Exercise priming to enhance therapeutic bond and behavioral activation in CBT for MDD: a randomized controlled target-engagement trial with remission signal

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Abstract

Major depressive disorder (MDD) is a debilitating condition with frequent relapses. Augmentation strategies may improve psychotherapy outcomes, particularly if they enhance mechanisms of change. Using an experimental therapeutics approach, this pilot trial evaluated whether 30 minutes of individual moderate exercise immediately before individual cognitive behavioral therapy (ActiveCBT) engages two mechanistic targets (behavioral activation and therapeutic alliance) compared to a time- and attention-matched control (CalmCBT). Forty adults with DSM-5 MDD were severity-stratified and randomized to 8 weeks of ActiveCBT (n=19) or CalmCBT (n=21). Primary outcomes were the Working Alliance Inventory–Short Revised (WAI; Bond, Task, Goals subscales) and Behavioral Activation for Depression Scale (BADS). Depression outcomes included Hamilton Rating Scale for Depression (HAMD) response (≥50% reduction) and remission (HAMD<8) from a masked assessor. Generalized estimating equations estimated group effects across time, standardized as Cohen's d, with a priori success defined as d≥0.35 for both or d≥0.55 for either WAI or BADS. The average standardized effect for WAI-Bond favoring ActiveCBT was *d*=0.36 (95% CI: -0.19, 0.90, *p*=0.20) and BADS was *d*=0.43 (-0.07, 0.94; *p*=0.09). Secondary exploratory analyses found a significant remission benefit for ActiveCBT over CalmCBT (69% vs 33%, *p*<0.05), with similar response rates. Exercise priming demonstrated directional mechanistic signals in both specific (behavioral activation) and nonspecific (therapeutic bond) targets, with potential remission benefits from exploratory analyses. These findings preliminarily suggest that exercising before therapy could augment CBT and offer a safe, accessible way to potentially boost its antidepressant effects.

Clinical Trial Registration: This study was prospectively registered at ClinicalTrials.gov (NCT06001346).

Keywords: exercise; depression treatment; therapy augmentation; treatment innovation; treatment mechanisms.

Introduction

Treatment of major depressive disorder (MDD), a common and debilitating disease (Kessler et al., 2012), is difficult. Just half of patients respond to front-line treatments for depression (Cuijpers et al., 2014), and relapses are common (Lemmens et al., 2019; Vittengl et al., 2007). Although psychotherapies and medications can be effective in treating depression (Cuijpers et al., 2021, 2020), there is substantial room to improve their efficacy. Augmentation approaches for treatment may hold the key to enhancing success rates (Strawbridge et al., 2019), particularly as augmentation is becoming more common in clinical practice. Determining how augmentation strategies influence the known mechanisms of change of current interventions is a critical first step in assessing strategies that may enhance treatment success and consistent with the experimental therapeutics approach whereby mechanism engagement must first be confirmed prior to large-scale efficacy trials (Zucker et al., 2025).

Decades of psychotherapy research have identified key process factors (both specific and nonspecific) that reliably predict treatment success in cognitive behavioral therapy (CBT). These factors include processes that are specific to CBT (i.e., only important for CBT) and nonspecific (i.e., important for any therapy) (Cuijpers et al., 2019b; Huibers and Cuijpers, 2015; Lorenzo-Luaces et al., 2015; Manos et al., 2010). Consistent predictors of CBT's antidepressant effects are high behavioral activation as the result of sessions (specific to CBT) (Alexopoulos et al., 2016) and the creation or development of a strong working alliance between the client and the therapist (nonspecific) (Arnow et al., 2013). Better engagement of these mechanisms of change should predict greater treatment effects; therefore, augmentation strategies that increase engagement of these process targets could be transformative.

