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Modular-based psychotherapy (MoBa) versus cognitive–behavioural therapy (CBT) for patients with depression, comorbidities and a history of childhood maltreatment: study protocol for a randomised controlled feasibility trial

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ABSTRACT

Introduction In depression treatment, most patients do not reach response or remission with current psychotherapeutic approaches. Major reasons for individual non-response are interindividual heterogeneity of etiological mechanisms and pathological forms, and a high rate of comorbid disorders. Personalised treatments targeting comorbidities as well as underlying transdiagnostic mechanisms and factors like early childhood maltreatment may lead to better outcomes. A modular-based psychotherapy (MoBa) approach provides a treatment model of independent and flexible therapy elements within a systematic treatment algorithm to combine and integrate existing evidence-based approaches. By optimally tailoring module selection and application to the specific needs of each patient, MoBa has great potential to improve the currently unsatisfying results of psychotherapy as a bridge between disorder-specific and personalised approaches.

Methods and analysis In a randomised controlled feasibility trial, N=70 outpatients with episodic or persistent major depression, comorbidity and childhood maltreatment are treated in 20 individual sessions with MoBa or standard cognitive–behavioural therapy for depression. The three modules of MoBa focus on deficits associated with early childhood maltreatment: the systems of negative valence, social processes and arousal. According to a specific questionnaire-based treatment algorithm, elements from cognitive behavioural analysis system of psychotherapy, mentalisation-based psychotherapy and/or mindfulness-based cognitive therapy are integrated for a personalised modular procedure.

As a proof of concept, this trial will provide evidence for the feasibility and efficacy (post-treatment and 6-month follow-up) of a modular add-on approach for patients with depression, comorbidities and a history of childhood maltreatment. Crucial feasibility aspects include targeted psychopathological mechanisms, selection (treatment algorithm), sequence and application of modules, as well as training and supervision of the study therapists.

Ethics and dissemination This study obtained approval from the independent Ethics Committees of the University of Freiburg and the University of Heidelberg. All findings will be disseminated broadly via peer-reviewed articles in scientific journals and contributions to national and international conferences.

Trial registration number DRKS00022093.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study to investigate the feasibility of a modular-based psychotherapy (MoBa) approach for patients with comorbid depression and a history of childhood maltreatment generating effect estimates for subsequent confirmatory trials.
⇒ Clinicians will be provided with an evidence-based treatment algorithm to combine available treatment modules systematically instead of ad libitum eclecticism.
⇒ Using cognitive–behavioural therapy (CBT) as control condition represents a strong comparator for a rigorous evaluation with a high generalisability to the clinical reality.
⇒ Since no a priori values are established, the algorithm cut-offs used here are based on general population means of self-rated questionnaires.
⇒ Due to the limited sample size of this feasibility study (N=70), statistical analyses will be limited to exploratory comparisons of MoBa versus CBT, since tests between different modules within the MoBa intervention arm are not sufficiently powered.

INTRODUCTION

Until recently, depressive disorders have been predominantly conceptualised and

researched with a focus on the primary diagnosis. This has led to the development of several disorder-specific approaches such as the cognitive–behavioural therapy (CBT)[1] and the interpersonal psychotherapy (IPT).[2] While these approaches (among others) have proven efficacy in unipolar major depression, there is a large proportion of patients who do not respond (more than 50%) or do not reach full remission (about two-thirds) with first-line treatment,[3] even when the procedure is in accordance with treatment guidelines.[4 5] Major reasons for individual non-response and non-remission include interindividual heterogeneity of etiological mechanisms of depression and high rates of comorbid disorders of up to 80% in clinical and epidemiological studies.[6–8] Particularly anxiety disorders and cluster C personality disorders are highly prevalent in major depressive disorder (MDD).[9] These comorbid disorders typically predict poorer treatment outcomes for MDD[10–13] or longer time to remission.[14]

