnetized-prepared rapid acquisition with gradient echo (MPRAGE) imaging sequence with the following acquisition parameters:176 sagittal slices, repetition (TR) = 2530 ms, echo times (TE) = 1.69 ms,3.55 ms, 5.41 ms, 7.27 ms, 7 deg. flip angle, 1x1x1 mm voxels, field of view = 256 mm. Functional images are acquired using a whole brain gradient echo T2*-weighted multiband echo planar imaging (EPI) sequence developed at the University of Minnesota Center for Magnetic Resonance Research (102,103) with the following acquisition parameters: TR/TE = 2000/30 ms; 80 deg. flip angle, voxels 1.5 × 1.5 × 1.5 mm, field of view = 204 mm, multiband factor 3, phase encoding (PE) direction A- > P). Fieldmap: Reversed PE blip spin-echo EPI-based field map scan will be acquired for distortion correction [69].

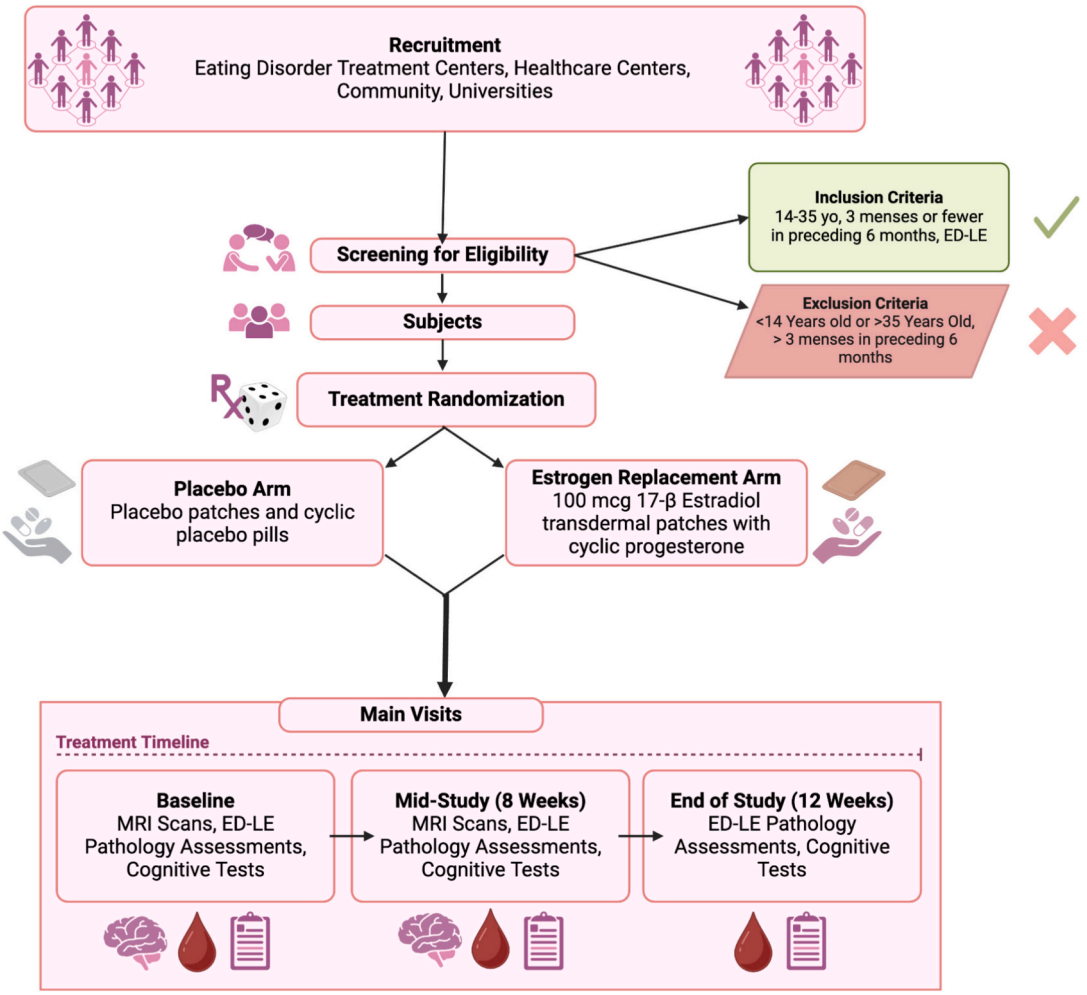

Fig. 2. Study design and timeline for the randomized, placebo-controlled, double-masked clinical trial of estrogen replacement in females with eating disorders characterized by low estrogen (ED-LE). The study uses an intent-to-treat design including all participants who complete the baseline visit. yo = years old; MRI = Magnetic Resonance Imaging.

