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Mechanisms of change in pharmacological, psychological and combined treatment of depression: a study protocol

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Abstract

Background:

Although both antidepressant medications (AD) and cognitive-behavioral therapy (CBT) are established treatments for major depressive disorder, their mechanisms of change, and potential synergistic or inhibitory interactions in combination therapy, remain insufficiently understood. Traditional outcome measures focus on symptom severity, often overlooking intraindividual dynamics that may explain differential treatment effects. Recent advances in temporal network modelling offer a promising framework to capture these dynamics and assess how interventions reshape the structure and regulation of symptom networks. The Dynamic Networks in Depression Treatment (DYNDET) study aims to investigate how pharmacotherapy, psychotherapy, and their combination affect symptom connectivity and change processes over time.

Methods:

DYNDET is a randomized, controlled, open-label trial with three parallel treatment arms: (A) selective serotonin reuptake inhibitor (SSRI) pharmacotherapy, (B) cognitive-behavioral group therapy for depression (CBGT-D), and (C) combined treatment. After individual screening by a study physician, a total of 90 participants will be randomized equally into the three groups. Following a 3-week ecological momentary assessment (EMA) baseline phase, participants receive an 8-week treatment. EMA data are collected seven times daily using a smartphone app (*mpath*) during the baseline phase. During treatment, participant data are collected once per day. The primary outcome of the DYNDET study is the change in the structure of symptom networks (the dynamic network from the baseline phase and the cross-sectional networks from the treatment phase), assessed via multilevel vector autoregressive (mlVAR) modelling across the EMA period and via network intervention analysis during the intervention period. Secondary outcomes include clinician-rated and self-report measures of depression severity, functioning, affect regulation, and cognition, as well as exploratory neuroimaging data in a subsample. The analytic strategy includes network intervention analysis, mixed-effects modeling, and moderation analyses based on baseline network features.

Discussion:

DYNDET is among the first clinical trials to explicitly examine how different treatment modalities modulate the dynamic structure of depressive symptom networks. By going beyond static symptom counts, this study will provide insights into differential and potentially complementary mechanisms of AD and CBT. Findings may inform more precise, individualized treatment planning and guide future research on network-based markers of therapeutic change.

Trial registration:

ClinicalTrials.gov: 2025-2718. Registered x

Keywords

Depression, Cognitive Behavioral Therapy, SSRIs, Network Analysis, Ecological Momentary Assessment

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Role of sponsor {5c}	Principal Investigator of the trial.
Composition of the coordinating centre and trial steering committee {5d}	Trial steering committee: Igor Nenadic, Oliver Grimm, Stefan G. Hofmann, Tobias Kube, Ulrich Stangier.

Introduction

Background and rationale {6a}

A large number of randomized controlled trials have confirmed the efficacy of both antidepressant medications (AD) and psychological therapies, such as cognitive–behavioral therapy) (CBT) in treating depression (Plessen et al., 2023; Cuijpers et al., 2023), although depending on severity and types of treatment. In addition, a combination of psychotherapy and antidepressants generally has been shown to enhance therapeutic outcomes (Cuijpers et al., 2020), suggesting that they may work through complementary mechanisms. However, Whiston et al. (2019) found in their meta-analysis of trials focusing on CBT as psychological treatment that a combination with SSRIs was inferior to CBT alone, indicating an inhibitory effect of combining both treatments. With regard to differential effects of AD and CBT on specific indicators of response, results are often insignificant or inconsistent, as related to cognitive changes (Quilty et al., 2014; Courtney et al., 2022), affective changes (Boschloo et al., 2019) or neural response (Dunlop et al., 2017 ; 2023).

Furthermore, there is a lack of knowledge about mechanisms of change in AD vs. CBT, as well as possible Complementary Mechanisms of change in the combination of both approaches. For instance, using network analyses of symptom change in depressed patients, Boschloo et al., (2022) found that the effects of SSRIs were primarily mediated by reduced depressed mood and anxiety, whereas changes in cognitions were found to be rather an indirect effect of the affective change. Lemmens et al. (2016) presented a scoping review of mediators of psychological treatments, which included, among others, cognitive change, activity level and rumination. However, in an RCT directly comparing the effects CBT and SSRIs with placebo (Fournier et al., 2013), a different pattern was observed, with medication leading to a greater reduction in cognitive symptoms and cognitive therapy to a greater reduction of atypical-vegetative symptoms than placebo.

Neurobiological theories may provide a framework for understanding how these two treatments may differ in their effects on the brain. A commonly accepted model suggests that psychotherapy primarily engages "top-down" processes, affecting prefrontal cortical regions involved in cognitive control, emotion regulation, and awareness of emotional states (DeRubeis et al., 2008). In contrast, antidepressant medications are

thought to work "bottom-up", acting directly on subcortical structures such as the amygdala or the limbic system, which are heavily involved in the generation and processing of affective states and visceral responses (Pizzagalli, 2011).

In contrast to this hypothesis, a recent meta-analysis analyzing fMRI-studies with regard to neural effects of antidepressants found no convergence across foci of treatment-associated alterations in functional imaging. As compared to untreated patients, patients treated with antidepressants showed changes in the left dorsolateral prefrontal cortex (Saberi et al., 2024). However, these changes are associated with working memory, attention and behavior, domains that are primarily supposed to be related to the effects of psychological treatments. Referring to the effects of psychological treatments, a former meta-analysis (Sankar et al., 2018) found that the activity of the left rostral anterior cingulate was increased in response to affective visual processing tasks, which was interpreted to reflect improvements in emotional responsivity following psychotherapy. Thus, it appears that both psychological and pharmacological treatments may act on prefrontal and limbic areas of the brain as well.

Comparing the neural effects of psychological treatments and antidepressants, meta-analyses also show inconsistent results. For instance, a former meta-analysis (Kalsi et al., 2017) indicated that psychological and pharmacological treatments lead to differential effects on the right paracingulate activity: whereas psychological treatments increase the activation of this area, pharmacological treatment might reduce this activity, supporting the hypothesis that psychological treatments may involve a top-down emotional regulation. However, this hypothesis was only partially supported by a recent meta-analysis (König et al., 2025) which found that CBT reduced limbic reactivity and altered activity in cingulate and prefrontal cortex, but the patterns of changes in various subregions of the cingulate cortex were inconsistent between studies, depending on task content, statistical evaluation, and interventions.