Childhood maltreatment

One major transdiagnostic factor associated with cognitive, emotional, behavioural and interpersonal dysfunctions common to a wide range of disorders is childhood maltreatment (CM). CM has most frequently been operationalised based on the Childhood Trauma Questionnaire (CTQ),[15] defined as onset reported before the age of 18 and meeting the criterion of at least 'moderate to severe' on one of the five trauma subtypes (emotional abuse, emotional neglect, physical abuse, physical neglect, sexual abuse). In depressive disorders, CM is highly prevalent (~46%),[16] especially in early-onset and persistent depression with up to 80%.[17 18] An emerging body of evidence suggests a significant relationship between emotional maltreatment (abuse and/or neglect) in particular and depression.[19–22] Maltreated individuals are 2.7–3.7 times more likely to develop depression in adulthood, have an earlier depression onset and are twice as likely to develop a chronic or treatment-resistant course.[16] CM was also associated with an elevated risk for comorbid disorders.[18 23] Treated with psychotherapy and pharmacotherapy, the probability of non-response is 1.9 times higher in depressed patients with early trauma compared with those without.[16] Taken together, study results indicate that interpersonal trauma exposure complicates the treatment of depression and reduces the impact of traditional cognitive therapy or treatments such as psychoeducation, treatment as usual (TAU) or pharmacotherapy.[24] However, some approaches like mindfulness-based cognitive therapy (MBCT)[25] or the cognitive behavioural analysis system of psychotherapy (CBASP)[26–28] show promising results in the subgroup of depressed patients with CM.

Impact of CM on social and emotional functioning

A growing body of evidence links interpersonal trauma in both youth and adults to difficulties in social and emotional functioning.[24] Among other sequelae, CM usually results in marked avoidance behaviour[9] with negative social consequences and in concomitant retardation of emotional maturational growth.[28 29] These deficits are also expressed in terms of social threat hyperresponsivity (ie, being highly sensitive to social rejection and anxiously expecting, readily perceiving and overreacting to it),[30–33] social stress and avoidance behaviour,[34 35] lack of empathy and theory-of-mind[36–38] and emotional dysregulation.[39 40] These emotional and social dysfunctions are mediated in common brain circuits for emotion and salience regulation, fear and mentalising, suggesting that abnormalities in these functional pathways may be induced by CM.[41 42] Despite these severe consequences of CM and their important implications for treatment, disorder-specific approaches for depression such as CBT or IPT do not specifically address the role of CM and the affected dimensions of functioning.

Personalised treatments

This calls for personalised treatments that target both comorbidities as well as underlying mechanisms and factors, which are central to the development and maintenance of psychological disorders. One of the challenges in the development of personalised approaches is to select treatment modules for targeted dysfunctions and to determine whether and in which sequence to combine them with standard treatment. In daily practice, it is left to the clinical judgement and expertise of the therapist to address the patient's individual needs and comorbidities by adding various therapeutic strategies to the disorder-specific interventions. However, this choice of add-on strategies is not backed up by empirical evidence and thus hardly conveyable to usual clinical practice in a systematic way.[43] Driven by these concerns, there has been growing consensus that a novel approach is needed in the way we classify, formulate, treat, and prevent depression and other mental disorders.[44 45] Insel and Cuthbert[46] postulated the concept of Research Domain Criteria (RDoC) to move 'towards a new classification system' of studying and validating transdiagnostic, dimensional constructs since psychiatric diagnosis seem to be no longer optimal as long as they remain restricted to symptoms and signs. The transdiagnostic procedure focuses on identifying the common and core maladaptive temperamental, cognitive, emotional, interpersonal and behavioural characteristics that underpin a broad array of diagnostic presentations[47] and addresses them via specific modules in treatment.[48] In this sense, a modular-based psychotherapy (MoBa) provides a structured approach of tailoring treatments to fit patient needs by allowing greater flexibility to consider interindividual differences and comorbidity.[49 50] The modules, as sets of independent but combinable functional units, focus on common transdiagnostic dysfunctions and offer skills to improve, for example, emotion regulation, social competence, empathy or self-motivation. There is only one study[51] in which emotion regulation skills were successfully added to CBT in depressed patients that had sufficient statistical power to detect a clinically significant effect.

