Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Network and control theory for difficult-to-treat mood and anxiety disorders (NECTAR): Study protocol for a randomized controlled trial

Hannah Fiehn

fiehn@psych.uni-frankfurt.de

Goethe University Frankfurt

Lucie Pahlen

Goethe University Frankfurt

Andreas Reis

Philipps University of Marburg

Marlon Westhoff

Philipps University of Marburg

Kilian Stenzel

Philipps University of Marburg

Mareike Ebert

Goethe University Frankfurt

Winfried Rief

Philipps University of Marburg

Stefan G. Hofmann

Philipps University of Marburg

Ulrich Stangier

Goethe University Frankfurt

Study protocol

Keywords: Process-based Therapy, Network Control Theory, Dynamic Networks, Personalized Psychotherapy

Posted Date: May 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9579102/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Improving treatment outcomes for unipolar depression and anxiety disorders remains a major challenge in mental health care, particularly for patients who do not respond sufficiently to established interventions. Personalized approaches that target individual processes of change may enhance effectiveness. Process-based therapy aims to tailor interventions based on empirically supported psychological processes using idiographic data. Network control theory provides a complementary framework to identify interventions that can optimally influence complex dynamic systems. The present study introduces a control-theory-informed process-based therapy and evaluates its efficacy compared to routine cognitive behavioral therapy in patients with difficult-to-treat depression and anxiety disorders.

Methods

In this randomized controlled trial, 80 outpatients with a primary diagnosis of a depressive or anxiety disorder and at least two prior unsuccessful treatments will be recruited. Participants will be randomly assigned to either control-theory-informed process-based therapy or routine cognitive behavioral therapy. Both conditions include a 5-week baseline phase followed by a 19-week treatment phase. In the experimental condition, ecological momentary assessment data will be used to construct individualized dynamic networks of psychological functioning. These networks inform treatment decisions using control-theoretic metrics, including average controllability and cumulative impulse response, to identify interventions expected to produce maximal system-wide change. The primary outcome is emotional distress at post-treatment and 6-month follow-up. Secondary outcomes include quality of life, psychological well-being, and process variables such as psychological flexibility and reflective functioning. Analyses will follow an intention-to-treat approach using repeated-measures repeated-measures ANOVAs for primary outcome and repeated-measures MANOVA for secondary outcomes.

Discussion

This trial is the first to combine process-based therapy with network control theory in a randomized controlled design. By integrating individualized assessment with formal decision-support tools, the proposed approach seeks to improve treatment outcomes in a clinically challenging population. The study may advance precision mental health by providing empirical evidence for a novel, data-driven framework of personalized psychotherapy. In addition, the investigation of mediators and moderators may improve understanding of mechanisms of change and help inform future treatment optimization.

Trial registration

Clinical Trial Registry: DRKS00037966, Date of registration in DRKS: 2025-11-21 (See for more details: German Clinical Trials Register, https://drks.de/search/en/trial/DRKS00037966/details)

Background

Improving the effectiveness of treatments for unipolar depression and anxiety disorders remains a central objective in mental health care. Despite substantial advances in psychological interventions, there is still considerable room for improvement in treatment outcomes. Unipolar depression and anxiety disorders are among the most prevalent mental health conditions encountered in clinical practice (1). They are frequently associated with prolonged suffering, marked psychosocial impairment, and significant socioeconomic burden (2). Meta-analytic evidence indicates that cognitive behavioral therapy (CBT) is an effective treatment for both depression (3) and anxiety disorders (4). However, remission rates following CBT for these conditions remain, on average, below 50% (5). Furthermore, concerns have been raised about stagnating outcomes in CBT for both depression (6) and anxiety disorders (7).

A promising strategy to enhance treatment outcomes is the personalization of interventions (8). Initial findings from randomized controlled trials suggest that tailored treatments can improve effectiveness (9). Moreover, emerging evidence indicates that individual patterns of psychological functioning may represent clinically meaningful features that extend beyond traditional diagnostic categories and symptom severity (10). Based on network theory and evolutionary psychology, Hofmann and Hayes (11) proposed personalizing treatment by identifying and directly targeting core psychological processes related to the patient's problem. They introduced Process-based therapy (PBT) as an approach that emphasizes empirically supported processes of change, rather than focusing on diagnostic labels or standardized treatment protocols. Focusing on change processes, interventions are conceptualized in line with fundamental evolutionary principles—variation, selection, and retention (12). Supporting this perspective, a recent scoping review, which is currently under review, integrated evidence-based change processes identified in psychotherapy research, offering a comprehensive synthesis of key processes of change (13). A central principle of PBT is the use of continuous idiographic assessment to detect change processes and guide data-driven treatment decisions. Recent developments have extended this approach by incorporating ecological momentary assessment (EMA) and dynamic idiographic network analyses within routine clinical practice (14, 15). The interpretation of idiographic dynamic networks and consequently the idenfitifcation of promising intervention targets is often based on structural aspects such as node centrality (16). At the same time, more recent literature points to limitations in the reliability and predictive power of centrality indices in dynamic networks (17, 18).

Network control theory (NCT), a discipline concerned with the control of complex dynamic systems, could offer a more comprehensive approach to quantify intervention effects and, consequently, selecting effecitve interventions based on idiographic network dynamics (18–20). Specifically, NCT examines the degree of control an intervention exerts over a dynamic system by providing metrics that quantify how a complex system behaves under the influence of the intervention directly and over time (19). Two particularly informative metrics in this context are average controllability (AC) and cumulative impulse

response (CIR) which quantify, respectively, the energy required to shift a system into nearby states and the accumulated short- and long-term effects of interventions, thereby providing useful tools for evaluating and optimizing treatments across interconnected symptoms (18). For example, when conceptualizing the human brain as a complex dynamic system, activation of brain regions with high AC can facilitate transitions into different states more efficiently, requiring less cognitive effort to influence overall brain dynamics (19).

In the context of psychotherapy, NCT has the potential to identify treatment targets and evaluate their effects on a person-specific network (18). For instance, Fechtelpeter et al. (21) demonstrated that interventions with higher AC produce larger changes in mental health states, indicating its potential utility in identifying effective interventions within data-supported psychotherapy. In the context of psychotherapy, methods from control theory could also help clinicians determine which interventions, among several available at a given time, are most effective in changing person-specific maladaptive dynamics (21, 22).