A clearer understanding of differential treatment mechanisms can be achieved through a network perspective on psychopathology, which reconceptualises depression as a system of mutually reinforcing symptoms (Borsboom & Cramer, 2013). Rather than modelling depression as a latent construct, this framework maps the conditional dependencies among individual symptoms and quantifies their mutual influences

(Borsboom, 2017). A growing body of evidence, as highlighted in the narrative review by Wichers et al. (2021) suggests that depression is best understood as dynamic system of mutually reinforcing affective, cognitive, behavioural states. At the symptom (macro) level, sadness, anhedonia, and fatigue often emerge as central "bridge" symptoms linking depression to comorbid conditions, underscoring their pivotal role across cross-sectional studies. Intensive longitudinal momentary assessment (EMA) data further clarify dynamics at the micro-level: during psychotherapy, Snippe et al. (2024) found that emotional and cognitive improvements (e.g. reductions in worry and negative self-thoughts, and changes in sad/happy mood) typically arise at the same time, whereas behavioural gains such as increased social interaction and activity tend to occur later, challenging classical models that posit behavioural activation precedes mood improvement. Randomized controlled trials of antidepressants and mindfulness-based cognitive therapy show symptomatic improvement occurs without consistent reductions in the dynamic connectivity among momentary affective states (Snippe et al., 2017), suggesting persistent underlying vulnerability despite symptom relief. Additionally, Helmich et al. (2023) empirically show that rising autocorrelation, a hallmark of "critical slowing down", in momentary affect states frequently precedes transitions toward reduced depression during treatment, whereas variance-based early warning signals are less reliable, highlighting both the promise and current limitations of using such signals for personalized prediction. In pharmacological research, Bos et al. (2018) employed network analysis to assess SSRI treatment for major depression, finding not only an overall reduction in symptom severity but significantly increasing interconnectivity. This suggests that network models can reveal subtle but clinically meaningful reorganizations in symptom architecture that global scores would miss. Yet, most pharmacological and psychotherapeutic trials still rely on aggregate sum-scores, obscuring the micro-processes and change mechanisms through which treatments might exert their impact.

Network Intervention Analysis (NIA) has begun to meet this need by embedding a treatment variable directly into the network and tracking which symptoms ("nodes") show the earliest and strongest connections ("edges") with the intervention node. Initial NIA work by Blanken et al. (2019) demonstrated that NIA can pinpoint not just which

symptoms of insomnia and depression improve during cognitive-behavioural therapy for insomnia (CBTI), but also the sequence in which these improvements emerge. Additionally, Jurado-González et al. (2024) applied NIA within a large randomized trial contrasting transdiagnostic group CBT plus usual care versus pharmacological treatment for emotional disorders. Their symptom-level network models revealed that psychological intervention had direct and lasting effects on core anxiety and depression symptoms (such as excessive worry, difficulty relaxing, and sad mood) that then have indirect benefits to associated symptoms across long-term follow-up. Furthermore, Fishbein et al. (2023) used NIA in a randomized controlled trial of Acceptance and Commitment Therapy (ACT) versus minimally enhanced usual care for anxious cancer survivors, examining both process and outcome variables. Contrary to traditional mediation expectations, they found that the ACT intervention produced direct improvements primarily in cancer-specific anxiety outcomes (fear of recurrence and cancer-related trauma symptoms) which then mediated indirect improvements in other psychological processes and outcomes. This network approach highlighted that certain outcomes, typically considered mere endpoints, functioned as active mechanisms transmitting treatment effects to other targets, thus capturing complex, multi-directional pathways of therapeutic change that cannot be seen with standard mediation models.

The necessity and unique contribution of our study arises from several significant gaps in the current literature on depression treatment. Despite advances in applying network frameworks to both symptom-level and EMA data, most studies have focused on examining changes within a single treatment modality, predominantly psychotherapy or pharmacotherapy in isolation, rarely comparing these directly, or integrating combination treatments. Furthermore, prior research has often relied on cross-sectional or short time-frame longitudinal data, leaving unanswered questions about how symptom interactions shift through various treatment stages. Our project directly addresses these limitations by systematically comparing the change of symptom networks with network intervention analysis across three distinct treatment arms: monotherapy with CBT group therapy, monotherapy with pharmacotherapy, and combination treatment, in a real-world sample of outpatients with depression. This design provides the rare opportunity to identify not only which specific symptoms or

processes respond most sensitively and rapidly within each treatment and how this might be connected to baseline EMA or fMRI data, but also whether, when, and how network structures reorganize differently depending on therapeutic modality or their combination.

Building on this foundation, the study tests a set of core hypotheses in an exploratory framework reflecting the limited prior research systematically comparing these treatments (especially combined treatment) on a network level. We hypothesize that the three treatment conditions will differ significantly in their direct and indirect effects on change processes within depressive symptom networks. We further expect differences in the timing of treatment effects, with early improvement predicted by baseline network connectivity patterns unique to each modality. Distinct treatment arms may result in divergent post-treatment network connectivity and stability profiles, reflecting alternative mechanisms of symptom reorganization. Combination therapy will be explored for synergistic, additive, or inhibitory interactions affecting symptom network structure. Additionally, features derived from the baseline EMA network (e.g. symptom centrality, increased autocorrelation and variance) are hypothesized to moderate treatment response and help identify non-responders prior to therapy onset.

Explanation for the choice of comparators {6b}

Comparators of combined treatment are psychological and pharmacological treatment. Since proven effective treatment are applied, the comparison of combined treatment with active treatments appears to be adequate and a placebo arm is not considered to be necessary. However, a baseline phase will be implemented to assess also nonspecific (placebo) effects.

Objectives {7}

The primary objective of this study is to systematically compare and clarify the mechanisms of symptom change in depression across three treatment modalities (CBT group therapy, SSRI pharmacotherapy, and their combination) by leveraging a network approach to psychopathology. The research aims to:

- Identify and contrast direct and indirect effects of each treatment on core depression symptoms, including affective, cognitive, and vegetative domains.

- Examine the timing, trajectory, and stability of treatment effects across modalities, with a focus on how specific symptoms and symptom networks reorganize over the course of treatment.
- Uncover potential synergistic, additive, or inhibitory interactions in combination therapy, clarifying whether combining treatments produces complementary or counteractive changes within symptom networks.
- Evaluate baseline predictors of treatment response, such as EMA-based network centrality, to better understand which patients may benefit most from each intervention and to identify non-responders early.