Modular-based psychotherapy

Empirical support for the effectiveness of modular approaches following decision flowcharts is emerging lately.[50 52] For instance, Weisz *et al*[49] conducted a large randomised controlled trial (RCT) in which a Modular Approach to Therapy for Children with Anxiety, Depression, Trauma or Conduct Problems (MATCH) outperformed standard manual TAU as care as usual (TAU/CAU). The superiority of MATCH was found to be sustained in a 2-year follow-up[53] and was replicated in a more recent trial.[54] Another example of a modular approach to psychotherapy is Behavioural Interventions for Anxiety in Children with Autism (BIACA).[55] By using a modular format and including an algorithm to guide the selection of modules, it offers a treatment approach for several anxiety disorders and obsessive–compulsive disorder for youths on the autism spectrum. BIACA was superior to waitlist and CAU in several RCTs.[56] In adults, a recent RCT[57] assessed the feasibility and efficacy of a modular transdiagnostic intervention for mood, stressor-related and anxiety disorders (HARMONIC trial) in preparation for a later-stage trial. The modular transdiagnostic intervention demonstrated superiority with moderate effect sizes compared with psychological treatment-as-usual.[58] This represents early signs of a significant paradigm shift away from single-diagnosis approaches towards dimensional, transdiagnostic and modular-based conceptualisations.[46 59]

The here proposed rationale for a MoBa for depressed patients with comorbidity and a history of CM is two-fold: First, to include patients regularly seen in clinical practice showing (1) more often comorbid and heterogeneous complaints than the samples usually included in RCTs and (2) a limited treatment response to standard disorder-specific approaches. Second, tailoring the treatment to the specific characteristics and needs of patients with CM and comorbid depression can ensure that the psychotherapeutic process is responsive and may reach better treatment results. The MoBa intervention aims at interpersonal and emotional maturation by overcoming social threat hypersensitivity and interpersonal avoidance patterns and improving poor mentalisation as well as poor emotion regulation capacities. The rationale is supported by previous trials with empirically supported treatments such as CBASP for chronic depression,[60–63] MBCT for depression prevention and treatment[64–67] and Mentalisation-Based Therapy (MBT)[68] for borderline personality disorder (BPD).[69 70] In the here used design, MoBa complements standard CBT with modules compiling specific elements from CBASP, MBCT, and MBT focusing on three disturbed systems (figure 1). Those systems are part of the RDoC model and have been shown to be critically related to CM.