Based on this idea, Hofmann (23) proposed a heuristic framework for the application of NCT to personalize psychotherapy using individual symptom networks. The framework uses control-theoretic principles to guide the selection of intervention strategies expected to produce the greatest change in a client's psychological system. Translating this conceptual framework into a quantitative approach, Pahlen et al. (24) recently demonstrated the simulation of theoretical intervention effects using clinical time-series data within a NCT framework, highlighting the computational feasibility of applying NCT to identify interventions based on elevated controllability.

In the present study, we integrate methods from NCT with PBT to enhance treatment effectiveness. Specifically, control-theoretic approaches are used to identify those interventions that are most likely to modify maladaptive, person-specific dynamics as represented in idiographic dynamic networks (22). To the best of our knowledge, this integrative approach has not yet been implemented in this form. In the following, we refer to this framework as c-PBT (control-theory-informed process-based therapy).

Given the increased effort c-PBT seems to be especially relevant for patients who do not respond to empirically supported treatments. In the context of depression, such patients have often been described as "treatment-resistant." In psychiatric care, treatment-resistance is defined as a non-response to an adequate treatment given a correct diagnosis (25). However, there is no universally accepted definition specifying how many or which prior treatments must have been unsuccessfully completed for patients to be classified as treatment-resistant. To address the challenges of categorically excluding any treatment response, the term "difficult-to-treat" has been proposed for depression (26, 27). A Delphi-method consensus extended this terminology to anxiety disorders due to its clinical (28).

Methods

Objectives

The primary aim of this study is to evaluate the efficacy of c-PBT in comparison to routine CBT (r-CBT) in outpatients with difficult-to-treat unipolar depression or anxiety disorders. Emotional distress serves as the primary outcome, while secondary outcomes include psychological well-being and quality of life. Beyond these outcomes, the study examines whether c-PBT induces changes in theoretically relevant mechanisms, including psychological flexibility as well as the processes of variation, selection, and retention of adaptive behavior. Additional process variables of interest comprise reflective functioning and the capacity to experience social and interpersonal pleasure. Furthermore, potential mediators of treatment effects will be investigated, including therapist adherence to the treatment protocol and patient-level changes in avoidance/behavioral control and cognitive style. Possible moderators will also be explored, such as patient characteristics (e.g., treatment expectations, experiential vs. analytical learning style) and the quality of the therapeutic alliance, both within and across treatment conditions. The primary hypothesis is that participants receiving c-PBT will show a greater reduction in emotional distress compared to those undergoing r-CBT, both at post-treatment and at 6-month follow-up. Additionally, we expect superior improvements in positive mental health and quality of life in the c-PBT condition. With regard to the proposed control-theory-based algorithm, we hypothesize that higher pre-treatment average controllability (AC) will be positively associated with greater changes in EMA-derived variables following treatment. In line with the treatment targets of c-PBT, we further expect stronger improvements in adaptive behavior, psychological flexibility, and reflective functioning compared to r-CBT.Moreover, we anticipate that reductions in avoidance/behavioral control and shifts in cognitive style will mediate treatment outcomes. Finally, treatment effects are expected to be moderated by patients' expectations, their preferred learning style, and therapists' adherence to the treatment manual. As an exploratory objective, pre- to post-treatment changes in network structure will be analyzed using Bayesian modeling approaches (29).

Design

This study is designed as an investigator-initiated, pragmatic, two-arm parallel-group randomized controlled trial with a superiority framework and a 1:1 allocation ratio. Participants will be assigned to either c-PBT or r-CBT, with equal group sizes. A total of 80 patients will be recruited from two university outpatient clinics. A CONSORT flow diagram is presented in Figure 1.

Study setting

The trial will take place at two sites: the outpatient clinic of the Department of Psychology at Goethe University Frankfurt and the outpatient clinic for psychological treatments (PAM) at Philipps University of Marburg.

Therapists are clinical psychologists in advanced CBT training and will be randomized to either c-PBT or r-CBT. Those assigned to c-PBT will receive a 20-hour training focusing on individualized, network-based treatment planning. This includes:

1) deriving a conceptual network model of the individual problem,

2) guiding patients through the collection of EMA data,

3) interpreting dynamic network models,

4) drawing control-theory informed treatment decisions, and

5) applying interventions with the goal to adaptively change the whole network dynamic and track progress of EMA-variables throughout treatment.

Therapists in the c-PBT condition will also receive a treatment manual and supervision from a PBT expert. Therapists assigned to r-CBT will follow standard CBT procedures and receive routine supervision without additional training.

Eligibility criteria

The study aims to include 80 participants meeting the following criteria: 1) a primary DSM-5 diagnosis of depressive or anxiety disorder, 2) at least two prior unsuccessful treatment attempts (psychological or pharmacological) according to German clinical guidelines (AWMF), 3) age between 18 and 65 years, 4) sufficient knowledge of the German language. Participants may continue psychopharmacological treatment, provided medication remains stable during the study period. Exclusion criteria include 1) acute suicidality, 2) substance abuse or dependency, 3) diagnosis of Borderline personality disorder, 4) pervasive developmental disorder, psychotic disorder, eating disorder, bipolar disorder, or severe physical illness. Eligibility will be assessed using the M.I.N.I. interview adapted for DSM-5 (30), along with a structured evaluation of previous treatment history.

Who will take informed consent?

Potential trial participants are initially informed about the purpose of the trial by therapists at intake interview after registration at the outpatient clinic of the Department of Psychology. Patients who are interested in a participation receive detailed information from trial management staff about potential benefits and risks; their right to refuse participation and to withdraw consent at any time; institutional affiliation of the trial at the university and sources of trial funding. Written consent is obtained according to the Declaration of Helsinki and as approved by the ethics committee of the Department of Psychology and Sports Sciences at Goethe University Frankfurt.

Interventions

Clinical guidelines of the Association of the Scientific Medical Societies in Germany (AWMF) recommend the application of evidence-based treatment manuals of CBT as standard therapy for patients with

anxiety disorders (31) and depression (32). For patients with prior treatment failure, recommendations remain non-specific, typically suggesting adaptation of existing approaches or a general change in treatment modality. Consequently, routine CBT reflects standard care and serves as an appropriate comparator, but not third wave therapies. Both treatment conditions consist of a 5-week baseline phase followed by a 19-week intervention phase.

Baseline phase In the c-PBT condition, an individualized network model is developed to represent the patient's psychological problem. EMA is then conducted based on key components of this model, including situational context, cognition, emotion, physiological responses, behavior, cognitive processing, and motivational schemas. Maladaptive patterns within these domains are identified, and corresponding adaptive targets are defined. Participants use a mobile application (Status, Vacay©) to repeatedly rate these dimensions in real-life contexts on a bipolar scale ranging from −100 (maladaptive) to +100 (adaptive).