By integrating intensive longitudinal EMA data at baseline, pre- and post-treatment fMRI, and additional behavioural measures, the study seeks to advance a nuanced, multimodal understanding of how diverse interventions shift both symptomatic and neurobiological processes in depression. The project is intentionally exploratory, reflecting the current lack of direct comparative and mechanistic research focusing on change mechanisms across these treatment arms (especially regarding combination therapy for depression) on a network level. This project aims to gain improved insight into the nuanced, modality-specific pathways through which diverse depression treatments exert their effects, thereby advancing mechanistic understanding beyond conventional aggregate symptom measures.

Trial design {8}

This study will employ a parallel-group design with three arms: selective serotonin reuptake inhibitor (SSRI) pharmacotherapy, cognitive behavioral therapy (CBT) delivered in a group format, and a combination of both interventions. Before randomization, all participants will undergo a screening conducted by a study physician, which may take place via telephone, video call, or in-person. During this screening, current psychological symptoms and possible physical comorbidities will be assessed. Based on this information, the study physician will determine whether all three treatment conditions are equally suitable for the participant. If that is not the case, the individual will be unable to participate in the study and will instead receive an appointment at the psychiatric outpatient clinic to plan further treatment options. Only those for whom all conditions are appropriate will proceed to random allocation. Suitable participants will

then be randomly assigned to one of the three treatment groups in a 1:1:1 ratio after completion of the baseline assessment, ensuring equal distribution across all arms. The total duration of the intervention will be eight weeks. Each treatment arm will include 30 participants, resulting in a total sample size of 90. The study is primarily exploratory in nature, aiming to generate preliminary insights into the comparative effects of the interventions.

Methods: Participants, interventions and outcomes

Study setting {9}

The study will be conducted in Germany across two locations encompassing three study centres: the outpatient clinic of the Department of Psychiatry and Psychotherapy at UKGM Marburg; the outpatient cognitive behavioral therapy clinic at the Institute of Psychology, Goethe University (GU) Frankfurt; and the psychiatric outpatient clinic of the Department of Psychiatry, Psychosomatics and Psychotherapy at GU Frankfurt. All treatment will take place in an outpatient setting and be delivered on-site at the respective centres. In addition to the on-site treatment, participants will complete Ecological Momentary Assessment (EMA) and self-report questionnaires in their everyday environments using the smartphone-based application m-path.

Eligibility criteria {10}

Participants must be between 18 and 65 years of age and have sufficient proficiency in German to understand study procedures and provide informed consent. Eligible individuals must currently be experiencing a mild to moderate depressive episode. Individuals presenting with a severe depressive episode will be excluded from participation following the clinical assessment, as random allocation would not be appropriate in such cases, given the recommendation to offer combined psychopharmacological and psychotherapeutic treatment according to current guidelines. Furthermore, participants should not be undergoing psychotherapy or taking antidepressant medication at the time of enrolment. Additionally, they must own a smartphone and have regular access to the internet, as participation involves completing

Ecological Momentary Assessment (EMA) and self-report questionnaires via the m-path smartphone app. Written informed consent is required prior to participation.

Individuals will be excluded if they have a diagnosis of bipolar disorder, exhibit acute suicidality, suffer from a substance use disorder, have a depression with psychotic symptoms, or have a severe medical or neurological illness. Participants with conditions that may interfere with fMRI and study procedures (e.g. metal implants, significantly impaired speech, or pregnancy) will also be excluded.

Therapists involved in the study must be either licensed psychotherapists or advanced trainees and must be trained in the study's group therapy manual. Physicians administering pharmacological treatment must be board-certified psychiatrists with experience in prescribing and monitoring SSRIs.

Interventions

Intervention description {11a}

Intervention description {11a}

All treatments comprise a 3-week baseline phase and an 8-week intervention phase.

Baseline phase: Participants are instructed to judge the intensity of depressive symptoms among others 5x/day over 21 days. A mobile app (m-Path) will be used to prompt users to enter data at regular intervals. In addition, daily sleep assessments are conducted in the morning, and assessments of social events are conducted in the evening.

Treatment phase: This phase comprises 8 weeks providing one of three treatments:

A) Psychopharmacological treatment.

B) Cognitive-behavioral group treatment (CBGT-D)

C) Combination of psychopharmacological and cognitive-behavioral group treatment.

Psychopharmacological treatment will be in accordance with the German guidelines for treatment of major depression ("Nationale Versorgungsleitlinie Unipolare Depression", AWMF-register number nvl-005, version 3.2 of 2022; online: awmf.org). For this purpose, a selective serotonine reuptake inhibitor (SSRI), escitalopram, will be selected for out-patient treatment. Prior to drug treatment, subjects will be informed about the substance as part of a routine clinical management, according to the national guidelines. Laboratory tests and ECG will be performed (not part of study, but GCP). Patients will then be started on a dose of escitalopram 5mg daily for three days, which will be subsequently raised to the target dose of 10mg daily. Clinical re-evaluation during short clinical visits in out-patients after two and four weeks will include side effect management, if necessary. In case of insufficient clinical response (as per guideline criteria), clinicians will be able to raise the daily dose of citalopram to 15mg.

CBGT-D includes the following components (Schaub et al., 2013):

A) Psychoeducation: information about depression, cognitive-behavioral model.

B) Behavioral Activation: enhancing engagement in pleasurable or meaningful activities.

C) Cognitive Restructuring: identification and modification of negative thoughts and cognitive distortions.

D) Social problem-solving.

E) Homework Assignments.

F) Relapse Prevention: Identification of early warning signs and coping strategies.

Treatment is delivered using a manual which had been conceptualized for clinical routine care and evaluated in a randomized-controlled study (Schaub et al., 2018).

Criteria for discontinuing or modifying allocated interventions {11b}

Suicidal symptoms; severe side effects resistant to side-effect management; physical illness unrelated to study interventions (e.g. accidents, accidental brain trauma etc.).

Strategies to improve adherence to interventions {11c}

All psychotherapeutic sessions in our study are conducted by licensed psychotherapists or psychotherapists in advanced training who have received specific training in the standardized group therapy manual, while pharmacological interventions are overseen by board-certified psychiatrists experienced in SSRI prescription and monitoring. This high level of professional qualification and structured training ensures a consistent and trustworthy therapeutic environment, which increases participant confidence and fosters ongoing engagement with the assigned interventions, thereby supporting adherence.