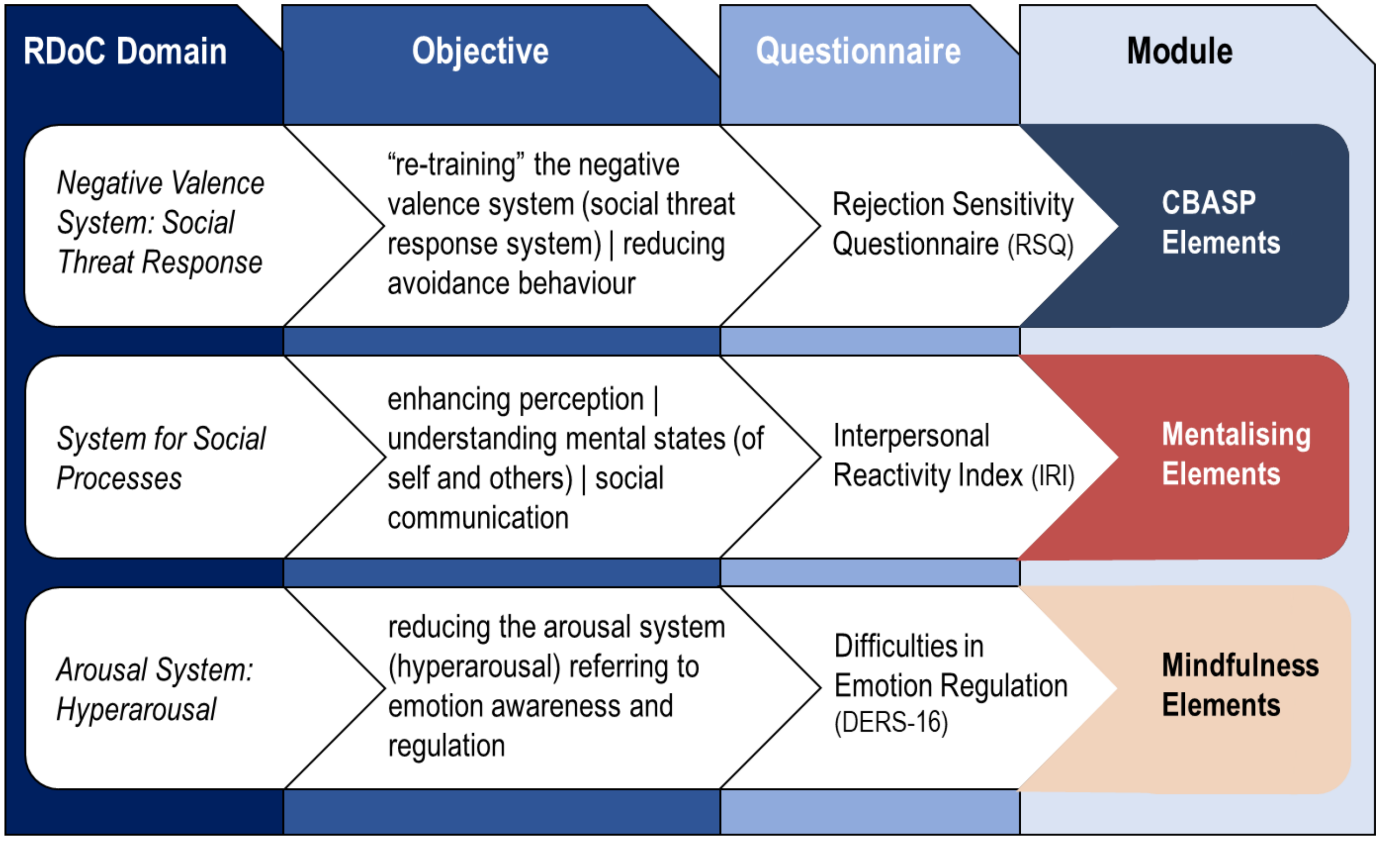

Figure 1 Overview of the targeted RDoC domains and their corresponding objectives, assessments and modules. A detailed description of the modules is given below. CBASP, Cognitive Behavioural Analysis System of Psychotherapy; RDoC, Research Domain Criteria.

1. The negative valence system (acute, potential and sustained threat): social threat response and avoidance behaviour.[9 34]
2. The system of social processes: perception and understanding of self and others (understanding mental states), social communication, attachment.[37 38 71]
3. The arousal system: emotion awareness and arousal regulation.[40 72–74]

Objectives

This pilot study has a number of objectives appropriate to its status as a feasibility study:

1. Providing initial evidence for the efficacy of MoBa (reduction of clinician-rated depressive symptoms) as well as generating pilot data for the power calculation in terms of effect and sample size for a subsequent multicentre confirmatory trial.
2. Investigating the planned study design regarding the feasibility of recruitment, feasibility of applying cut-off values of self-reported deficits to select the modules, acceptability of the programme to therapists and patients as well as patient ratings of 'usefulness' (both overall and in terms of individual modules). A crucial goal is to refine the algorithm for the selection of modules based on questionnaires.
3. Explore potential moderators of the primary outcome (in a hypothesis-generating exercise and to help refine the intervention).