Data are gathered in the situational context related to the problem. Therapists support patients during weekly sessions in refining EMA items, identifying relevant situations, and ensuring accurate data entry. EMA data collection is completed once at least 50 observations have been obtained. Subsequently, a dynamic network analysis is computed to examine autoregressive and cross-lagged effects of the variables (33). These are visualized as networks in which variables are represented as nodes, directional associations as edges, and autoregressive effects as 'self-loops'.

During the baseline phase in the r-CBT group, participants complete daily EMA two times a day for five weeks assessing psychological well-being and social functioning. However, these data are not used to estimate a network model or to guide the subsequent therapy; rather, the procedure serves to control for potential effects of daily EMA monitoring.

Treatment phase This phase consists of 19 sessions for both treatment conditions. In the network-based condition, treatment is initiated by a collaborative interpretation of the dynamic network model based on EMA data collected during the baseline. Therapists are instructed to identify influential nodes based on high average controllability values, and also interpret significant edges, self-loops and positive or negative feedback loops between the nodes. An algorithm based on control-theory metrics AC and CIR identifies three potentiall effective, evidence-based intervention strategies to change the dynamic system. The applied approach was developed by our research group and simulated the effects of 31 evidence-based interventions based on a literature review of intervention efficacy and relevant change processes (e.g. meditational concept associated with an intervention). The goal is to choose an intervention that maximally perturbates the entire network (18). The procedure was previously used by Fechtelpeter et al. (21) in the context of selection of ecological momentary interventions and applied in a simulation by Pahlen et al. (24) in the context of therapeutic interventions. During treatment, the induced changes of all network variables are monitored by once-a-day EMA assessment during treatment phase, referred to as EMA-tracking. These EMA-data are not used for network estimations. During treatment phase, therapists are instructed to regularly monitor the progress-chart of daily EMA variables, and

difference of mean values before and after an intervention. In further treatment planning, the structured approach by Hofmann (23) can be reapplied based on the current conceptual model and empirical EMA-tacking data whereby therapists select evidence-based interventions by identifying relevant change processes.

In contrast to c-PBT, treatment decisions in r-CBT are made within a naturalistic clinical framework. Treatment planning is guided by established theoretical models regarding the maintenance of mental disorders. For example, interventions for anxiety disorders typically focus on avoidance and exposure processes, whereas in depression, reduced reinforcement and behavioral activation are central targets (34). Interventions are selected based on standard, diagnosis-specific CBT manuals (e.g., CBT for depression). To tailor the techniques to the problem behaviors or dysfunctional thoughts of patients, individual data from the behavioral analysis are implemented. Thereby, treatment process focuses mainly on the implementation of the manualized interventions adapted to the individual patient as recommended in the German guidelines for treatment of depression and anxiety disorders according to the AWMF.

Criteria for discontinuing or modifying allocated interventions

Adverse events will be monitored by the therapists, discussed in the supervisions and reported to the Principal Investigators (PIs; US and SH) throughout the study.

Study treatment will be discontinued if a) the participant withdraws consent or b) the investigator decides to terminate treatment. Investigator-initiated discontinuation may occur in cases of a) serious adverse events requiring termination of treatment, including acute suicidality, or b) substantial non-adherence to the study protocol.

If treatment is terminated by the investigator, the participant will be informed accordingly, and the primary reason for discontinuation will be documented. In cases where participants withdraw prematurely, data collected up to that point may still be used, provided that consent for follow-up assessments has been obtained. In case of clinical worsening ot the patient, treatment adaptations may be implemented in consultation with the supervising clinician.

Strategies to improve adherence to interventions

Adherence to treatment will be supported through strategies outlined in the respective treatment manuals. In r-CBT, these strategies include identifying and addressing barriers to compliance, providing psychoeducation, and clarifying treatment goals. In c-PBT, adherence is fostered through the exploration of motivational processes, validation of potential barriers, and shared decision-making regarding the selection of interventions.

Relevant concomitant care permitted or prohibited during the trial

Psychopharmacological treatment will be permitted if prescribed by a psychiatrist. Concurrent psychotherapy is not allowed during the study period and will result in exclusion from the trial.

Provisions for post-trial care

If continuation of treatment is considered as necessary by the patient and the therapist at post-treatment, patients will be offered further psychotherapy in the outpatient clinic.

Outcomes

Primary outcomes The primary outcome is emotional distress, assessed using the total score of the DASS-10 (35) following completion of treatment (20 sessions in both conditions).

Secondary outcomes Health-related quality of life will be measured using the EuroQol-5D (EQ-5D; (36)). Positive mental health, encompassing emotional, psychological, and social well-being, will be assessed using the Positive Mental Health Scale (PMH; (37)).

Interpersonal pleasure will be evaluated using the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS; (38)), a 17-item self-report instrument. Psychological flexibility will be measured with the Acceptance and Action Questionnaire-II (AAQ-2; (39)).

Reflective functioning will be assessed using the Reflective Functioning Questionnaire (RFQ; (40)), which captures individuals' capacity to understand their own and others' mental states across the dimensions of certainty and uncertainty. Patient satisfaction with treatment will be evaluated post-treatment using the Client Satisfaction Questionnaire (CSQ-8; (41)). Weekly and daily patients' self-ratings of treatment process. The Process-Based Assessment Tool (PBAT; (42)) consists of 18 items assessing variation, selection, and retention of adaptive behavior across therapeutic processes. The Cognitive-Behavioral Therapy Skills Questionnaire (CBTSQ; (43)) is a 6-item measure assessing the use of CBT-related skills, specifically behavioral activation and cognitive restructuring.

Therapists' ratings Diagnostic assessments will be conducted using the Mini International Neuropsychiatric Interview (M.I.N.I., Version 7.0 for DSM-5; (30)), covering 18 diagnostic modules. All modules will be administered at baseline to determine eligibility and comorbidity, while certain modules (e.g., eating disorders, prolonged grief) will be completed only if indicated.

Personality disorders will be assessed monthly using the Structured Clinical Interview for DSM-5 Personality Disorders (SCID-PD; (44)).

Therapist adherence will be evaluated after each session using a checklist of interventions based on existing literature and meta-analyses (45–49). In addition, adherence to process-based principles will be assessed using the self developed Process-Based Decision-Making Questionnaire (PBDMQ).