Harnessing the acute benefits of exercise is a novel and potentially impactful way to improve therapy mechanisms of change. We have shown that a single session of moderate

intensity cycling exercise increases markers of neuroplasticity (e.g., brain-derived neurotrophic factor (BDNF) (Meyer et al., 2016a)) and improves the primary symptoms of depression (depressed mood state and state anhedonia (Meyer et al., 2016b, 2022a)) in adults experiencing a major depressive episode, with greater neuroplastic potential and lower symptoms related to treatment success (Khazanov et al., 2020; Polyakova et al., 2015). We have developed an exercise priming of therapy approach (i.e., exercise right before each therapy session), finding in our randomized controlled n=10 pilot that exercise priming of CBT led to greater working alliance and behavioral activation across treatment (Hedges' g = 1.10 and 1.40, respectively) (Meyer et al., 2022b). This aligns with initial small-sample research investigating the beneficial effects of exercise priming in other conditions (e.g., post-traumatic stress disorder) (Bryant et al., 2023) and intervention modalities (e.g., group-based psychotherapy) (Schmitter et al., 2025). Exercise priming holds significant promise for improving therapy effectiveness for depression, yet rigorous research focused on mechanisms of change is needed to lay the foundation for future trials targeting clinical benefits.

Acute aerobic exercise has well-documented effects on cognitive and emotional systems relevant to psychotherapy which could be involved in enhancement in alliance and activation. First, exercise can reduce stress reactivity and improve emotion regulation (Morava et al., 2024; Wang et al., 2024), creating a psychological state conducive to openness and disclosure. In clinical contexts, single exercise sessions improve social interaction and mood among psychiatric inpatients (Brand et al., 2018), suggesting that exercise may prime interpersonal engagement in difficult conversations and trust which are key components of developing a strong therapeutic alliance. Second, a single bout of moderate exercise enhances executive function and attentional control (Chang et al., 2025), which may help clients sustain focus and engage more fully in cognitively demanding CBT tasks in-session. Neurobiologically, exercise increases cerebral blood flow and neuroplasticity markers such as

BDNF (Meyer et al., 2016a), supporting learning and memory processes critical for acquiring CBT skills and implementing activation strategies. Collectively, these mechanisms provide a plausible basis for hypothesizing that exercise priming could enhance both nonspecific (therapeutic bond) and specific (behavioral activation) processes that predict antidepressant response from CBT.

The present pilot and target engagement double-blind (therapist, assessor) trial was designed to evaluate the potential for exercise priming augmentation of CBT (termed "ActiveCBT") to better engage important mechanisms of change in CBT (working alliance and behavioral activation) compared to a closely matched comparator condition (termed "calm priming" and CalmCBT) across an 8-week manualized CBT program. In line with the National Institute of Mental Health's experimental therapeutics approach (Zucker et al., 2025), this trial was designed to detect directional engagement of mechanisms of change via the ActiveCBT condition (i.e., greater working alliance and behavioral activation as important steps to enhancing the efficacy of CBT) and not powered for clinical efficacy testing. As a result, changes in interviewer-assessed depression and remission were evaluated only as secondary, exploratory outcomes. The *a priori*-defined and pre-registered rule for progressing to a larger trial was to find a standardized effect (i.e., similar to Cohen's *d* (Cohen, 1969)) favoring ActiveCBT on both primary outcomes of working alliance and behavioral activation ≥ 0.35 standard deviation or either one at ≥ 0.55 standard deviation (Meyer et al., 2024).

Methods

Study Design and Participants

This study was a 1:1 severity-stratified (mild, moderate-to-severe) parallel-group randomized controlled clinical trial of ActiveCBT (pre-therapy exercise) vs. CalmCBT (quiet rest pre-therapy) for the treatment of major depression with masked assessors and interventionists called the 'CBT+ Study.' Methods for the present trial have been registered in

a published protocol paper (Meyer et al., 2024) and at ClinicalTrials.gov (NCT06001346) and recruitment ran from September 2023 until August 2024 and ended after filling the 40-person randomization target. Methods and procedures reported below are those relevant to the primary outcome analyses (working alliance and behavioral activation) and reporting of the overall effects on depression across the initial 8-week treatment. This study was approved by the local Institutional Review Board (#23–026-00). All participants provided electronic, written informed consent to participate.