EMA during baseline and daily assessments during treatment will play a central role in our study. To enhance compliance and minimize missed assessments, participants will receive automated reminders via their mobile devices to complete EMA entries at the scheduled times. The study employs a contingency-based incentive scheme, in which the monetary reward is directly linked to the quantity and timeliness of completed EMA entries. This approach is designed to maximize participant engagement with the daily assessments, thereby improving data integrity and allowing immediate identification of adherence challenges. Monitoring of the EMA data throughout the study will allow for the prompt identification of deviations or non-adherence. Participants identified as non-adherent will be contacted in a timely manner to address barriers and support re-engagement with the study procedures.

Relevant concomitant care permitted or prohibited during the trial {11d}

During study participation, all concomitant pharmacological and psychotherapeutic treatments will be systematically documented. Concomitant somatic treatments required for general medical care (e.g., antihypertensive medication, antidiabetics, thyroid medication, analgesics) are permitted throughout the trial, provided that they are prescribed according to routine clinical practice and, where possible, kept stable. Such treatments, as well as any changes, will be recorded. In contrast, additional

psychopharmacological treatments (e.g. initiation of further antidepressants, mood stabilizers, antipsychotics, or augmentation strategies outside the assigned study arm) and structured psychotherapeutic interventions (e.g. individual or group psychotherapy outside the assigned study arm) are not permitted during the randomized treatment phase, as they would confound the comparison of treatment conditions. If initiation of such treatment becomes clinically indispensable (e.g. due to symptom deterioration or emerging risk), this will be decided by the responsible clinician in accordance with good clinical practice. In these cases, participation in the allocated study intervention will be discontinued and the participant will be transitioned to routine care. Short-term symptomatic medications may be used as clinically indicated at the discretion of the treating physician and will likewise be documented. All concomitant medications and psychotherapeutic or counselling contacts will be monitored to evaluate their potential impact on study outcomes and to allow appropriate sensitivity analyses.

Outcomes {12}

The primary outcome of the DYNDET study is the change in the structure of symptom networks (the dynamic network from the baseline phase and the cross-sectional networks from the treatment phase), assessed via multilevel vector autoregressive (mlVAR) modeling across the EMA period and via network intervention analysis during the intervention period. Rather than focusing exclusively on symptom severity, the study emphasizes intraindividual network dynamics such as changes in node centrality, edge strength, and global connectivity measures. These include metrics such as outstrength and network temperature, which capture the stability and reactivity of the symptom system over time (Grimes et al., 2025).

Secondary outcomes include observer-rated depression severity based on validated clinical interviews (HAM-D, MADRS, IDS-C), as well as patient-reported outcomes assessing functional impairment (SOFAS), affective and cognitive functioning (e.g., PANAS-SF, PTQ, AAQ-II, PDQ), and interpersonal factors (e.g., F-SozU, CSI-4). Data are collected using a combination of structured assessments and high-frequency ecological momentary assessment (EMA) to ensure both breadth and temporal precision.

Functional MRI (pre- and post-treatment) data will be collected and may be used in exploratory analyses to investigate neural correlates of treatment-related change (Zhou et al., 2021; Boschloo et al., 2022). Integration of neuroimaging data into the main analytical framework is planned as a future extension, contingent on data quality and sample size.

Ecological Momentary Assessment (EMA) via mpath

In the baseline phase, participants will complete EMA via the mobile application mpath over a period of three weeks, with assessments administered five times per day, as well as each morning and evening. Items are rated on continuous visual analogue scales ranging from 0 to 100, capturing real-time variations in affect, cognition, motivation, physiology, social context, and daily functioning. Morning and evening surveys include items on sleep, expectations, emotional state, cognitive flexibility, social contact, and daily activities. High-frequency prompts assess momentary affect, energy levels, bodily complaints, repetitive negative thinking, and social needs. Additionally, participants provide a brief daily voice recording. During the subsequent 8-week treatment phase, participants complete a brief daily assessment focusing on key mechanisms of change and depression-related items. This reduced set of daily measures is specifically designed to monitor clinically relevant depressive symptoms throughout the course of treatment.

Participant timeline {13}

		Inclusion	**Baseline**	**Pre-Treatment**	**Treatment**	**Mid-Treatment**	**Post-Treatment**
	Week **Instrument**	0	0-2	2	3-10 (8 weeks)	7	11
Therapist	fMRI	X					X
	EEG	X					
	AAT	X					
	Speech Task	X					
	Mini-Dips	X					
	TALD	X					

	HAM-D	X					X
	HAM-A	X					X
	SOFAS	X					
	D2	X					
	RWT	X					
	Pfadfindertest	X					
	ZST	X					
	Combination interview HAMD-D MADRS, IDS-C	X					X
	YMRS	X					X
Patient	EMA		X Daily (5x/d)				
	EMA DYNDET				X Daily (1x/d)		
	Speech Task		X Daily				
	FsozU	X				X	
	CSI-4	X				X	
	EE-Item	X				X	
	ASQ	X				X	
	PDQ	X				X	
	PANAS-SF	X				X	
	AAQ-2 (7 Items)	X				X	
	BSI-18	X				X	
	PTQ	X				X	
	NEO	X				X	
	PATHEV	X					X
	CTQ			X			
	SISI			X			
	WHODAS 2.0			X			

	PSS			X			
	LEQ			X			
	AUDIT			X			
	BDI-II			X			X

Abbreviations:

fMRI, Functional Magnetic Resonance Imaging;
EEG, Electroencephalography;
AAT, Approach-Avoidance Task;
Speech Task, Behavioral Speech Task;
Mini-Dips, Mini-International Neuropsychiatric Interview;
TALD, Thought and Language Disorder Scale;
HAM-D, Hamilton Depression Rating Scale;
HAM-A, Hamilton Anxiety Rating Scale;
SOFAS, Social and Occupational Functioning Assessment Scale;
D2, D2 Test of Attention;
RWT, Regensburger Wortflüssigkeitstest;
Pfadfindertest, Trail Making Test;
ZST, Number-Symbol Test;
Combination Interview (HAM-D/MADRS/IDS-C), Combination Interview encompassing the Hamilton Depression Rating Scale, Montgomery-Åsberg Depression Rating Scale and Inventory of Depressive Symptomatology Clinician-Rated;
YMRS, Young Mania Rating Scale;
EMA, Ecological Momentary Assessment;
EMA DYNDET, Ecological Momentary Assessment (DYNDET study);
Speech Task, Behavioral Speech Task as part of EMA;
FsozU, Fragebogen zur Sozialen Unterstützung (22 Items);
CSI-4, Couples Satisfaction Index (4-Item Version);
EE-Item, Single-Item Expressed Emotion;
ASQ, Affective Style Questionnaire;
PDQ, Perceived Deficits Questionnaire ;
PANAS-SF, Positive and Negative Affect Schedule – Short Form;
AAQ-2 (7 Items), Acceptance and Action Questionnaire – version 2;
BSI-18, Brief Symptom Inventory;
PTQ, Perseverative Thinking Questionnaire;
NEO, NEO Personality Inventory – Neuroticism Scale;