Moderators Potential moderators of treatment outcome include learning style, treatment expectancy, and therapeutic alliance. Learning style will be assessed at baseline using the Kolb Learning Style Inventory

(KLSI; (50)), distinguishing between experiential and abstract learning preferences.Treatment credibility and expectancy will be measured using the Credibility/Expectancy Questionnaire (CEQ; (51)). Therapeutic alliance will be assessed using the Helping Alliance Questionnaire (HAQ-11; (52)), completed by both patients and therapists at pre- and post-treatment.

Participant timeline

Eligibility for study participation will be determined by clinicians based on the predefined inclusion and exclusion criteria. Eligible patients will receive detailed information about the study. Those who provide informed consent will proceed to pretreatment assessment (see Table 1). Patients who decline participation or do not meet eligibility criteria will be offered standard treatment at the outpatient clinic.

Table 1 Overview of measurements

		Screening	Baseline	Pre	Treatment	Post	Follow-Up
	Week / Instrument	**0**	**1-3**	**4-6**	**7-31**	**32**	**44**
Therapist	Diagnosis according to MINI DIPS	**X**				**X**	**X**
	WAI-3				**X** Weekly (PBT only)		
	Intervention checklist			**X**	**X** Weekly	**X**	
	FAMOS			**X**			
	TAUEN			**X**		**X**	
	PBDMQ				**X** every 4 weeks		
Patient	EQ-5D-5L	**X**		**X**		**X**	**X**
	BSI-18	**X**		**X**		**X**	**X**
	FAMOS	**X**		**X**			
	PMH	**X**		**X**		**X**	**X**
	ACIPS	**X**		**X**		**X**	**X**
	AAQ-II	**X**		**X**		**X**	**X**
	WAI-3				**X** Weekly (PBT only)		
	KLSI			**X**			
	CEQ			**X**			
	RFQ	**X**		**X**		**X**	**X**
	CSQ/ ZUF-8					**X**	
	PBAT	**X**		**X**	**X** Weekly	**X**	**X**

	DASS-10	**X**		**X**	**X** Weekly	**X**	**X**
	CBTSQ	**X**		**X**	**X** Weekly	**X**	**X**
	EMA/Self-observation		**X** 3x vs. 1x daily Week 3-6		**X** 1x daily (PBT only)	**X** 3x vs. 1x daily (Weeks 28 – 30)	

M.I.N.I., Mini-International Neuropsychiatric Interview;

WAI-3: Brief Working Alliance Inventory
FAMOS, Fragebogen zur Analyse Motivationaler Schemata;
PBDMQ, Process-based decision-making questionnaire;
TAUEN, Therapist attitude towards utility of EMA and networks Scale;
EQ-5D-5L, EuroQol 5 Dimensionen 5 Level;
BSI-18: Brief Symptom Inventory-18 Items;
PMH, Positive Mental Health Scale;
ACIPS, Anticipatory and Consummatory Interpersonal Pleasure Scale;
AAQ, Fragebogen zu Akzeptanz und Handeln Version II;
KLSI-12, Kolb Learning Style Inventory;
CEQ, Credibility Expectancy Questionnaire;
RFQ: Reflective Functioning Questionnaire;
CSQ-8, Client Satisfaction Questionnaire/ ZUF, Fragebogen zur Patientenzufriedenheit PBAT, Process-Based Assessment Tool;
DASS-10, Depression Anxiety Stress Scale 10 Items;
CBTSQ, Cognitive Behavioral Therapy Skills Questionnaire
EMA: Ecological Momentary Assessment.
PAUEN, Patient attitude towards utility of EMA and networks Scale;

Sample size

Sample size estimation is based on the expected outcome in DASS-10, with treatment condition as between-subjects factor and a within-subjects repeated measurement factor (pre, post, follow-up). Since no previous trial has examined the effects of PBT using control-theory to guided clinical decision-making, the expected effect size is set to a moderate effect of f= .25. Using an alpha level (α) of = .05 and a power of = 0.8 with correlation among repeated measures estimated at r= 0.4, 78 patients are

needed (39 in each arm) to detect significant differences. To compensate for non-starters, a total sample of 80 patients will be randomized.

Recruitment

Participant recruitment will take place through the outpatient clinics, which treat approximately 1,000 patients annually. Based on prior experience, sufficient recruitment within the planned timeframe is expected.

Assignment of interventions: allocation

Following confirmation of eligibility and provision of informed consent, participants will be randomly assigned to one of the two treatment conditions. The randomization sequence will be generated by the data management team using R Statistical Software (53). The group allocations is printed out individually and placed in sealed envelopes. For each enrolled participant, a member of the study team will draw an envelope and assign the participant accordingly. The same procedure will be used to allocate therapists to treatment conditions. Due to the nature of the interventions, no blinding of participants, therapists, outcome assessors, or data analysts is planned.

Data management

For conducting the EMA we will use electronic data collection and documentation, which is hosted by the company Vacay©. Entry of questionnaires will be performed by the participants. Coding, security and storage of data will be ensured by the staff of the study management. Access to the data is only allowed for persons who are documented as study personnel and have received a training. The given data will be checked electronically for its plausibility and consistency in a multistage procedure. Detected inconsistencies and missing or implausible data will be clarified with queries (electronically or paper-based) and necessary changes will be carried out. At the end of trial, the database will be closed after data cleaning process. The pseudonymized patient data recorded are stored by Vacay in accordance with legal requirements. All patient and therapist assessments were conducted digitally using a university-internal version of SoSciSurvey, ensuring that all data were stored on a local server.Personal information about potential and enrolled participants will be pseudonymized and collected, shared, and maintained in accordance with the European data protection regulation.

Statistical methods

Statistical methods for primary and secondary outcomes The primary outcome measure is the change in emotional distress from pre - to post treatment, using the DASS-10 as primary outcome measure. Analysis will follow an intention-to-treat analysis.

To evaluate treatment effects on the primary outcome, a repeated-measures ANOVA will be conducted with treatment condition as the between-subjects factor and time (pre vs. post) as the within-subjects factor. Secondary outcomes will be analyzed using a repeated-measures MANOVA, including the interaction between time and treatment condition. Given expected intercorrelations among secondary outcomes, significant multivariate effects will be followed by univariate analyses.