Participants (n=40) were recruited via referral from university and community partners (i.e., student counseling services, on-campus medical clinic, therapist wait-lists, and surrounding clinics), mass emails, flyers, and contacts in large corporations in Ames, Iowa and surrounding communities. To be included in the sample, participants were diagnosed with major depressive disorder and in a major depressive episode via the Structured Clinical Interview for Depression (SCID), had at least mild clinical symptoms of depression (Hamilton Rating Scale for Depression [HAMD] ≥8), aged 18-65, on a stable mental health medication or psychotherapy treatment regimen for at least eight weeks, willing to refrain from changing mental health treatment for the duration of the intervention, had not participated in structured CBT in the past 5 years, and reported they could safely participate in physical activity (via Physical Activity Readiness Questionnaire). Exclusion criteria were: body mass index ≥40; pose an imminent risk of harm to others or self-harm (Columbia Suicide Severity Rating Scale of 5); current substance use disorder; lifetime bipolar, mania, or psychosis; pregnant or planning to become pregnant during study enrollment; currently used tobacco or other nicotine products; or exhibited behavioral disturbance (e.g., aggression, mild-moderate cognitive impairment) that would significantly interfere with study participation, as assessed by clinical research personnel during intake.

Study Flow

See **Figure 1** for the CONSORT diagram. All interested participants completed an online screening survey via REDCap (n=379) followed by a subsequent phone screening performed by senior research staff that determined potential eligibility. Participants that met preliminary eligibility criteria during the phone screening were invited to an in-person intake visit (n=84) consisting of an informed consent, tour of the facilities, clinical interview to confirm eligibility, and a series of questionnaires including demographics. Interviewers were senior Counseling Psychology Ph.D. students or trained clinical interviewers with at least a bachelor's degree in psychology with structured training on diagnosis and assessment using the SCID and supervised by a licensed psychologist [NW]. Eligible participants began their 8 weekly visits roughly one week after their intake visit (n=40). At the start of the first therapy visit, randomization to ActiveCBT and CalmCBT groups occurred via severity-stratified (mild vs. moderate-to-severe; HAMD <18 vs. 18+) blocked randomization using the REDCap randomization module based on a pre-specified randomization schedule generated and uploaded by the study statistician. After completing the 8-weekly therapy sessions, participants came back for a post-intervention visit roughly one week following their eighth therapy session. The post-intervention visit included a clinical interview and a series of questionnaires. All therapy sessions and the post-intervention visit occurred within 12 weeks of the intake visit.

Pre-Therapy Conditions

Pre-therapy, individuals randomized to ActiveCBT completed 30 minutes of cycling on a recumbent stationary bicycle (Lode Corival Recumbent, Lode BV, Groningen, The Netherlands) at moderate intensity (rating of perceived exertion [RPE] of 13 on the 6-20 scale (Borg, 1998)) while individuals in the CalmCBT condition sat quietly (RPE of 6). Standardized instructions for RPE were provided to all participants. All participants were asked to report their RPE and heart rate (Polar H10, Polar Electro Oy, Kempele, Finland) was

recorded every minute for the first 3 minutes (ActiveCBT warm-up), at 5-minute increments starting at minute 5, and then at every minute for the last 3 minutes starting at minute 27 (ActiveCBT cool-down). ActiveCBT participants were instructed to achieve a moderate intensity to coincide with the end of the 3-minute warm-up and maintain that intensity by self-adjusting the workload until cool-down. Exercise workload (e.g., watts, cadence) was recorded at the same intervals for ActiveCBT particiants.

Both the ActiveCBT and CalmCBT conditions were presented with equipoise, and each participant was aware that they may be randomly assigned to either condition. Each condition was described simply as a pre-therapy condition, and participants were informed that the study aimed to examine how these experiences might influence therapy. To provide a standardized experience across conditions, all participants watched 30 minutes of a standardized nature video.

Nature Videos

All participants watched a standard 30-minute segment from the nature documentary, Blue Planet II, Season 1 (*Blue planet II*, 2017). This was selected as it provided a neutral video stimulus, was available for the duration of the study, and a new segment could be used for all 8 study visits with episodes and start times in the protocol paper (Meyer et al., 2024).

Therapy Sessions

Following the pre-therapy condition, participants completed questionnaires prior to the start of their therapy session. Ten minutes post-condition, participants began a 50-minute standardized therapy session with a trained mental health counselor, masked from group assignment. Each session had a theme and was standardized based upon the CBT manual developed by the South Central MIRECC (Cully and Teten, 2008). Additional content details are provided in the protocol paper. Each session was audio and video recorded using Lyssn (Lyssn, Seattle, WA), for ongoing supervision and fidelity checks. The Lyssn platform

provides an algorithm-generated rating score for the Cognitive Therapy Rating Scale (CTRS (Young and Beck, 1980)) using an artificial intelligence-trained machine learning model based on the conversational content within each recorded session (e.g., (Imel et al., 2024)). Participants were instructed to not discuss their assigned pre-therapy condition/group assignment during therapy or clinical assessments with any incidental disclosure recorded. Therapists and clinical interviewers provided their best guess to condition assignment of each participant post-intervention. Immediately following each therapy session, participants completed a series of questionnaires.