PATHEV, Patient Questionnaire on Therapy Expectation and Evaluation;
CTQ, Childhood Trauma Questionnaire;
SISI, Single-item social identification measure;
WHODAS 2.0, WHO Disability Assessment Schedule 2.0;
PSS, Perceived Stress Scale;
LEQ, Life Events Questionnaire (without free text);
AUDIT, Alcohol Use Disorders Identification Test;
BDI-II, Beck's Depression Inventory II;

Sample size {14}

The target sample size for the DYNDET study is 90 participants, equally distributed across three treatment arms (SSRI, CBT group therapy, and combination therapy). This allocation reflects both methodological requirements and feasibility considerations rather than being based on formal power calculations. If the final sample is smaller than planned, the statistical scope will be adjusted accordingly, and network inference will be interpreted with appropriate caution. Exploratory analyses will still be reported transparently, even if not sufficiently powered for confirmatory inference.

Recruitment {15}

Participants will be recruited from three outpatient clinics in Germany: the Department of Psychiatry and Psychotherapy at the University Hospital Marburg and two associated units at Goethe University Frankfurt (Department of Clinical Psychology and Psychiatric Outpatient Unit). Recruitment strategies via clinician referrals, online platforms (e.g., university websites), printed flyers, and internal registries. After initial contact, interested individuals are screened via structured clinical interviews and standardized eligibility checklists. EMA feasibility and technological prerequisites (e.g., smartphone access, compliance capacity) are also evaluated prior to enrollment.

Assignment of interventions: allocation

Sequence generation {16a}

Participants will be assigned to study arms using a computer-generated randomization sequence (in RStudio) to ensure allocation is unpredictable and free from systematic bias. The allocation sequence will be developed prior to participant enrollment and will use block randomization to maintain balanced group sizes across study arms. No stratification factors will be applied.

Concealment mechanism {16b}

To prevent prior knowledge of allocation and minimize selection bias, allocation concealment will be rigorously maintained. The sequence will be concealed from investigators enrolling and assessing participants by employing sequentially numbered, opaque, sealed envelopes. The envelopes will be prepared in advance, sealed, and numbered in strict order, and will only be opened after completion of the baseline assessment of the respective patient.

Implementation {16c}

An independent staff member, not involved in the assessment or enrollment of participants, will generate the allocation sequence. Enrollment and eligibility determination will be performed by trial investigators, while group assignment will occur via the concealed allocation mechanism described above. This separation of roles ensures that allocation is both secure and unbiased throughout the recruitment process.

Blinding

Due to the nature of the interventions, full blinding is not feasible. Participants are aware of their assigned treatment condition, as the interventions differ in format. Similarly, therapists and prescribing physicians are not blinded. However, clinical outcome assessments, specifically structured interviews such as the HAM-D, are conducted by trained raters who remain blinded to group allocation wherever possible. To reduce analytical bias, data analysis will be conducted on pseudonymized datasets, with group identifiers masked during preprocessing and statistical modeling stages (Schulz et al., 2010).

Who will be blinded {17a}

The clinical outcome ratings post-treatment are conducted by trained raters who are not involved in treatment delivery and remain blinded to treatment allocation wherever feasible.

Procedure for unblinding if needed {17b}

If a blinded outcome rater inadvertently becomes aware of group allocation, this will be documented, and, where possible, subsequent ratings will be reassigned to a different rater who remains blinded. Any instances of loss of blinding and resulting deviations will be reported in the trial documentation and considered in sensitivity analyses.

Data collection

Plans for assessment and collection of outcomes {18a}: An overview over assessments and collection of outcome during baseline, treatment and post-treatment period is given in Table 1.

Plans to promote participant retention and complete follow-up {18b}: Participant retention during baseline, treatment and post-treatment will be supported by the staff of the trial management. Participants who discontinue or deviate from intervention protocols will be requested to complete questionnaires at the measurement points according to the schedule presented in Table 1.

Data management {19}

All data will be managed in accordance with the EU General Data Protection Regulation (GDPR) and institutional data protection protocols. Self-report and interview data will be pseudonymized at the point of entry. EMA data are collected via a secure mobile application (m-path) and transmitted using encrypted channels. Study data will be stored on secure servers with access restricted to authorized personnel. Data integrity is ensured through automated quality checks, regular manual audits, and double entry for critical clinical variables. After the study concludes, data may be shared in anonymized form

for secondary analysis, contingent on ethical approval and data use agreements. Long-term archiving (minimum 10 years) is guaranteed in line with university policy and good scientific practice.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}:

Analyses will be conducted in accordance with current standards in network psychometrics and time-series modeling. To examine the effects of treatment allocation on symptom dynamics (Research Question 1), we will use network intervention analysis (Fishbein et al., 2023), a method capable of capturing both direct and indirect effects of experimental conditions on network structure. Group comparisons of network connectivity and structure (Research Questions 2 and 4) will be conducted using network comparison tests and global strength metrics (van Borkulo et al., 2015; Blanken et al., 2019). Differences in early versus delayed treatment response will be assessed using logistic regression (Zhou et al., 2021). To address Research Questions 5 and 6, mixed-effects models and moderated logistic regressions will be used to evaluate whether baseline temporal characteristics, such as outstrength and symptom variance, moderate treatment response (Grimes et al., 2025). These models will include time-by-group interactions and random effects to account for within-subject dependency.

The analytic strategy may vary depending on the operationalization of change processes (e.g., as nodes or edges). Planned analyses will be implemented in R using appropriate packages for temporal and multilevel network modeling (e.g., mlVAR, qgraph, mgm).

Methods for additional analyses {20b}:

Additional exploratory analyses may incorporate fMRI data, particularly to investigate associations between changes in psychological networks and neural circuits. However, these neuroimaging analyses are considered supplementary and not part of the primary inferential framework.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}:

Per-protocol analysis will include all participants attending at least 80% of treatment sessions. For intend-to-treat analysis, missing data will be replaced, multiple imputation by chained equations will be used, employing the “mice” R Package.