Methods for additional analyses To investigate potential mediators and moderators of treatment effects, structural equation modeling (SEM) and cross-lagged panel models (CLPM) will be applied using the R package *lavaan* (54). Dynamic network analysis of EMA data at baseline and at post-treatment will be computed using the R package *graphicalVAR*, with penalization paramaters optimizing network structure (33,55) and detrending using the R package *forecast* (56). Interpretation will focus on the control theory metrics AC and CIR based on EMA data using a Python script provided by Fechtelpeter et al. (21).

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data *Per*-protocol analysis will include all participantes attending at least 12 treatment sessions. For intention-to-treat analysis, missing data will be replaced, multiple imputation by chained equations will be used, employing the R Package *mice* (57).

Plans to give access to the full protocol, participant level-data and statistical code Individual participant data are intended to be shared after deidentification on a third-party website.

Monitoring

A Data Monitoring Committee will not be established for this study. This is due to the low-risk profile of the intervention. Data quality and study conduct will be ensured by the study team as part of a predefined monitoring process. Due to the small scale of our trial, no independent Trials steering committee has been planned. The PIs, will coordinate the trial.

Adverse event reporting and harms

All therapists will receive ongoing supervision from experienced licensed clinicians. Adverse events, including symptom deterioration or serious incidents such as suicidality, will be continuously monitored and discussed in supervision. Serious adverse events will be reported immediately to the PIs. In case of emergencies, immediate referral to psychiatric inpatient services will be ensured. Given that treatment is delivered by trained clinical psychologists under supervision, any clinical deterioration can be promptly identified and addressed. Medical conditions will be assessed prior to study entry. Although risks are considered low, all potential adverse effects will be carefully documented. Medication use will be regularly monitored in collaboration with treating psychiatrists, and participants will be instructed not to alter medication without consultation.

Adverse events will be summarized descriptively, and regression analyses will be conducted to explore relations between adverse events and treatment.

Discussion

EMA represents a central component of PBT and may itself influence treatment outcomes through mechanisms such as self-monitoring and increased self-awareness (58). To account for this potential confounding effect, EMA is also implemented in the r-CBT control condition. Nevertheless, several challenges related to EMA need to be considered, including whether participants adhere to the intended response format, as well as issues of compliance and data quality (59). We assume that the collaborative development of individualized EMA items at the beginning of treatment may enhance participant adherence. In addition, continuous monitoring of EMA entries by therapists and study staff is intended to ensure data quality. However, it remains an open question whether the resulting data structure will be sufficient for reliable network estimation. Encouragingly, pilot and analogue studies with student samples suggest that EMA data collected via the Status-PBT application can yield meaningful idiographic dynamic networks (60, 61).

A second key component of process-based therapy is the personalization of treatment based on a) information derived from the individual network structure and b) the selection of interventions targeting central nodes through their active components (23). In the present study, we extend this approach by integrating a control-theory-based algorithm to support intervention selection. This strategy is in line with recent developments in precision mental health, where controllability metrics are used to complement clinical judgment by identifying patient-specific leverage points rather than relying on uniform treatment strategies. Empirical support for this perspective is provided by findings from our research group showing variability in high-average-controllability targets across patients. Furthermore, the feasibility of NCT-informed intervention selection could be demonstrated, although certain methodological prerequisites must be met (24). The current vectroautoregressive approach assumes linearity and stationarity, implying that the distributional properties of the variables remain constant over time and that the system returns to a stable equilibrium following interventions (62). Consequently, the theoretical treatment effects indexed by AC and CIR assume that the system behavior observed during and after the EMA assessment phase is stable. However, this neglects systematic temporal changes in psychological processes, which are not only likely but explicitly intended in the context of therapeutic interventions (17, 63).

In contrast to r-CBT, which is based on diagnosis-driven treatment protocols consisting of predefined intervention modules, c-PBT aims to tailor treatment more closely to the individual. By incorporating idiographic data on temporal and causal relationships among maintaining factors, c-PBT may enhance treatment effectiveness (64). However, an important limitation remains: although treatment decisions in PBT are informed by individual-level data, the selection of interventions is still grounded in nomothetic evidence derived from group-based research and diagnostic categories (e.g., depression: (48)). Future developments of idiographic approaches could address this limitation by implementing continuous dynamic network analyses throughout the course of treatment. Such an approach would allow for ongoing monitoring of changes in the individual network structure and enable adaptive adjustment of interventions at different stages of therapy (18).

Despite these limitations, the present trial may provide an important proof of concept for applying a process-based, control-theory-informed approach in a clinically relevant sample of patients with difficult-to-treat depression and anxiety disorders. By employing a randomized controlled design, a structured manual for network-based assessment, and algorithm-guided personalization of treatment, the study extends previous single-case research (21) and allows for a systematic evaluation of c-PBT relative to r-CBT. In addition, the planned mediation and moderation analyses will contribute to a better understanding of underlying processes of change and the conditions under which treatment is most effective. Finally, post-treatment EMA assessments will offer novel insights into how idiographic network structures evolve over the course of therapy. Taken together, this study has the potential to advance the field of precision mental health by providing empirical evidence for a novel, integrative approach that combines individualized process-based treatment with formal decision-support tools derived from network control theory.

Abbreviations

ANOVA: Analysis of variance
AWMF: Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften)
CBT: Cognitive behavioral therapy
CIR: Cumulative impulse response
c-PBT: Control-theory-informed process-based therapy
CONSORT: Consolidated Standards of Reporting Trials
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
MANOVA: Multivariate analysis of variance
NCT: Network control theory
PAM: Outpatient clinic for psychological treatments (Philipps University Marburg)

PI: Principal Investigator
PBT: Process-based therapy
RCT: Randomized controlled trial
r-CBT: Routine cognitive behavioral therapy

Declarations

Ethics approval and consent to participate

The protocol has been approved by the Ethics Committee of the Faculty of Medicine, Philipps University of Marburg (Registration number: 2025-30v-rev). Protocol amendments will be communicated at https://drks.de/search/en/trial/DRKS00037966/details .

Consent for publication

Not applicable.

Availability of data and materials

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, after deidentification and in accordance with the European General Data Protection Regulation (GDPR). To gain access, researchers requesting data will need to sign a data access agreement and contact the study sponsor.

Competing interests

All authors declare that they have no conflicts of interest.

Funding

The NECTAR study is funded by the DYNAMIC center, which is funded by the LOEWE program of the Hessian Ministry of Science and Arts (Grant Number: LOEWE1/16/519/03/09.001(0009)/98). The present study protocol did not receive separate external funding beyond this framework and was not subject to a dedicated external peer-review process for protocol funding.