Primary Measures

Working alliance and behavioral activation were the *a priori*-selected primary outcomes for the present study. Working alliance related to each session was recorded following each therapy session via the client version of the Working Alliance Inventory – Short Revised (WAI) (Hatcher and Gillaspy, 2006). The WAI is a 12-item assessment utilizing a 5-point Likert-scale ranging from 1 (seldom) to 5 (always). The survey is scored via three 4-item subscales for components of the therapeutic alliance: bond (the quality of the emotional bond between patient and therapist), goals (the agreement between the client and therapist on the goals of treatment), and task (the agreement between the client and therapist on the tasks to achieve the goals), as well as with a total, or sum, score with higher scores indicating greater patient-therapist alliance.

Behavioral activation over the preceding week was assessed at intake, the start of each therapy session, and the post-intervention visit using the Behavioral Activation for Depression Scale (BADS) (Kanter et al., 2006). The BADS consists of 25 questions asking about activation, avoidance/rumination, work/school impairment, and social impairment occurring over the past week. The BADS is scored using a total score with higher scores indicating greater behavioral activation. The change in BADS from the baseline score at week 1 (which

reflected activation in the week preceding the start of treatment) to each subsequent assessment at weeks 2-8 and the post-intervention visit (each reflecting activation in the preceding week corresponding to activation in response to each of the therapy sessions) was the primary outcome of interest.

Secondary Outcomes

Clinical Outcomes

Depression diagnoses were made via the SCID at the intake visit and post-intervention visit. The clinician-rated Hamilton Depression Rating Scale (HAMD) and the Columbia Suicide Severity Rating Scale (C-SSRS) were also completed at these time. The SCID is a semi-structured interview used to diagnose mental disorders according to the diagnostic criteria published within the American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders (DSM-5 (First et al., 2015)). The HAMD was administered to assess depression symptom severity utilizing the 17-item GRID – HAMD scale recording severity of depressed mood, feelings of guilt, suicidal ideation, insomnia, agitation or retardation, anxiety, weight loss and somatic symptoms (Hamilton, 1967; Williams et al., 2008). The assessment uses a sum score with higher scores indicating greater symptom severity categorized as: no depression (0-7), mild depression (8-16), moderate depression (17-23), and severe depression (≥24) (Zimmerman et al., 2013). The C-SSRS (Posner et al., 2008) was administered at all study visits to assess any suicidality concerns and to engage mitigation practices, if appropriate. A safety plan was developed during the intake that was referenced and revised, as appropriate, throughout the intervention.

Additionally, the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001) was completed by the participant at every visit. The PHQ-9 was created based on the DSM-IV depression criteria with each question ranging from 0 (not at all) to 3 (nearly every day) with a total score ranging from 0 to 27.

Additional Session Measures

In addition to working alliance, the Session Evaluation Questionnaire (SEQ) (Stiles, 1980), an additional measure of in-session processes, and the Automatic Thoughts Questionnaire (ATQ) (Hollon and Kendall, 1980), a measure of the believability of automatic negative thoughts, were recorded as additional assessments of exercise priming. The SEQ was completed by the participant following each therapy session, and the ATQ was completed at the start of each visit.

Other Assessments

Additional mental health and quality of life assessments were collected at baseline, and throughout the study: DSM-5 Level 1 Cross-Cutting Symptoms Measure, WHO Disability Assessment Schedule, Quality of Life, GAD-7, Adverse Childhood Experiences, Intervention Satisfaction, and Nature Connectedness Inventory (Meyer et al., 2024). Blood draws were also completed at weeks 1, 4, and 8 at three separate times on each visit (before the Active/Calm condition, between the condition and the therapy session, and after the therapy session).