Composition of the data monitoring committee, its role and reporting structure {21a}. The risk profile of this study is classified as minimal, as the interventions do not pose a significant threat to the physical or psychological well-being of the participants. Consequently, a dedicated, independent Data and Safety Monitoring Board (DSMB) is not required. General data quality and participant safety will be continuously monitored and reviewed within the framework of the LOEWE Dynamic Centre and its integrated Data Hub, ensuring high standards of oversight and scientific integrity

Interim analyses {21b}: N/A (An interim analysis is not planned).

Adverse event reporting and harms {22}

All interventions in this study, including pharmacological treatment with SSRIs and CBT group therapy, are recognized and established therapies delivered in accordance with current clinical guidelines. Nevertheless, monitoring for adverse events remains a core part of the study's safety procedures. Adverse events will be systematically documented throughout the trial, regardless of their suspected relationship to the intervention. Reports of symptoms, side effects, or other medical occurrences will be collected via participant self-report. Each reported adverse event will be evaluated by qualified study personnel for its severity and potential relationship to the intervention in line with standard clinical practice. Any serious adverse events, including those requiring hospitalization or resulting in significant health changes, will be promptly reported, as required by applicable regulations. These safety protocols are designed to align with established good clinical practice, ensuring the well-being of participants even though the treatments themselves are not experimental or investigational. Regular review of adverse events will be conducted to identify any emerging safety concerns, and appropriate measures will be taken as needed. At the conclusion of the trial, an aggregated summary of all reported (serious) adverse events will be provided, maintaining full transparency.

Frequency and plans for auditing trial conduct {23}

The conduct of the study will not be audited by an independent committee.

Research ethics approval {24}

Applied for (Ethikkommission des Fachbereiches Medizin, Philipps-Universität) Marburg / Ethics committee, Marburg University Medical School, Marburg, Germany)

Plans for communicating important protocol amendments to relevant parties {25}

Changes to the study protocol will be communicated to the ethics committee and the trial registry.

Who will take informed consent? {26a}

Written informed consent is obtained from all participants prior to any study-related procedures. During the consent process, individuals are informed about the aims, structure, duration, and potential burdens of participation, including frequent EMA prompts and optional neuroimaging assessments. Participants are also informed of their right to withdraw from the study at any time without providing a reason and without penalty. Consent materials are formulated in accessible language, and study staff ensure comprehension through verbal explanation and clarification. All consent procedures follow institutional guidelines and the ethical standards outlined in the Declaration of Helsinki.

Additional Consent Provisions for Collection and Use of Participant Data and Biological Specimens in Ancillary Studies {26b}

At present, no ancillary studies involving additional collection or use of participant data or biological specimens are planned within this trial. Should any ancillary studies be considered in the future, additional informed consent will be obtained from participants, detailing the purpose, procedures, and data use specific to such studies, in accordance with applicable ethical and legal requirements.

Confidentiality {27}: Personal information about potential and enrolled participants will be pseudonymized and collected, shared, and maintained in accordance with the European data protection regulation.

Provisions for post-trial care {30}

All interventions provided in this trial, including group cognitive behavioral therapy and pharmacological treatment with SSRIs, are established treatments delivered according to recognized clinical guidelines. After study completion, participants will continue to receive standard care from their usual healthcare providers, and clear guidance will be given, where appropriate, to support the ongoing management of their mental health. Should any medical or psychological support be required as a consequence of trial participation, referral to appropriate care services will be arranged. In line with ethical and regulatory requirements, any harm clearly related to study procedures will be documented and managed in accordance with institutional policies; participants will be informed about the available support should the need arise. No further care or additional post-trial interventions beyond standard clinical care are planned for this study in accordance with current guidelines and the nature of the interventions used.

Dissemination plans {31a}

Study results will be disseminated through peer-reviewed publications, with at least one main manuscript reporting the primary analyses of symptom network change over time. Further publications will address secondary and exploratory outcomes, including potential neurobiological correlates of symptom dynamics. Findings will also be presented at national and international scientific conferences in the fields of clinical psychology, psychiatry, and network science. In line with open science practices, key study materials (e.g., analysis scripts, preregistration protocols) will be made available via platforms such as the Open Science Framework (OSF). Anonymized datasets may be shared upon reasonable request and subject to ethical approval. Participants will receive a lay summary of results following study completion, made available in accessible language and format.

Authorship eligibility guidelines and any intended use of professional writers {31b}

Authorship for all study publications will be determined in accordance with internationally recognized standards. Individuals who have made substantial contributions to the conception, design, conduct, analysis, or interpretation of the study, as well as drafting or critically revising manuscripts, will qualify for authorship. All authors will be required to approve the final version of any manuscript prior to submission for publication. Contributions that do not meet full authorship criteria will be acknowledged appropriately. No professional writers will be employed in the preparation of study manuscripts; all publications will be authored by members of the research team and collaborators involved in the study.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

Access to the full, final study protocol, anonymized participant-level data, and the statistical analysis code will be made available to qualified researchers upon reasonable request. Data sharing will comply with all relevant legal and ethical regulations. Requests can be submitted to the principal investigators, who will review and facilitate access in accordance with institutional policies.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable.

Discussion

This paper outlines the study protocol for a randomized controlled trial (RCT) examining mechanisms of change in group cognitive behavioral therapy (CBT), antidepressant medication, and a combination of both treatments in patients with depression. Ecological momentary assessment (EMA) will be employed to monitor symptom fluctuations during a baseline phase. Changes in network structure during the treatment phase will then be compared from baseline to post-treatment. Additionally, brain imaging data will be collected at both baseline and post-treatment to investigate

the relationship between network perturbations and alterations in brain activation patterns.

Limitations

Several limitations of the study should be acknowledged:

(a) Lack of a placebo or waitlist control condition.

Although there are valid arguments against including a non-active control condition in clinical trials, its absence may affect the internal validity of the study. Any observed differences in change processes across treatment conditions cannot be clearly attributed to the interventions themselves, as they may reflect the passage of time or other non-specific study effects. However, the inclusion of a baseline phase without active treatment may help control for these factors.

(b) Treatment preference and compliance.

Because randomization occurs after the baseline assessment, participants are blinded to treatment allocation when completing baseline measures. Nevertheless, individual treatment preferences may influence willingness to proceed with the assigned condition, potentially leading to a higher number of non-starters and threatening internal validity.