Table 1
Measures completed at the study screening visit(s) to determine eligibility.

Constructs	Measure	Description/Study Purpose
Eating Disorder Psychopathology	Structured Clinical Interview for DSM-5- Research Version (SCID - Eating and Feeding Disorders Module) [49]	The SCID-5-RV is a semi-structured interview performed to screen for the presence of restrictive eating disorders.
	Eating Disorder Inventory-3 (EDI- Drive for Thinness) [50]	The EDI-3 is a 91-item self-report assessment of eating attitudes. EDI-Drive for Thinness subscale was administered to confirm restrictive eating pathology core to ED-LE.
General Psychopathology	Mini International Neuropsychiatric Interview (MINI) 7.02 [51]	The MINI is a structured clinical interview for DSM-5 diagnoses administered to determine eligibility and characterize comorbidity.
	Structured Clinical Interview for DSM-5 - Research Version (SCID-5-ADHD Module only) [49]	The SCID-5-RV is a semi-structured interview performed to assess ADHD.
Estrogen Exposure	Screening labs	Blood was collected to rule out other causes of amenorrhea, including thyroid-stimulating hormone, follicle-stimulating hormone, and prolactin.
	Case Report Form (CRF)	The CRF is a standardized set of medical history questions and physical exam findings completed by study clinicians and research coordinators. Specific questions pertain to lifetime estrogen exposure (e.g., age of menarche, menstrual irregularities) to characterize estrogen history.
Exercise	Compulsive Exercise Test (CET) [52]	The CET is a 24-item self-report assessment of core features of excessive exercise in eating disorders. The CET is used to characterize excessive exercise.
	Exercise Log	Standardized set of questions to assess the frequency and quantity of exercise and/or physical activity. Types of exercise were categorized as Aerobic, Resistance, Combined Aerobic/ Resistance, or Light/Low exercise and confirmed via certified exercise scientist. This exercise log captures exercise patterns spanning the 0–5 years prior to study entry.

2.4.3.2. fMRI preprocessing and analysis. Neuroimaging data are preprocessed using fMRIPrep 20.0.1 [39], which provides standardized anatomical and functional data pipelines. T1-weighted anatomical scans are skull-stripped, segmented, and normalized to MNI space. Functional images undergo slice-time correction, motion correction, spatial normalization, and ICA-based denoising (ICA-AROMA [40]). First-level task analyses are conducted using general linear models (GLMs) implemented in SPM12, modeling task conditions with a hemodynamic response function. Detailed preprocessing parameters and software versions are included in the Supplement. See online supplement for additional details.

2.4.3.3. fMRI paradigms. Cognitive Flexibility is measured using a task-switching paradigm that robustly activates the brain network underlying cognitive flexibility. Participants randomly switch between two choice-reaction tasks: categorizing visually presented letters as vowels/consonants or upper/lower case, by providing manual responses (button presses). Participants complete five blocks of each of the three task conditions: vowel-consonant discrimination, upper-lower case discrimination, and a task-switch condition. Each block consists of 24 trials, with a total of 360 trials across all conditions. In all three conditions, the stimulus is presented for 1500 ms, followed by a jittered inter-trial interval (ITI) in which a fixation cross appears on the screen for a duration ranging between 500 ms and 4500 ms.

Reward responsiveness and delay discounting are captured via two paradigms:

The delay discounting task, in which subjects choose between smaller immediate vs. larger delayed monetary rewards, will be used to measure delay discounting. In 50 % of trials, the immediate reward will be available now, in the other 50 %, within two weeks [53]. The delay discounting task is conducted over two runs, with each run containing 30 trials for a total of 60 trials. On each trial, participants are presented with a choice between a smaller immediate monetary reward and a larger delayed reward. They have up to 4000 ms to make their selection using left or right button presses, with the response mapping randomized across participants. Following their choice, participants receive feedback for 1000 ms, where a check mark appears if they select the delayed reward, and an "X" appears if they select the immediate reward. A fixation cross is displayed during the ITI, and any unused response time is added to the jittered ITI.