Adverse Event Reporting

Adverse events were systematically documented on REDCap after each study visit by the research team. Briefly, the research team would select "Yes" or "No" based on if a potentially reportable event was disclosed by the participant or research team during the study visit. If "Yes" was selected, a Reportable Event Monitoring Form detailing the event was completed. During the post-intervention visit, participants responded to the prompt, "Have you experienced changes in medical conditions since you've started this trial that is/are potentially related to your enrollment in the study?" Participants were asked to provide detail via free text response with follow-up performed according to reporting requirements.

Statistical Analysis

The sample size was chosen to ensure a high probability for achieving the study progression criteria for target engagement for mechanisms of change under the expected effects of $d \geq 0.50$ and a low probability for achieving the Go criteria when $d=0$ with a conservative 80% retention. Progression criteria were based on NIH experimental therapeutics guidance to determine mechanistic plausibility before scaling to efficacy. The probability of achieving the progression criteria (observing $d \geq 0.35$ on both WAI and BADS or $d \geq 0.55$ on at least one) if true target engagement was absent on both endpoints ($d=0$), was low (<2% chance), and conversely if true target engagement is moderate on both endpoints ($d \geq 0.5$) or strong ($d \geq 0.75$) on one endpoint, then the progression criteria was likely to be achieved (>74% chance).

All analyses were conducted following the intention-to-treat (ITT) principle and included outcome data from all randomized participants including those who did not complete all 8 therapy sessions. Due to the sample size and generally limited missingness for a clinical trial, we did not attempt to multiply impute missing outcome data and instead conducted analyses using all available observed data.

To estimate condition effects (i.e. ActiveCBT versus CalmCBT) on the WAI overall score across therapy sessions at weeks 1 to 8, we used a generalized estimating equation (GEE) with an AR(1) working correlation matrix and factorial session by condition effects. We then averaged the session specific condition effects across the 8 weeks, and obtained the standardized average condition effect estimate by dividing by the estimated residual standard deviation. Our emphasis was on effect size rather than statistical significance testing per the funding mechanism for this trial. Estimates of condition effects on the three WAI subscales were obtained similarly. We conducted an analysis of change in BADS total score from week

1 across weeks 2 to 8 and the post-intervention visit similarly using a GEE but also adjusted for the week 1 (pre-condition) BADS total score.

To understand which items on the WAI questionnaire were implicated in any condition effects, we used mixed models with participant and session within-participant random effects to conduct item-specific analyses (i.e., each item from the WAI was a repeated measure outcome). We carried out an omnibus Chi-squared test to determine whether there was a statistically significant condition effect on any item across the 8 assessment time points.

Secondary outcomes were analyzed using appropriate methods given the outcome type (i.e. continuous, binary, ordinal) and repeated measures structure. The ATQ, PHQ-9, and the SEQ scores were analyzed using a GEE similarly to the primary analyses. We estimated condition effects on change in HAMD and change in GAD-7 between intake and post-intervention using linear regression with an adjustment for baseline. We estimated risk differences and Miettinen-Nurminen 95% confidence intervals (Miettinen and Nurminen, 1985) for HAMD response and remission, as well as for SCID diagnosis rates.

Results

Baseline Characteristics and Participant Flow

Table 1 contains the baseline characteristics of the cohort by condition group. The study randomized 40 participants between September 2023 and August 2024 with n=21 assigned to the CalmCBT condition and n=19 assigned to the ActiveCBT condition with unequal numbers due to severity stratification (**Figure 1**).

Session Completion

Thirty-four out of forty (85%) participants completed ≥6/8 CBT sessions with 33 completing all 8 sessions (82.5%). Across groups, 281/320 total visits were attended (87.8%). By condition group, 15/19 (78.9%) ActiveCBT participants completed all 8 sessions versus 18/21 (85.7%) CalmCBT condition participants. As intended, the median was 7 days between

each weekly CBT session. Of the 7 participants who did not complete all 8 sessions, there were two participants (one in each condition group) who completed 1, 2, and 3 sessions prior to dropping out (shown in **Fig. 1**). There was also one ActiveCBT participant who only completed 5 sessions but returned for a post-intervention visit. One participant was withdrawn after the first session due to having previously unknown social relationships with study therapists, whereas the remaining dropouts declined to continue.