(c) Influence of depression severity and pretreatment course.

Severity of depression and pretreatment course (i.e., chronic, recurrent, or first episode) are known to moderate treatment effects and may significantly impact change processes (Van Borkulo et al., 2015; Kelley et al., 2023). Due to the limited sample size, we are unable to control for both factors simultaneously. We have therefore opted to stratify participants by severity and conduct post hoc analyses on the impact of pretreatment course. However, any imbalance between conditions with regard to pretreatment course may still compromise internal validity.

(d) Challenges in long-term follow-up.

Given the high relapse rate associated with depression, long-term follow-up is necessary to evaluate the sustainability of change processes and the prevention of relapse or

recurrence. Although we intend to assess long-term outcomes, we anticipate a high attrition rate, which may limit the validity of the longitudinal findings.

Strengths

A major strength of this study is its inclusion of three active treatment conditions, allowing for direct comparisons of change processes in monotherapies and combined treatment. This design enables the identification of both synergistic and potentially antagonistic interactions between group CBT and pharmacological treatment.

To our knowledge, this is the first study to examine differences in network changes using a design that compares combined psychological and pharmacological interventions with the respective monotherapies. As treatment personalization becomes increasingly important for enhancing therapeutic outcomes, identifying mechanisms of change represents a significant advancement. With this study, we aim to contribute to the development of more precise and individualized treatment allocation strategies for patients with depression.

Trial status

Research protocol, version x.

Declarations

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Authors' contributions

IN, ME, TM and US conceived the trial and drafted the study protocol. ME and AN developed the EMA assessment and dynamic network analyses. LS, OG, SGH and TK contributed to the trial design and protocol development and obtained ethical approval.

All authors conduct recruitment and data collection. IN, ME and US drafted the article and all authors read, edited, and approved the final manuscript.

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Availability of data and material

The study protocol is made publicly available through this publication. The main results are intended to be published in a high-impact peer reviewed journal within 6 months after the trial end date. Individual participant data will be available for investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose. Data will be available beginning 6 months and ending 36 months following article publication.

Ethics approval and consent to participate

The protocol has been approved by the Ethics Committee at the Department of Psychology (Registration number: 2025-2718). Protocol amendments will be communicated at https://clinicaltrials.gov and detailed in publications.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no conflicts of interest.

References

Bernstein, E. E., Phillips, K. A., Greenberg, J. L., Curtiss, J., Hoeppner, S. S., & Wilhelm, S. (2023). Mechanisms of cognitive-behavioral therapy effects on symptoms of body dysmorphic disorder: A network intervention analysis. *Psychological Medicine*, *53*(6), 2531-2539.

Blanken, T. F., Van Der Zweerde, T., Van Straten, A., Van Someren, E. J., Borsboom, D., & Lancee, J. (2019). Introducing network intervention analysis to investigate sequential, symptom-specific treatment effects: a demonstration in co-occurring insomnia and depression. *Psychotherapy and Psychosomatics*, *88*(1), 52-54.

Borsboom, D. (2017). A network theory of mental disorders. *World psychiatry*, *16*(1), 5-13.

Borsboom, D., & Cramer, A. O. (2013). Network analysis: an integrative approach to the structure of psychopathology. *Annual review of clinical psychology*, *9*(1), 91-121.

Bos, F. M., Fried, E. I., Hollon, S. D., Bringmann, L. F., Dimidjian, S., DeRubeis, R. J., & Bockting, C. L. (2018). Cross-sectional networks of depressive symptoms before and after antidepressant medication treatment. *Social psychiatry and psychiatric epidemiology*, *53*(6), 617-627.

Boschloo, L., Bekhuis, E., Weitz, E. S., Reijnders, M., DeRubeis, R. J., Dimidjian, S., ... & Cuijpers, P. (2019). The symptom-specific efficacy of antidepressant medication vs. cognitive behavioral therapy in the treatment of depression: Results from an individual patient data meta-analysis. World psychiatry, 18(2), 183-191.

Courtney, D. B., Watson, P., Krause, K. R., Chan, B., Rodak, T., Zentner, K., Bennett, K., Gunlicks-Stoessel, M., Neprily, S., & Szatmari, P. (2022). Predictors, moderators, and mediators associated with treatment outcome in randomized clinical trials among

adolescents with depression: A scoping review. *JAMA Network Open, 5*(2), e2146331. https://doi.org/10.1001/jamanetworkopen.2021.46331

Cuijpers, P., Karyotaki, E., Weitz, E., Andersson, G., Hollon, S. D., & van Straten, A. (2014). The effects of psychotherapies for major depression in adults on remission, recovery and improvement: A meta-analysis. *World Psychiatry, 13*(3), 318–326. https://doi.org/10.1002/wps.20701

Cuijpers, P., Miguel, C., Harrer, M., Plessen, C. Y., Ciharova, M., Ebert, D., & Karyotaki, E. (2023). Cognitive behavior therapy vs. control conditions, other psychotherapies, pharmacotherapies and combined treatment for depression: A comprehensive meta-analysis including 409 trials with 52,702 patients. *World Psychiatry, 22*(1), 105–115. https://doi.org/10.1002/wps.21069

DeRubeis, R. J., Siegle, G. J., & Hollon, S. D. (2008). Cognitive therapy versus medication for depression: Treatment outcomes and neural mechanisms. *Nature Reviews Neuroscience, 9*, 788–796.

Dunlop, B. W., Cha, J., Choi, K. S., Mayberg, H. S., et al. (2023). Shared and unique changes in brain connectivity in remission from major depression with medication or cognitive-behavioral therapy. *American Journal of Psychiatry, 180*(3), 218–229. https://doi.org/10.1176/appi.ajp.21070727

Dunlop, B. W., Kelley, M. E., Aponte-Rivera, V., Mletzko-Crowe, T., Cole, R., Wald, L., Mayberg, H. S., et al. (2017). Benefits of sequentially adding cognitive-behavioral therapy or antidepressant medication for nonremitting depression. *American Journal of Psychiatry, 174*(6), 533–545. https://adaa.org/sites/default/files/2019_AJP_SequentialComboPReDICT.pdf

Fishbein, J. N., Haslbeck, J., & Arch, J. J. (2023). Network intervention analysis of anxiety-related outcomes and processes of acceptance and commitment therapy (ACT) for anxious cancer survivors. *Behaviour Research and Therapy*, *162*, 104266.