METHODS AND ANALYSIS

Study design

The bicentric study will be conducted at the Department of Psychiatry and Psychotherapy, University Medical Centre Freiburg, Germany and the Department of General Psychiatry, University Medical Centre Heidelberg, Germany. It is a parallel-arm RCT (N=70) comparing MoBa with CBT in 20 individual sessions over 16 weeks of treatment (twice weekly in weeks 1–4, then once per week in weeks 5–16). Participants will be assessed at screening, baseline, post-treatment and follow-up (6 months after end of treatment).

Study population and recruitment

Seventy outpatients with episodic/persistent major depression, comorbidity and CM will be recruited. Key inclusion and exclusion criteria are:

Inclusion criteria

1. Age eligibility: 18–65 years.
2. Episodic or persistent MDD or MDD superimposed on Dysthymia ('double depression') as the primary diagnosis (according to the Structured Clinical Interview for DSM-5 Disorders, SCID-5).[75]
3. A score of >18 on the Hamilton Rating Scale for Depression (HRSD-24).[76]
4. History of CM: at least moderate to severe in one or more of the five CTQ-categories (emotional neglect, emotional abuse, physical neglect, physical abuse, sexual abuse).[15]
5. At least one psychiatric comorbidity or more according to the SCID-5 (except for those described in the exclusion criteria below).
6. Exceeding the 'cut-off' value of at least one of the following measures (module questionnaires): (1) Rejection Sensitivity Questionnaire (RSQ,[77])≥9.88, 2) Interpersonal Reactivity Index (IRI,[78])<45, or 3) Difficulties in Emotion Regulation Scale-16 (DERS-16,[79])≥55.73.
7. Written informed consent.

Exclusion criteria

1. Acute risk of suicide.
2. Other current psychiatric disorders as primary diagnosis.
3. Comorbid schizophrenia, bipolar I disorder, neurocognitive disorder or substance dependence fulfilling criteria within the last 6 months.
4. A diagnosis of antisocial personality disorder or more than three traits of BPD according to SCID-5 PD.
5. Severe cognitive impairment.
6. Serious medical condition (interfering with participation in regular sessions).
7. Other ongoing psychotherapy or psychotropic medication except antidepressant (eg, selective serotonin reuptake inhibitor/ serotonin–norepinephrine reuptake inhibitor) and/or sleep-inducing treatment at baseline if stable for at least 3 weeks before inclusion (4 weeks for fluoxetine). The continuous intake of benzodiazepine is prohibited; the selective use of benzodiazepine as rescue medication on-demand for a maximum of 2 weeks is permitted.

Patients will be recruited through psychiatric and psychotherapeutic outpatient clinics and private practices by announcement of the psychotherapy treatment offers. Approximately 120 patients will be prescreened for eligibility by research assistants via telephone with a brief prescreening guide that has been successfully used in prior depression studies. A total of N=70 patients will be randomised (figure 2).

Sample size

Due to the exploratory nature of the design and the lack of comparable studies, no formal sample size calculation is possible. One of the major aims of this trial is to generate pilot data for a subsequent sample size calculation for a confirmatory study. With reference to Billingham *et al*[80] a medium sample size of 30 patients per group in pilot trials seems to be reasonable for the generation of pilot data for such estimation. That results in a total of 60 patients. Non-compliance and/or dropout of patients after randomization are assumed to be at most 14%. Therefore, 70 patients have to be randomised to observe the desired number of compliant patients, split in two groups for each of the two participating centres (FR=35, HD=35; figure 2).