Condition Adherence

As intended, participants assigned to the ActiveCBT condition had significantly higher RPE (mean ± SD, ActiveCBT: 13.0 ± 0.19, CalmCBT: 6.22 ± 0.53, $p<0.001$) and heart rate (ActiveCBT: 124.0 ± 17.5 bpm, CalmCBT: 74.9 ± 12.1 $p<0.001$) than CalmCBT participants during the pre-therapy condition periods.

CBT Fidelity

The mean overall score and standard deviation on the CTRS from Lyssn was 36.8 ± 5.1 (36.9 ± 5.4 Active, 36.7 ± 4.9 Calm, $p=0.89$), demonstrating similarity of the fidelity of the received therapy across the two groups.

Primary Outcome Results – Target CBT Mechanisms

Table 2 contains results of the primary analyses for the key mechanism of change outcomes. The average standardized effects on WAI total score and change in BADS were 0.14 and 0.43, respectively. Differences in the WAI Total score were driven entirely by the Bond subscale such that the standardized effect on the WAI Bond subscale was 0.36.

Working Alliance (WAI)

The average effect on WAI Total was 1.02 (95% CI: -2.84 to 4.87; $p=0.60$). This effect favoring the ActiveCBT condition was predominately driven by the bond subscale. Both groups demonstrate improving WAI Bond over time (**Figure 2**) with the ActiveCBT condition group exhibiting a non-significantly higher alliance across all 8 assessments.

The item-specific analyses showed that items 3, 7, and 9 exhibited the largest condition effects of 0.47, 0.23 and 0.22, respectively, with all three being from the Bond subscale and favoring the ActiveCBT condition. There was a significant condition effect when comparing to a nested mixed model without condition effects (p=0.005).

Behavioral activation (BADS)

The average effect on change in BADS was 7.78 (-1.31 to 16.86; p=0.093; **Table 2**). Both condition groups exhibited improved BADS over time (**Figure 3**) with the ActiveCBT condition group exhibiting a non-significantly larger improvement across all 8 assessments.

Secondary Outcome Analyses

The HAMD results indicate a modest general benefit for ActiveCBT over CalmCBT conditions (d=0.20), limited benefit on response (risk difference: 0.12), and a large benefit on remission (risk difference: 0.35 [0.01-0.62]; **Table 2**). There was not a significant group difference for any of the other secondary outcomes.

Adverse Events

Overall, there were no unanticipated adverse events reported in either group across the 131 Active conditions, the 150 Calm conditions, or the subsequent 281 therapy sessions. At post-intervention, 0/34 participants reported an adverse event had occurred during the intervention. Three reportable events were recorded during the intervention period: a previous social relationship with the therapist (resulted in study exit; classified as an unexpected problem), a foot cramp (resolved during therapy session), and faintness from a blood draw (resolved quickly with rest and hydration).

Blinding Results

Group membership was disclosed by 3 participants either during the interviews (0 ActiveCBT; 1 CalmCBT) or therapy (1 ActiveCBT; 1 CalmCBT). At post-intervention among participants without a prior group disclosure, the therapist accurately predicted

condition membership 53% of the time (7/15 ActiveCBT, 10/17 CalmCBT), and the clinical interviewer accurately predicted condition membership 58% of the time (9/16 ActiveCBT, 10/17 CalmCBT), neither of which were statistically significantly different from chance (i.e., 50%).

Discussion

This randomized, controlled trial of the effects of exercise priming of CBT for depressed adults in a major depressive episode showed that moderate exercise immediately prior to therapy sessions (i.e., ActiveCBT vs. CalmCBT) non-significantly enhanced the therapeutic bond and increased behavioral activation across therapy, two key factors determining the efficacy of CBT. The degree of enhancement of working alliance (particularly the bond subscale; d=0.36) and behavioral activation (d=0.43) met *a priori*-defined benchmarks of both ≥0.35, though confidence intervals included zero and findings should be considered preliminary. Although exploratory, the HAMD results suggested a potentially important remission benefit (i.e., HAMD<8) in the ActiveCBT over CalmCBT groups after the intervention (69% vs 33%; p<0.05). The high adherence (87.8% of visits), successful masking of assessors and therapists, similar therapy fidelity, and no adverse or serious adverse events suggests highlight strengths of the study design and show that this approach is feasible and safe for adults with depression. Overall, the present results met the progression rules and support subsequent testing of this augmentation approach.