The monetary reward task involves participants viewing four different types of slot machines, which are presented pseudo-randomly with 24 trials per slot machine type, totaling 96 trials. Each trial begins with the presentation of a cue stimulus, which displays one of the four slot machines for 1500 ms. This is followed by a jittered ISI, during which a fixation cross appears. Participants then observe three spins of the slot machine. The first two spins last 1000 ms each, while the third spin has a variable duration to simulate anticipation of the outcome. After the third spin, the outcome is displayed for 500 ms, followed by feedback for 1500 ms, indicating whether participants have won money (represented by gold coins) or receive no reward ($0). A fixation cross is shown during the jittered ITI. Throughout the task, participants make responses using button presses to indicate which slot machine is presented, both at the cue stimulus and during the outcome phase. Initial response to reward receipt is assessed by analyzing brain activation during the outcome phase, contrasting trials with reward receipt to those without reward delivery despite >0 % chance of reward receipt [14].

2.5. Randomization

Randomization is performed based on a computer-generated template developed by the study statistician and maintained by the Research Pharmacy. This is a double-masked study, with the participant, study staff and investigators masked to allocation. Because the age range of 14–35 years is wide in the context of neurodevelopment, we will use block randomization to ensure even randomization; blocks include age ranges: 14.0–20.9 years, 21.0–28.9 years, and 29.0–35.9 years. Randomization avoids biasing the study in favor of the estrogen arm. Although females with ED-LE randomized to estrogen/progesterone may have cyclic menses, this is not uniformly seen, and females with ED-LE randomized to placebo may have intermittent menses as well. Thus, occurrence of menses or the lack thereof should not un-mask study participants. Participants will be counseled at the screening and subsequent visits that the combination of the transdermal 17-β E2 patch with

Table 2
Measures completed at main study visits.