Winfried Rief received research funding from the excellence center LOEWEDYNAMIC from the Hessian Ministry of Science and Arts, (Grant Number: LOEWE1/16/519/03/09.001[0009]/98), and from the German Research Foundation DFG (CRC Treatment Expectation;Project-ID).

Ulrich Stangier receives financial support from the DYNAMIC center, the DYNAMIC center, funded by the LOEWE program of the Hessian Ministry of Science and Arts (Grant Number: LOEWE1/16/519/03/09.001(0009)/98).

Stefan Hofmann receives financial support by the Alexander von Humboldt Foundation (as part of the Alexander von Humboldt Professur), the Hessische Ministerium fur Wissenschaft und Kunst (as part of the LOEWE Spitzenprofessur), and the DYNAMIC center, funded by the LOEWE program of the Hessian Ministry of Science and Arts (Grant Number: LOEWE1/16/519/03/09.001 (0009)/98). He also receives compensation for his work as editor from SpringerNature and royalties and payments for his work from various publishers.

Authors' contributions

US and SH conceived the trial, drafted the study protocol and treatment manual, trained therapists and diagnosticians, and supervised implementation and coordination of the study. WR, AR, LP and HF contributed to the trial design and protocol development and obtained ethical approval. LP was

responsible for developing the control-theory module, while ME contributed to the EMA assessment and dynamic network analyses.

AR, MW, KS, HF and LP conduct recruitment and data collection. HF and US drafted the article and all authors read, edited, and approved the final manuscript.

References

1. Ten Have M, Tuithof M, Van Dorsselaer S, Schouten F, Luik AI, De Graaf R. Prevalence and trends of common mental disorders from 2007-2009 to 2019-2022: results from the Netherlands Mental Health Survey and Incidence Studies (NEMESIS), including comparison of prevalence rates before vs. during the COVID-19 pandemic. World Psychiatry. 2023 Jun;22(2):275–85. doi:10.1002/wps.21087
2. Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. European Neuropsychopharmacology. 2011 Sep;21(9):655–79. doi:10.1016/j.euroneuro.2011.07.018
3. Cuijpers P, Miguel C, Harrer M, Plessen CY, Ciharova M, Ebert D, et al. 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. 2023 Feb;22(1):105–15. doi:10.1002/wps.21069
4. Van Dis EAM, Van Veen SC, Hagenaars MA, Batelaan NM, Bockting CLH, Van Den Heuvel RM, et al. Long-term Outcomes of Cognitive Behavioral Therapy for Anxiety-Related Disorders: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2020 Mar 1;77(3):265. doi:10.1001/jamapsychiatry.2019.3986
5. Springer KS, Levy HC, Tolin DF. Remission in CBT for adult anxiety disorders: A meta-analysis. Clinical Psychology Review. 2018 Apr;61:1–8. doi:10.1016/j.cpr.2018.03.002
6. Cuijpers P, Miguel C, Harrer M, Ciharova M, Karyotaki E. The outcomes of mental health care for depression over time: A meta-regression analysis of response rates in usual care. Journal of Affective Disorders. 2024 Aug;358:89–96. doi:10.1016/j.jad.2024.05.019
7. Bhattacharya S, Goicoechea C, Heshmati S, Carpenter JK, Hofmann SG. Efficacy of Cognitive Behavioral Therapy for Anxiety-Related Disorders: A Meta-Analysis of Recent Literature. Curr Psychiatry Rep. 2023 Jan;25(1):19–30. doi:10.1007/s11920-022-01402-8
8. Cohen ZD, Delgadillo J, DeRubeis RJ. Personalized treatment approaches. 2021.
9. Nye A, Delgadillo J, Barkham M. Efficacy of personalized psychological interventions: A systematic review and meta-analysis. Journal of Consulting and Clinical Psychology. 2023 Jul;91(7):389–97. doi:10.1037/ccp0000820
10. Ebrahimi OV, Borsboom D, Hoekstra RHA, Epskamp S, Ostinelli EG, Bastiaansen JA, et al. Towards precision in the diagnostic profiling of patients: leveraging symptom dynamics as a clinical

characterisation dimension in the assessment of major depressive disorder. Br J Psychiatry. 2024 May;224(5):157–63. doi:10.1192/bjp.2024.19

11. Hofmann SG, Hayes SC. The Future of Intervention Science: Process-Based Therapy. Clinical Psychological Science. 2019 Jan;7(1):37–50. doi:10.1177/2167702618772296
12. Hayes SC, Hofmann SG, Wilson DS. Clinical psychology is an applied evolutionary science. Clinical Psychology Review. 2020 Nov;81:101892. doi:10.1016/j.cpr.2020.101892
13. Hofmann SG, Pahlen L, Westhoff M, Quintarelli H, Usée F, Stenzel S, et al. Processes in Psychotherapy A Scoping Review. under review.
14. Stangier U, Strauß B, Rief W, Hofmann SG. Prozessbasierter Ansatz in der Psychotherapie. Psychotherapie. 2024 Jan;69(1):15–23. doi:10.1007/s00278-023-00690-6
15. Ciarrochi J, Hernández C, Hill D, Ong C, Gloster AT, Levin ME, et al. Process-based therapy: A common ground for understanding and utilizing therapeutic practices. Journal of Psychotherapy Integration. 2024 Sep;34(3):265–90. doi:10.1037/int0000348
16. Fisher AJ, Reeves JW, Lawyer G, Medaglia JD, Rubel JA. Exploring the idiographic dynamics of mood and anxiety via network analysis. Journal of abnormal psychology. 2017;126(8):1044.
17. Bringmann LF, Albers C, Bockting C, Borsboom D, Ceulemans E, Cramer A, et al. Psychopathological networks: Theory, methods and practice. Behaviour Research and Therapy. 2022 Feb;149:104011. doi:10.1016/j.brat.2021.104011
18. Henry TR, Robinaugh DJ, Fried EI. On the Control of Psychological Networks. Psychometrika. 2022 Mar;87(1):188–213. doi:10.1007/s11336-021-09796-9
19. Gu S, Pasqualetti F, Cieslak M, Telesford QK, Yu AB, Kahn AE, et al. Controllability of structural brain networks. Nature communications. 2015;6(1):8414.
20. Pasqualetti F, Zampieri S, Bullo F. Controllability Metrics, Limitations and Algorithms for Complex Networks. IEEE Trans Control Netw Syst. 2014 Mar;1(1):40–52. doi:10.1109/TCNS.2014.2310254
21. Fechtelpeter J, Rauschenberg C, Jalalabadi H, Boecking B, Van Amelsvoort T, Reininghaus U, et al. A control theoretic approach to evaluate and inform ecological momentary interventions. Int J Methods Psych Res. 2024 Dec;33(4):e70001. doi:10.1002/mpr.70001
22. Stocker JE, Koppe G, Reich H, Heshmati S, Kittel-Schneider S, Hofmann SG, et al. Formalizing psychological interventions through network control theory. Sci Rep. 2023 Aug 24;13(1):13830. doi:10.1038/s41598-023-40648-x
23. Hofmann SG. A Network Control Theory of Dynamic Systems Approach to Personalize Therapy. Behavior Therapy. 2025 Jan;56(1):199–212. doi:10.1016/j.beth.2024.10.006
24. Pahlen L, Fechtelpeter J, Hufschmidt B, Kohl V, Ebert M, Fiehn H, et al. Network Control Theory in Personalized Intervention Selection: A Proof-of-Concept Approach to Simulating Therapeutic Intervention Effects in Clinical Time-Series Data.
25. Howes OD, Thase ME, Pillinger T. Treatment resistance in psychiatry: state of the art and new directions. Mol Psychiatry. 2022 Jan;27(1):58–72. doi:10.1038/s41380-021-01200-3