The current trial supports the use of exercise priming to enhance mechanisms of change related to CBT's antidepressant effects. Both the bond component of working alliance and behavioral activation were higher in the ActiveCBT over the CalmCBT group, exceeding the pre-specified effect size milestone of 0.35. There is ongoing debate about whether therapy's effectiveness is due to specific factors inherent to the therapy or non-specific factors common across all therapies (Cuijpers et al., 2019b; Huibers and Cuijpers, 2015; Wampold,

2015; Wampold and Flückiger, 2023). However, the potential benefit of exercise priming to both non-specific (therapeutic alliance) and specific (behavioral activation) factors is noteworthy. This suggests that exercise priming could enhance the efficacy of any form of psychotherapy by improving the therapeutic alliance and may also specifically benefit CBT by increasing behavioral activation across treatment. Given that both pathways were supported, exercise priming emerges as a promising, low-cost augmentation approach that warrants rigorous testing in larger trials to determine its potential to boost psychotherapy (and particularly CBT) efficacy.

The therapeutic alliance effects warrant careful consideration. Specifically, working alliance was pre-specified as a primary mechanism, whereas the Bond subscale emerged as a driver of alliance effects, exceeding the pre-specified effect-size threshold for ActiveCBT even though the total WAI score did not (**Table 2**). This pattern is consistent with theoretical expectations: the total WAI score combines bond, goals, and tasks, diluting any bond-specific effect. Based on prior work (Meyer et al., 2022a, 2022b, 2016a), we hypothesized that exercise would reduce state anhedonia and depressed mood and increase neuroplasticity markers such as BDNF, creating a psychological state conducive to interpersonal engagement. These changes are directly relevant to the bond dimension (e.g., "I feel that my therapist appreciates me"), which reflects emotional connection rather than agreement on tasks or goals. Acute exercise also improves emotion regulation and reduces stress reactivity (Morava et al., 2024; Wang et al., 2024), and single sessions have been shown to enhance social interaction and affiliative behaviors in clinical populations (Brand et al., 2018). Together, these mechanisms provide a plausible basis for expecting exercise priming to strengthen the therapeutic bond without necessarily influencing task or goal agreement.

Behavioral models of CBT suggest that increasing engagement with valued activities and contact with environmental reward is a core mechanism of change. In a large

non-inferiority RCT, BA achieved outcomes comparable to CBT at 12 months, underscoring the clinical relevance of activation-focused strategies (Richards et al., 2016). Meta-analytic work further shows that BA not only reduces depressive symptoms but also increases activation (e.g., BADS-indexed activation/approach (Stein et al., 2021)), supporting activation as a plausible pathway of benefit. Given that BA is a core behavioral mechanism within CBT, the between-session activation gains observed here align with BA's established change pathway (more approach behavior and environmental reward) and with evidence that BA is increases activation, suggesting that priming may have amplified clients' post-session enactment of these CBT-embedded behaviors.

It is plausible that the improvements we observed in behavioral activation and depressive symptoms reflect benefits of engaging in moderate-intensity exercise per se rather than a mechanism unique to pre-CBT exercise. However, contemporary dose–response data evidence (Noetel et al., 2024; Tang et al., 2024) shows that one exercise session per week is unlikely to produce substantial antidepressant effects at the symptom level. Clinically meaningful benefits typically emerge around 600-1000 MET-min/week of exercise, typically achieved through 3–4 moderate-intensity sessions per week, well above the dose produced by one 30-minute session (~90–180 MET-min). Therefore, although repeated exercise across the intervention may contribute to general symptom improvement, the acute, session-proximal mechanisms we targeted remain the more plausible explanation for the observed pre-CBT effects than an antidepressant response generated from a once-weekly exercise dose.

Early alliance development is critical for CBT outcomes, with alliance typically peaking in sessions 3–4 and strongly predicting symptom change (Horvath et al., 2011; Wampold, 2015; Wampold and Flückiger, 2023). Prior research also shows that bond specifically relates to CBT outcomes (Zimmermann et al., 2021). In the present trial, the largest group differences in bond occurred early in treatment (**Figure 2**), suggesting that

exercise priming may accelerate the formation of a strong therapeutic relationship during this crucial window. Although these bond-specific effects should be interpreted cautiously given the sample size and confidence intervals, they align with mechanistic expectations and highlight a promising pathway for enhancing psychotherapy engagement.