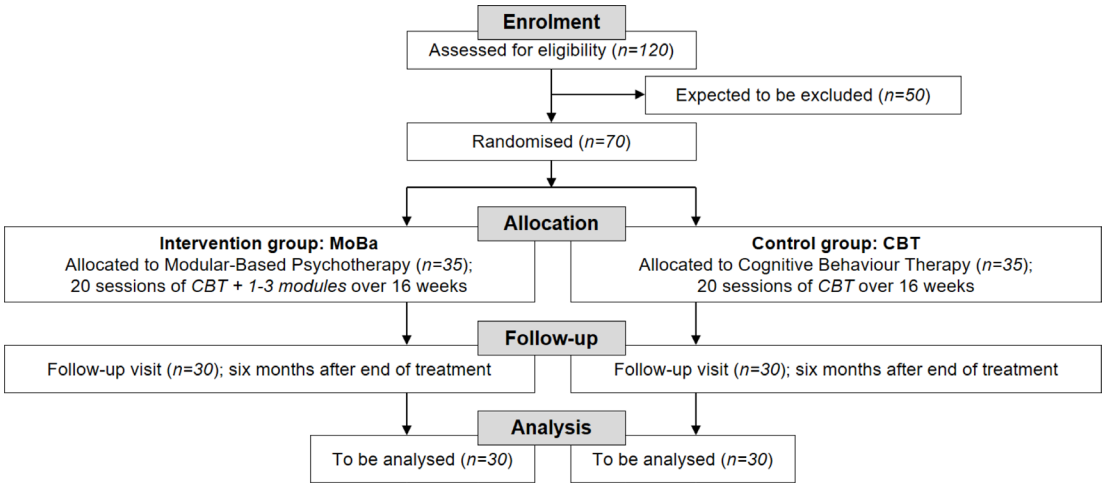

Figure 2 Trial design and flow of patients. CBT, cognitive–behavioural therapy; MoBA, modular-based psychotherapy.

Outcomes

The primary endpoint is the HRSD-24 measured by blind, independent raters at the conclusion of the 16 week treatment period. All secondary endpoints are describe in table 1.

A comprehensive overview about the frequency and scope of all trial visits including all assessments and measures is depicted below (figure 3).

Adherence

Study psychotherapists are in a completed or far advanced stage of psychotherapy training. All therapist will execute CBT as well as MoBa interventions after thorough training to ensure a high treatment quality (1.5-day training course in CBT, 2.5-day training course in MoBa). All trainings are led by clinical experts in the field. The training process for therapists includes the supervision of one pilot case in each arm and an adherence rating for study certification. To check for adherence in the further process and to support the supervision, a 'Therapeutic Element Checklist' is filled out by the therapists immediately after each session. Supervisors will review the 'Therapeutic Element Checklist' regularly in ongoing supervision. All therapy sessions will be videotaped for adherence and supervision. Every fifth session will be supervised by the responsible supervisor in biweekly video conference meetings and/or by written feedback. Two clinical experts will conduct the diagnostic training of raters in SCID-5, HRSD-24 and Social and Occupational Functioning Assessment Scale and inter-rater reliability will be ensured.

Experimental intervention: MoBa

The MoBa model complements standard CBT for depression with modules aiming at socioemotional cognitive deficits and compiling specific strategies from CBASP, MBT and mindfulness (figure 1). Content and implementation of the three modules are illustrated in table 2.

Selection of modules

The application of the modular intervention is preceded by a diagnostic assessment of the patient's impaired systems (negative valence system, system of social processes or arousal system) according to the scores on the self-rated (1) RSQ (social threat response); (2) IRI (mentalisation, empathy) and (3) Brief Version of the DERS-16 (emotion awareness and regulation). The corresponding modular interventions will be applied if the cut-off value in one or more of these measures is exceeded. Since no a priori values are established, the cut-offs used here are defined as one SD above the general population mean, that is, the upper 16%.[79 81] The problem(s) thus identified is/are assigned as the target for one, two or three of the modules (figure 3) according to the systematic treatment algorithm (figure 4).