26. Rush AJ, Aaronson ST, Demyttenaere K. Difficult-to-treat depression: A clinical and research roadmap for when remission is elusive. Aust N Z J Psychiatry. 2019 Feb;53(2):109–18. doi:10.1177/0004867418808585
27. McAllister-Williams RH, Arango C, Blier P, Demyttenaere K, Falkai P, Gorwood P, et al. The identification, assessment and management of difficult-to-treat depression: An international consensus statement. Journal of Affective Disorders. 2020 Apr;267:264–82. doi:10.1016/j.jad.2020.02.023
28. Domschke K, Seuling PD, Schiele MA, Bandelow B, Batelaan NM, Bokma WA, et al. The definition of treatment resistance in anxiety disorders: a Delphi method-based consensus guideline. World Psychiatry. 2024 Feb;23(1):113–23. doi:10.1002/wps.21177
29. Siepe BS, Kloft M, Heck DW. Bayesian estimation and comparison of idiographic network models. Psychological Methods. 2024 Sep 30. doi:10.1037/met0000672
30. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J clin psychiatry. 1998;59(Suppl 20):22–33.
31. Bandelow B, Aden I, Alpers GW, Benecke A, Benecke C, Deckert J, et al. S3-Leitlinie Behandlung von Angststörungen: Version 2. 2021.
32. Schneider F, Härter M, Schorr S. S3-leitlinie/nationale versorgungsleitlinie unipolare depression. Springer-Verlag; 2017.
33. Epskamp S, Cramer AO, Waldorp LJ, Schmittmann VD, Borsboom D. qgraph: Network visualizations of relationships in psychometric data. Journal of statistical software. 2012;48:1–18.
34. Wenzel A. Strategic decision making in cognitive behavioral therapy. [Internet]. Washington: American Psychological Association; 2013 [cited 2026 Apr 28]. Available from: https://content.apa.org/books/14188-000 doi:10.1037/14188-000
35. Kim Halford W, Frost ADJ. Depression Anxiety Stress Scale-10: A Brief Measure for Routine Psychotherapy Outcome and Progress Assessment. Behav change. 2021 Dec;38(4):221–34. doi:10.1017/bec.2021.12
36. Janssen M, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Quality of life research. 2013;22(7):1717–27.
37. Lukat J, Margraf J, Lutz R, van der Veld WM, Becker ES. Psychometric properties of the positive mental health scale (PMH-scale). BMC psychology. 2016;4(1):8.
38. Gooding DC, Pflum MJ. The assessment of interpersonal pleasure: introduction of the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS) and preliminary findings. Psychiatry research. 2014;215(1):237–43.
39. Bond FW, Hayes SC, Baer RA, Carpenter KM, Guenole N, Orcutt HK, et al. Preliminary psychometric properties of the Acceptance and Action Questionnaire–II: A revised measure of psychological inflexibility and experiential avoidance. Behavior therapy. 2011;42(4):676–88.

40. Fonagy P, Luyten P, Moulton-Perkins A, Lee YW, Warren F, Howard S, et al. Development and validation of a self-report measure of mentalizing: The reflective functioning questionnaire. PloS one. 2016;11(7):e0158678.
41. Attkisson CC, Zwick R. The Client Satisfaction Questionnaire: Psychometric properties and correlations with service utilization and psychotherapy outcome. Evaluation and program planning. 1982;5(3):233–7.
42. Ciarrochi J. Assessing processes of change in psychological interventions: the process-based assessment tool (PBAT). 2021.
43. Jacob KL, Christopher MS, Neuhaus EC. Development and validation of the cognitive-behavioral therapy skills questionnaire. Behavior Modification. 2011;35(6):595–618.
44. First M, Williams J, Benjamin L, Spitzer R. Structured clinical interview for DSM-5 personality disorders (SCID-5-PD). Testkatalog. 2016;30.
45. Hayes SC, Hofmann SG. Process-based CBT: The science and core clinical competencies of cognitive behavioral therapy. New Harbinger Publications; 2018.
46. Curtiss JE, Levine DS, Ander I, Baker AW. Cognitive-behavioral treatments for anxiety and stress-related disorders. Focus. 2021;19(2):184–9.
47. Adams TG, Brady RE, Lohr JM, Jacobs WJ. A meta-analysis of CBT components for anxiety disorders. The Behavior Therapist. 2015.
48. López-López JA, Davies SR, Caldwell DM, Churchill R, Peters TJ, Tallon D, et al. The process and delivery of CBT for depression in adults: a systematic review and network meta-analysis. Psychological medicine. 2019;49(12):1937–47.
49. Pompoli A, Furukawa TA, Efthimiou O, Imai H, Tajika A, Salanti G. Dismantling cognitive-behaviour therapy for panic disorder: a systematic review and component network meta-analysis. Psychological medicine. 2018;48(12):1945–53.
50. Kolb DA. The Kolb learning style inventory. Hay Resources Direct Boston, MA; 2007.
51. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. Journal of behavior therapy and experimental psychiatry. 2000;31(2):73–86.
52. Alexander LB, Luborsky L. The Penn helping alliance scales. 1986.
53. R: A language and environment for statistical computing. R Foundation for Statistical Computing [Internet]. Vienna, Austria: R Core Team. Available from: https://www.R-project.org/.
54. Rosseel Y. lavaan : An *R* Package for Structural Equation Modeling. J Stat Soft. 2012;48(2). doi:10.18637/jss.v048.i02
55. Epskamp S, Kruis J, Marsman M. Estimating psychopathological networks: Be careful what you wish for. Marinazzo D, editor. PLoS ONE. 2017 Jun 23;12(6):e0179891. doi:10.1371/journal.pone.0179891
56. Hyndman RJ, Athanasopoulos G. Forecasting: principles and practice. OTexts; 2018.