Importantly, the magnitude of the benefits are potentially meaningful in the context of recent therapy research. A meta-analysis of psychotherapy dismantling trials for depression indicates a modest d=0.21 effect size for the added benefit of therapies that include the purportedly key therapy factors compared to therapies without (Cuijpers et al., 2019a). Therefore, the relative benefits of exercise priming in the present trial of 0.36 and 0.43 may have meaningful benefits in augmenting therapy if these effects on candidate mechanisms translate into effects on depression. The small sample size requires cautious interpretation of the present data, though provides compelling support for larger trials.

Although exploratory, the interviewer-assessed depression remission results suggests an important clinical benefit. Remission rates according to the interviewer-administered HAMD were significantly different between groups with 69% in the ActiveCBT group and 33% in the CalmCBT group achieving remission (HAMD<8). This is encouraging as post-treatment symptom severity is a significant predictor of the likelihood of relapse (Thase et al., 1992; Wojnarowski et al., 2019). If these preliminary results showing a low general rate of depressive symptoms and high remission after exercise-primed therapy is confirmed in larger trials or persists at longer-term follow-up, exercise priming holds promise to meaningfully increase the short- and long-term efficacy of psychotherapy for depression.

The design and execution of this trial provide strong internal validity and lead to relatively high confidence in the results albeit within the context of the small sample size. The CalmCBT comparator condition was time- and attention-matched with no group differences in CBT quality (see Lyssn results) and provided strong clinical equipoise, which is missing

with most comparator conditions (Mohr et al., 2009). Additionally, we successfully masked the therapist and clinical interviewers to treatment allocation. Further, the structured reporting and zero adverse events during this trial highlights the safety of this approach. Finally, adherence was high with only 3 dropouts/group for a total dropout rate of 15%, below the 20-40% who do not complete therapy in community settings (Fenger et al., 2011; Gersh et al., 2017). Overall, this trial's high internal validity lends confidence to its directional support of exercise priming increasing working mechanisms of therapy and remission rates.

Nevertheless, the trial is not without limitations. Primarily, the trial was not designed to provide an efficacy test, but rather to determine the plausibility of augmentation of working alliance and behavioral activation via exercise priming. As a result, the sample size is low for efficacy testing but was able to provide necessary effect size data to justify progression to a larger trial to determine clinical efficacy. Although an interesting and related question, we did not test whether uncoupled, once-weekly exercise alone augments CBT, rather, our trial examined the clinically relevant question of session-proximal (pre-session) exercise as a real-time priming strategy. Additionally, the exclusion criteria (e.g., BMI cutoff, some comorbid mental health conditions) and limited participant heterogeneity limit generalizability. Further, the lack of follow-up prevents examination of the durability of potential benefits on relapse rates.

Conclusion

This 40-person randomized controlled trial of 8 weeks of moderate intensity acute exercise priming compared to quiet rest immediately before standardized CBT sessions, found sufficient directional engagement of an increased therapeutic bond and greater self-reported behavioral activation in the exercise priming condition with potential benefits on depression remission. Although these results should be interpreted cautiously considering the small

497 sample size and confidence intervals on mechanistic findings that include zero, they met a
498 priori-defined benchmarks of directional mechanistic signals and warrant further study of this
499 approach. Further, signals in both non-specific (therapeutic bond) and specific (behavioral
500 activation) working mechanisms of therapy success provide potential generalizability of the
501 exercise priming approach to other therapies while also highlighting its potential as a safe and
502 accessible augmentation approach to specifically increasing the antidepressant effects of CBT.

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Figure legends

Fig. 1. CONSORT diagram for CBT+ trial from screening to post-intervention.

Abbreviations: BMI: body mass index, PHQ2: Patient Health Questionnaire-2, PHQ8: Patient Health Questionnaire-8, CSSRS: Columbia-Suicide Severity Rating Scale, MDD: major depressive disorder, CBT: cognitive behavioral therapy.

Fig. 2. Estimated expected working alliance inventory (WAI) Bond with 95% confidence intervals (A) by condition across all eight sessions, and (B) the relative difference between the groups across sessions.

Fig. 3. Estimated expected change in behavioral activation for depression scale (BADS) total from week 1 with 95% confidence intervals (A) by condition across all eight sessions, and (B) the relative difference between the groups across sessions.