Constructs	Measure	Description/Study Purpose	Timepoint(s)
Eating Disorder Psychopathology	Eating Disorder Examination (EDE) [53]	The EDE is a semi-structured interview that features four eating disorder subscales and a global severity score.	Baseline, 12-week
	Eating Disorder Inventory-3 (EDI-3) [50]	The EDI-3 is a 91-item self-report assessment of eating attitudes that includes subscales to measure core restrictive eating features of drive for thinness and body dissatisfaction.	Baseline, 8-week, 12- week
	Longitudinal Interval Follow-up Evaluation Eating and Feeding Disorders Version 3 (LIFE-EAT-3) [54,55]	The LIFE-EAT-3 is a semi-structured clinical interview used to track the course of eating disorder symptoms on a weekly basis over the past 12 weeks.	Baseline, 12-week
	Eating Pathology Symptoms Inventory (EPSI) [56]	The EPSI is a 45-question self-report assessment that measures restrictive eating habits, cognitive restraint, and exercise patterns.	Baseline, 8-week, 12- week
	4-day food record (4DFR)	The 4DFR captures detailed self-report food intake and includes 3 weekdays and 1 weekend day.	Baseline, 12-week
	24-Hour Recall	The 24-Hour Food Recall is an administered set of prompts designed to collect data on all food and drink consumed within the past 24 h.	
Body Measurements	Height	Measured on a wall-mounted stadiometer in triplicate	Baseline, 8-week, 12- week
	Weight	Measured on an electronic scale	Baseline, 8-week, 12- week
Estrogen Exposure	Estradiol levels	Blood	Baseline, 8-week, 12- week
	Case Report Form (CRF)	The CRF is a standardized set of medical history questions and physical exam findings completed by study clinicians and research coordinators. Specific questions pertain to estrogen exposure over the course of the study.	Baseline, 8-week, 12-week
Exercise	Compulsive Exercise Test (CET) [52]	The CET is a 24-item self-report assessment of core features of excessive exercise in eating disorders.	Baseline, 8-week, 12- week
	Exercise Log	A standardized set of questions to assess the frequency and quantity of exercise and/or physical activity during the course of the study. Types of exercise are categorized as Aerobic, Resistance, Combined Aerobic/Resistance, or Light/Low exercise and confirmed via certified exercise scientist.	Baseline, 8-week, 12- week
	International Physical Activity Questionnaire (IPAQ) [57]	The IPAQ is a physical activity questionnaire that assesses physical activity across several domains: leisure time, domestic and gardening (yard) activities, work-related, and transport-related activity. For each domain, physical activity is assessed at a variety of levels, including walking, moderate intensity, and vigorous-intensity activities. Sitting time is also collected.	Baseline, 12-week
Cognitive Flexibility	Delis-Kaplan Executive Function System Color Word Interference Test (D-KEFS CWIT) [58]	The Inhibition-Switching component of the D-KEFS CWIT assesses cognitive flexibility, with shorter completion time and higher accuracy indicating more flexibility. Participants name the color of words representing colors printed in dissonant ink colors (e.g., the word "blue" in red ink). However, if words are framed by a box, they will be instructed to read the word instead.	Baseline, 8-week, 12- week
Reward Responsiveness	Temporal Experience of Pleasure Scale (TEPS) [59]	The 18-item TEPS assesses traits such as openness and flexibility with a variety of pleasurable stimuli/experiences for anticipatory and consummatory components of pleasure experience.	Baseline, 8-week, 12- week
	Snaith-Hamilton Pleasure Scale (SHAPS) [60]	The 14-item SHAPS assesses current symptoms of anhedonia.	Baseline, 8-week, 12- week
Delay Discounting	Monetary Choice Questionnaire (MCQ) [61]	In this computerized task/verbal administration of the MCQ, we assess an individual's extent of discounting the value of future rewards with increasing delay to reward receipt. Subjects will make 27 binary choices between smaller immediate and larger delayed monetary rewards of varying value and delay to reward receipt. From their responses, their Delay Discounting Parameter k is Calculated and indicates the extent of discounting future rewards.	Baseline, 8-week, 12- week
MRI	Task-based functional magnetic resonance imaging (fMRI) (detailed information below)	Tasked-based fMRI data will be acquired on a 3 T Prisma scanner with a 64-channel head-neck coil. In scanner fMRI tasks include a Task Switching paradigm, a Monetary Reward paradigm, and a Delay Discounting paradigm.	Baseline, 8-week
	Structural MRI	High-resolution anatomical data (T1- and T2-weighted).	Baseline, 8-week
Other psychopathology	Beck Depression Inventory-II (BDI-II) [62]	The 21-item BDI-II provides a dimensional rating of depressive symptom severity.	Baseline, 8-week, 12- week
	State-Trait Anxiety Inventory (STAI State) [63]	The 40-item STAI is a dimensional self-report questionnaire of current and general anxiety. The State scale captures current anxiety. Participants completed the measure before and after cognitive tasks (all main visits) and MRI scans (baseline and 8 week) (i.e., pre-cog, post-cog, pre-MRI, and post-MRI).	Baseline, 8-week, 12- week
	Obsessive-Compulsive Inventory (OCI) [64]	The OCI is a 42-item self-report measure of current symptoms of obsessive-compulsive disorder.	Baseline, 8-week, 12- week
	Toronto Alexithymia Scale (TAS-20) [65]	The TAS-20 is 20-item self-report measure of alexithymia, or difficulty identifying, describing, or processing emotions.	Baseline, 8-week, 12- week
	Positive and Negative Affect Schedule (PANAS) [66]	The 20-item PANAS assesses current levels of positive and negative affect. Participants completed the questionnaire before and after cognitive tasks (all main visits) and MRI scans (baseline and 8-week) (i.e., pre-cog, post-cog, pre-mri, and post-mri).	Baseline, 8-week, 12- week
General Intelligence	Wechsler Abbreviated Scale of Intelligence (WASI) [67]	The WASI was used to test (and control for) general intellectual ability. For the vocabulary portion, participants will define given words, and responses will be scored based on definition match (crystallized intelligence). For the Matrix Reasoning portion, participants will complete gridded patterns by choosing the correct of 5 options (fluid intelligence).	Baseline or 12-weeks

Table 3
Primary and secondary outcomes.