Fournier, J. C., DeRubeis, R. J., Hollon, S. D., Gallop, R., Shelton, R. C., & Amsterdam, J. D. (2013). Differential change in specific depressive symptoms during antidepressant medication or cognitive therapy. *Behaviour research and therapy*, *51*(7), 392-398.

Grimes, P. Z., Murray, A. L., Smith, K., Allegrini, A. G., Piazza, G. G., Larsson, H., ... & Kwong, A. S. (2025). Network temperature as a metric of stability in depression symptoms across adolescence. *Nature Mental Health*, 1-10.

Helmich, M. A., Smit, A. C., Bringmann, L. F., Schreuder, M. J., Oldehinkel, A. J., Wichers, M., & Snippe, E. (2023). Detecting impending symptom transitions using early-warning signals in individuals receiving treatment for depression. *Clinical Psychological Science*, *11*(6), 994-1010.

Jurado-González, F., García-Torres, F., Contreras, A., Muñoz-Navarro, R., González-Blanch, C., Adrián Medrano, L., ... & Moriana, J. A. (2024). Comparing psychological versus pharmacological treatment in emotional disorders: A network analysis. *Plos one*, *19*(4), e0301675.

Kalsi, N., Altavilla, D., Tambelli, R., Aceto, P., Trentini, C., Di Giorgio, C., & Lai, C. (2017). Neural Correlates of Outcome of the Psychotherapy Compared to Antidepressant Therapy in Anxiety and Depression Disorders: A Meta-Analysis. *Frontiers in psychology*, *8*, 927. https://doi.org/10.3389/fpsyg.2017.00927

Kelley, S. W., Fisher, A. J., Lee, C. T., Gallagher, E., Hanlon, A. K., Robertson, I. H., & Gillan, C. M. (2023). Elevated emotion network connectivity is associated with fluctuations in depression. *Proceedings of the National Academy of Sciences of the United States of America*, *120*(45), e2216499120.

Lancee, J., Harvey, A. G., Morin, C. M., Ivers, H., Van Der Zweerde, T., & Blanken, T. F. (2022). Network Intervention Analyses of cognitive therapy and behavior therapy for

insomnia: Symptom specific effects and process measures. *Behaviour Research and Therapy*, *153*, 104100.

Lemmens, L. H., Müller, V. N., Arntz, A., & Huibers, M. J. (2016). Mechanisms of change in psychotherapy for depression: An empirical update and evaluation of research aimed at identifying psychological mediators. *Clinical psychology review*, *50*, 95-107.

Pizzagalli, D. A. (2011). Frontocingulate dysfunction in depression: Toward biomarkers of treatment response. *Neuropsychopharmacology, 36*(1), 183–206. https://doi.org/10.1038/npp.2010.166

Quilty, L. C. (2014). Pharmacotherapy for depression. *International Journal of Cognitive Therapy, 7*(3), 235–250.

Saberi, A., Ebneabbasi, A., Rahimi, S., Sarebannejad, S., Sen, Z. D., Graf, H., Walter, M., Sorg, C., Camilleri, J. A., Laird, A. R., Fox, P. T., Valk, S. L., Eickhoff, S. B., & Tahmasian, M. (2024). Convergent functional effects of antidepressants in major depressive disorder: A neuroimaging meta-analysis. *medRxiv: the preprint server for health sciences*, 2023.11.24.23298991. https://doi.org/10.1101/2023.11.24.23298991

Sankar, A., Melendez, R., & Sagar, R. (2018). A systematic review and meta-analysis of the neural correlates of psychological therapies in major depression. *Psychiatry Research: Neuroimaging, 279*, 31–39. https://doi.org/10.1016/j.pscychresns.2018.07.002

Schaub A, Roth E, Goldmann U (2013): Kognitiv-psychoedukative Therapie zur Bewältigung von Depressionen. Ein Therapiemanual. Göttingen, Hogrefe

Schaub A, Goldmann U, Mueser TK, Goerigk S, Hautzinger M, Roth E, Charypar M, Engel R, Möller HJ. Efficacy of extended clinical management, group CBT, and group plus individual CBT for major depression: Results of a two-year follow-up study. *J Affect Disord.* 2018 Oct 1;238:570-578. doi: 10.1016/j.jad.2018.05.081.

Snippe, Evelien, et al. "The temporal order of emotional, cognitive, and behavioral gains in daily life during treatment of depression." *Journal of Consulting and Clinical Psychology* (2024).

Snippe, E., Viechtbauer, W., Geschwind, N., Klippel, A., de Jonge, P., & Wichers, M. (2017). The impact of treatments for depression on the dynamic network structure of mental states: Two randomized controlled trials. *Scientific Reports,* 7(1), 46523.

van Borkulo, C., Boschloo, L., Borsboom, D., Penninx, B. W., Waldorp, L. J., & Schoevers, R. A. (2015). Association of Symptom Network Structure With the Course of [corrected] Depression. *JAMA psychiatry*, *72*(12), 1219–1226.

Van Borkulo, C. D., van Bork, R., Boschloo, L., Kossakowski, J. J., Tio, P., Schoevers, R. A., ... & Waldorp, L. J. (2023). Comparing network structures on three aspects: A permutation test. *Psychological methods*, *28*(6), 1273.

Wang, W., Liu, Z., & Zhang, Y. (2017). Neural correlates of outcome of the psychotherapy compared to antidepressant therapy on functional brain activity in anxiety and depression: A meta-analysis. *Frontiers in Psychology, 8*, 927. https://doi.org/10.3389/fpsyg.2017.00927

Wang, Y., Zhang, X., Li, L., Wang, Y., Li, C., Wang, H., Li, S., & Zhang, T. (2025). Brain functional effects of cognitive behavioral therapy for depression: A systematic review and meta-analysis of fMRI studies. *Journal of Affective Disorders, 368*, 1–12. https://doi.org/10.1016/j.jad.2024.09.084

Wichers, M., Riese, H., Hodges, T. M., Snippe, E., & Bos, F. M. (2021). A narrative review of network studies in depression: What different methodological approaches tell us about depression. *Frontiers in psychiatry*, *12*, 719490.

Zhou, J., Liu, S., Mayes, T. L., Feng, Y., Fang, M., Xiao, L., & Wang, G. (2022). The network analysis of depressive symptoms before and after two weeks of antidepressant treatment. Journal of Affective Disorders, 299, 126-134.