57. Van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. Journal of statistical software. 2011;45:1–67.
58. Korotitsch WJ, Nelson-Gray RO. An overview of self-monitoring research in assessment and treatment. Psychological Assessment. 1999;11(4):415.
59. Stone AA, Schneider S, Smyth JM. Evaluation of Pressing Issues in Ecological Momentary Assessment. Annual Review of Clinical Psychology. 2023 May 9;19(1):107–31. doi:10.1146/annurev-clinpsy-080921-083128
60. Nemani A, Hufschmidt B, Kohl V, Sendig L, Ebert M, Bonarius D, et al. Bipolar vs. unipolar scaling in dynamic network analyses of Ecological Momentary Assessment data. PloS one. 2025;20(3):e0314102.
61. Kohl V, Ebert M, Pahlen L, Hufschmidt B, Nemani A, Müller S, et al. Measurement and Analysis of Situation as a Context Variable: A Feasibility Study using EMA and Network Modeling. Cognitive Therapy and Research. 2026;1–30.
62. Hamaker EL, Ceulemans E, Grasman RPPP, Tuerlinckx F. Modeling Affect Dynamics: State of the Art and Future Challenges. Emotion Review. 2015 Oct;7(4):316–22. doi:10.1177/1754073915590619
63. Scheffer M, Bockting CL, Borsboom D, Cools R, Delecroix C, Hartmann JA, et al. A Dynamical Systems View of Psychiatric Disorders—Theory: A Review. JAMA Psychiatry. 2024 Jun 1;81(6):618. doi:10.1001/jamapsychiatry.2024.0215
64. Hayes SC, Ciarrochi J, Hofmann SG, Chin F, Sahdra B. Evolving an idionomic approach to processes of change: Towards a unified personalized science of human improvement. Behaviour research and therapy. 2022;156:104155.

Figures

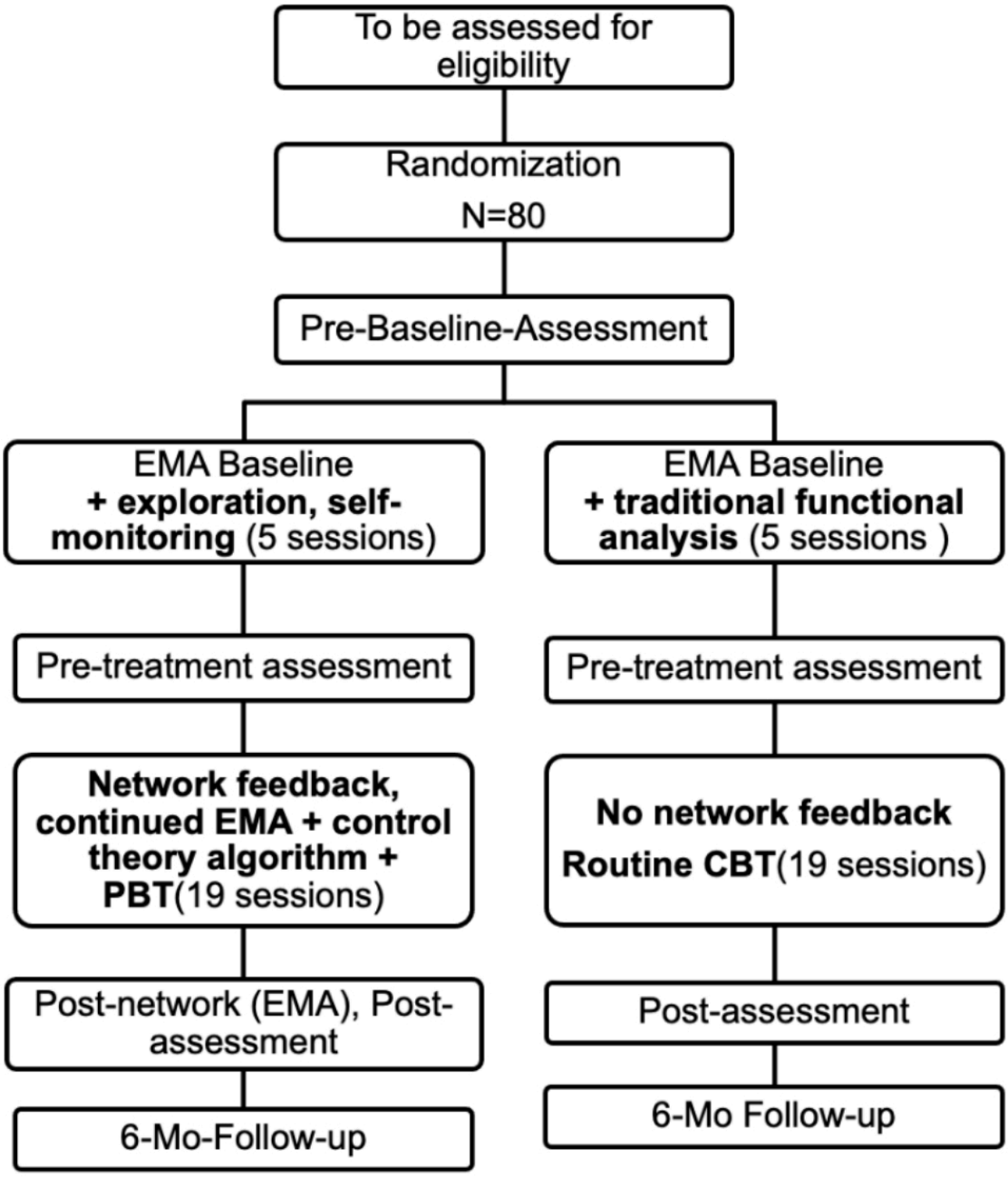


Figure 1

Consort Flow diagram of the study design.

EMA: Ecological Momentary Assessment

PBT: Process-based Therapy

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITNECTAR.docx