Primary Outcomes	Measure	Timepoints	Aims
Cognitive Flexibility	DKEFS Color Word Interference Test [58]	Change from baseline to 8-weeks	1,3
Reward Responsiveness	TEPS Consummatory pleasure scale [59]	Change from baseline to 8-weeks	1,3
Delay Discounting	Monetary Choice Questionnaire [61]	Change from baseline to 8-weeks	1,3
Eating Disorder Psychopathology	EDI - Drive for thinness [50]	Change from baseline to 12-weeks	2,3
	EDI - Body dissatisfaction [50]	Change from baseline to 12-weeks	2,3
Secondary Outcomes			
fMRI Cognitive Flexibility	Task Switching	Change from baseline to 8-weeks	1,3
fMRI Reward Responsiveness	Monetary Reward Paradigm	Change from baseline to 8-weeks	1,3
fMRI Delay Discounting	Delay Discounting Task	Change from baseline to 8-weeks	1,3
Eating Disorder Pathology	EDE - Dietary Restraint Scale [53]	Change from baseline to 12-weeks	2,3
	4-day food diary caloric intake	Change from baseline to 12-weeks	2,3
	CET [52]	Change from baseline to 12-weeks	2,3

Notes. D-KEFS = Delis-Kaplan Executive Function System; TEPS = Temporal Experience of Pleasure Scale; EDI = Eating Disorder Inventory; fMRI = Functional Magnetic Resonance Imaging; EDE = Eating Disorder Examination; CET = Compulsive Exercise Test.

cyclic progesterone has no contraceptive efficacy, and will be provided with information regarding acceptable methods of non-hormonal contraception during the study period.

2.6. Intervention

2.6.1. Estrogen replacement (transdermal 17-β E2)

We will use transdermal 17-β E2 at a dose of 100 μg daily (patch will be replaced twice weekly). This is the natural form of estradiol, and the transdermal route avoids hepatic first pass effects and suppression of IGF-1, which is associated with cognitive decline in older individuals [34,51]. It is also associated with fewer side effects than equivalent doses of oral estradiol [70].

Full replacement of estrogen can cause endometrial hyperplasia and in the long-term increase cancer risk [71]. Cyclic progesterone protects against this risk. Therefore, ED-LE randomized to 17-β E2 will take 200 mg of micronized progesterone (natural progesterone) daily in two 10-day courses. The first course occurs five weeks after the first day of estrogen, and the second course after the 8-week study visit, given that this visit occurs at least four weeks after the five-week progesterone course. A third course may be administered if needed for subjects remaining in the study for >12 weeks. This mimics the higher progesterone levels in the luteal phase of the cycle. To minimize progesterone effects on study endpoints, we will time study visits such that they occur ≥4 days after the last progesterone dose. As previously noted, effects of progesterone on study endpoints are either minimal and/or change within days of changing progesterone levels [13,72].

2.6.2. Placebo

For the placebo patches, we use transparent adhesive patches obtained from retail pharmacies that are similar in size to the 17-β E2 patch. The active and placebo patches will have Avery labels fixed on them by the unblinded study coordinator for blinding purposes. Active micronized progesterone pills are blinded by the Research Pharmacy, which also prepares the placebo pills.

2.6.3. Study discontinuation

Participants may be withdrawn from the study under specific medical and safety circumstances including: (i) pregnancy, (ii) the therapeutic use of medications that may affect gonadal status during the study period (other than stable and ongoing use of thyroid hormone replacement), (iii) serious protocol-related adverse effects such as thromboembolism, and (iv) active suicidality. Additionally, participants may be withdrawn upon request by the participant or their guardian (for minors), in cases where severe adverse events occur that cannot be addressed without study discontinuation, or at the discretion of the study clinician to ensure participant safety.

3. Outcomes

3.1. Primary outcomes

Primary: 8-week change across groups in Cognitive Flexibility (improved inhibition-switching performance on the Color Word Interference Test (CWIT) using the Delis-Kaplan Executive Function System [D-KEFS]) (Aim 1). We selected this as the primary outcome because we have shown this measure is sensitive to changes in cognitive flexibility following estrogen replacement in amenorrheic adolescents/young adults with high drive for thinness [36].

Co-Primary: 8-week change across groups in: (i) Temporal Experience of Pleasure Scale (TEPS) consummatory pleasure scores, and (ii) Amount of discounting the value of rewards with increasing delay to reward receipt (delay discounting parameter k using the Monetary Choice Questionnaire) (Aim 1). The TEPS is a well-validated measure that captures both anticipatory and consummatory components of pleasure. Anticipatory pleasure refers to the expectation of future rewards, while consummatory pleasure assesses the experience of pleasure in the present moment. Given that blunted reward responsiveness is a hallmark feature of restrictive EDs, TEPS allows us to assess whether estrogen replacement improves an individual's ability to experience pleasure from food and non-food rewards. 12-week change across groups in: EDI-3 Drive for Thinness and Body Dissatisfaction scores (Aim 2).

3.2. Secondary outcomes

Secondary: 8-week change across groups in: (i) dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) activation in response to task-switching paradigm, and (ii) ventromedial prefrontal cortex (vmPFC) and ventral striatum activation in response to reward receipt and during delay discounting (Aim 1); 12-week change across groups in (i) EDE (dietary restraint subscale), (ii) Caloric intake (4-day food diary) (Aim 2); Mediation effect of 8-week change (Δ) in Cognitive Flexibility, Initial Response to Reward, and Delay on 12-week change in ED symptoms/caloric intake (Aim 3).

4. Statistical analysis plan

Aim 1 evaluates the effects of estrogen replacement on cognitive flexibility, reward responsiveness, and delay discounting using linear mixed-effects models (LMMs). Models will include fixed effects for time, treatment group, and their interaction, with random intercepts and slopes to account for individual variability.

Aim 2 examines changes in ED symptoms, caloric intake, and compulsive exercise across 12 weeks using similar LMMs. Model assumptions will be tested, and results reported as estimated marginal means with 95 % confidence intervals.

Aim 3 assesses whether 8-week changes in cognitive and

motivational outcomes mediate 12-week improvements in ED symptoms, using general linear models and mediation analyses, with bootstrapping for inference. Sensitivity analyses will adjust for psychotropic treatment and BMI if necessary.

Full statistical modeling procedures and sensitivity analyses are provided in the Online Supplement.

5. Ethical and safety considerations

The MassGeneral Brigham IRB approved this study. Written informed consent is obtained from participants ≥18 years; and written consent and assent are obtained from parents and participants <18 years, respectively. This study trial is registered on ClinicalTrials.gov (NCT03740204).

5.1. Data safety and monitoring board (DSMB)

An independent external DSMB, including experts in clinical psychology, endocrinology, and biostatistics monitors trial safety and data integrity. The DSMB meets every six months and is available immediately (in person, by conference call, or electronically) should a serious study-related adverse event occur. Study specific adverse events that are monitored include abnormal medical signs and symptoms, or disease changes.

6. Discussion

We describe the rationale, design, method, and analytic plan for a randomized, double-masked, placebo-controlled, mechanistic clinical trial of physiologic estrogen in hypoestrogenic individuals with ED-LE [31,32]. The primary objectives of the study are to explore the impact of estrogen deficiency and its replacement on cognitive and motivational dysfunctions associated with restrictive EDs, which are significant contributors to illness maintenance and poor outcomes.

Restrictive EDs, including AN and related conditions, present considerable treatment challenges, with high rates of relapse and refractoriness to existing therapeutic approaches [6]. These disorders are characterized by cognitive inflexibility, reduced responsiveness to typical rewards combined with a preference for delayed rather than immediate rewards, which perpetuate restrictive behaviors and maintain the disorders [8,73]. Given that low estrogen levels are commonplace in those with EDs characterized by restriction, the relationship between estrogen and these neurocognitive and motivational deficits is of particular interest [17,18]. Estrogen replacement is routinely used to address physical outcomes in low estrogen conditions (e.g., optimizing bone health [29]), but its potential to target the neurocognitive and motivational dysfunctions associated with ED-LE has not been well-explored. Accordingly, this study will provide critical insights into whether estrogen replacement can serve as a targeted intervention to disrupt the cyclic nature of restrictive ED pathology by improving cognitive flexibility and reward responsiveness, ultimately reducing ED symptoms.

6.1. Strengths and challenges

The strengths of this study include its rigorous randomized controlled design, the mechanistic focus on neurocognitive and motivational pathways, and the comprehensive assessment of both behavioral and neural outcomes using functional MRI paradigms. The use of a well-defined population—females aged 14–35 years with ED-LE—allows for the exploration of estrogen's effects in a group particularly vulnerable to cognitive and reward-processing deficits. However, the single-site nature of the study may limit the generalizability of the findings, and the relatively short duration of estrogen replacement (12 weeks) may not capture long-term effects on ED pathology. Larger, multi-site trials with longer follow-up periods will be needed to confirm and extend the findings from this study.

6.2. Future directions

Future research should expand the findings from this trial to broader and more diverse populations, including other forms of EDs and males. Additionally, exploring the impact of estrogen replacement over longer durations and in combination with other evidence-based therapeutic interventions, such as family-based treatment or cognitive-behavioral therapy for EDs, could enhance understanding of how to best incorporate hormonal treatments into comprehensive care models for ED-LE. Further studies could also investigate the differential effects of estrogen on various presentations of restrictive EDs and the specific neural mechanisms by which estrogen modulates cognitive and reward processing in this population.

This study will be the first to investigate the mechanistic role of estrogen in altering the cognitive and reward systems at the core of ED-LE pathology, generating key data on the mechanisms responsible for ED-LE maintenance. These findings have the potential to guide the development and testing of novel, mechanism-based therapeutic interventions aimed at improving outcomes for individuals with restrictive EDs characterized by low estrogen levels.

CRediT authorship contribution statement

Lauren Breithaupt: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Meghan Slattery:** Writing – review & editing, Project administration, Data curation. **Meghan Lauze:** Writing – review & editing, Project administration, Data curation. **Felicia Petterway:** Writing – review & editing, Project administration, Data curation. **Lauren Lindman:** Writing – review & editing, Project administration, Data curation. **Mia Cravitz:** Writing – review & editing, Project administration, Data curation. **Sarah Naticchia:** Writing – review & editing, Project administration. **Siddarth Seenivasa:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Data curation, Conceptualization. **Macy Powers:** Writing – review & editing, Project administration, Data curation. **Kristin N. Javaras:** Writing – review & editing, Supervision, Data curation. **David J. Alperovitz:** Writing – review & editing, Supervision, Resources, Data curation. **Judith Halperin:** Writing – review & editing, Data curation. **Esther Dechant:** Writing – review & editing, Supervision, Data curation. **Jennifer J. Thomas:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Elizabeth A. Lawson:** Writing – review & editing, Supervision, Investigation. **Hang Lee:** Writing – review & editing, Methodology, Formal analysis. **Diego A. Pizzagalli:** Writing – review & editing, Resources, Methodology, Investigation, Conceptualization. **Adrienne L. Romer:** Writing – review & editing, Supervision, Methodology, Data curation. **Poornima Kumar:** Writing – review & editing, Supervision, Investigation, Formal analysis, Data curation. **Franziska Plessow:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Data curation, Conceptualization. **Madhusmita Misra:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Kamryn T. Eddy:** Writing – original draft, Visualization, Supervision, Resources, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

KTE and JJT receive authorship royalties from Cambridge University Press and consulting fees from Equip Health. KJ has owned equity shares in Sanofi and Centene Corporation, served on the Clinical Advisory Board for Beanbag Health, and received research funding from the National Institute of Diabetes and Digestive and Kidney Diseases and the Brain & Behavior Research Foundation. MM is a consultant for Regeneron, receives study drug donation from Tonix Pharmaceuticals, and receives royalties from UpToDate and Medscape. Over the past 3 years, DP has received consulting fees from Boehringer Ingelheim, Compass Pathways, Engrail Therapeutics, Neumora Therapeutics (formerly BlackThorn Therapeutics), Neurocrine Biosciences, Neuroscience Software, Sage Therapeutics, Sama Therapeutics, and Takeda; he has received honoraria from the American Psychological Association, Psychonomic Society and Springer (for editorial work) and from Alkermes; he has received research funding from the Brain and Behavior Research Foundation, BIRD Foundation, the Dana Foundation, DARPA, Millennium Pharmaceuticals, NIMH, and Wellcome Leap MCPsych; he has received stock options from Compass Pathways, Engrail Therapeutics, Neumora Therapeutics, and Neuroscience Software. EAL receives grant support and research study drug from Tonix Pharmaceuticals and receives royalties from UpToDate. EAL and/or immediate family member holds stock in Thermo Fisher Scientific, Zoetis, Danaher Corporation, Intuitive Surgical, Merck and West Pharmaceutical Services. EAL is an inventor on US provisional patent application no. 63/467,980 (Oxytocin-based therapeutics to improve cognitive control in individuals with attention deficit hyperactivity disorder). No funding from these entities was used to support the current work, and all views expressed are solely those of the authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2025.107924.

Data availability

Data collection are underway; data will be made publicly available through National Data Archive

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