Treatment modules are selected according to the evidence-based treatment algorithm on the basis of the self-rated module-specific questionnaires. However, the selection of specific treatment strategies or techniques within a specific module (eg, BA or cognitive restructuring in CBT, use of Kiesler's circumplex model or interpersonal discrimination exercise in CBASP) and the sequence of treatment strategies or techniques between modules are based on the clinical judgement and expertise of the therapist and the supervisors, since there is no reliable evidence to implement a data-driven decision algorithm for sequencing yet. The individual case conceptualisations are formulated in consultation with the supervisors who regularly check on the weekly intraindividual Patient Health Questionnaire-9 courses and the utilisation of treatment techniques within each session according to the Therapy Elements Checklist and the videorecordings.

Application of modules (time distribution)

The modules are not simply added as separate components, but rather integrated into the therapeutic process and course as add-on to the standard CBT procedure as basis for both interventions. Consequently, the amount of time spent with single CBT-techniques (eg, cognitive restructuring) will be reduced with increasing number of modules and the procedure will be condensed to

Table 1 Primary and secondary endpoints and corresponding measures

Endpoint	Measure
Severity of depression (post-treatment)	Primary endpoint: Hamilton Rating Scale for Depression (HRSD-24)[76]at the end of treatment rated by trained and blinded clinicians.
Feasibility	Assessed by recruitment rates, distribution rates to the modules and therapists' as well as patients' ratings (Therapeutic Element Checklist; Working Alliance Inventory-Short Revised, WAI-SR)[91]
Severity of depression (FUP)	HRSD-24 6 months after end of treatment rated by trained and blinded clinicians.
Social threat response system	Module questionnaire: The Rejection Sensitivity Questionnaire (RSQ) is a self-report questionnaire comprising 18 hypothetical interpersonal interactions with potential rejections by others (eg, "You ask someone you don't know well out on a date"). It assesses the level of anxiety the patient feels about the outcome of each situation on a six point Likert scale ranging from "very unconcerned" to "very concerned". The RSQ shows good internal consistency and test-retest reliability, and is a reliable measure of the anxious-expectations-of-rejection component of rejection sensitivity. For the German version, the original has been translated, adapted, and shown to be a homogeneous measure with good psychometric properties[81].
Mentalising of others' mental states/empathy	Module questionnaire: The Interpersonal Reactivity Index (IRI) is a 28-item self-report instrument that measures both cognitive and emotional aspects of empathy. Items are rated on a five-point Likert scale ranging from 0 ('does not describe me well') to 4 ('describes me very well'). The questionnaire comprises four subscales (seven items each): Perspective Taking (eg, "I sometimes find it difficult to see things from the 'other guys' point of view."), Fantasy (eg, "I daydream and fantasize, with some regularity, about things that might happen to me."), Empathic Concern (eg, "I often have tender, concerned feelings for people less fortunate than me."), and Personal Distress (eg, "I sometimes feel helpless when I am in the middle of a very emotional situation."). The German version of the IRI[92]was reduced to only four items per scale and showed good psychometric properties.
	The Mentalisation Questionnaire (MZQ)[93] is a self-rating instrument for the assessment of mentalisation in patients with mental disorders and consists of 15 items. The MZQ can be considered a practicable instrument with acceptable reliability and sufficient validity to assess mentalisation in patients with mental disorders.[93]
Emotion awareness and regulation	Module questionnaire: A validated shorter version of the Difficulties in Emotion Regulation Scale[79 94]with 16 items (DERS-16). For each of the DERS-16 items, participants are asked to "indicate how much it applies to your emotions right now" with response options ranging from 1 ('not at all') to 5 ('completely'). The questionnaire has four subscales: non-acceptance (ie, non-acceptance of current emotions), modulate (ie, difficulties modulating emotional and behavioural responses in the moment), awareness (ie, limited awareness of current emotions) and clarity (ie, limited clarity about current emotions). Results of the study provide support for the reliability and validity of the DERS-16 as a measure of emotion regulation difficulties.
Response and remission rates	Response is defined as a reduction in the HRSD-24 score by at least 50% from baseline and a total score of less than 16; remission is defined a priori as an HRSD-24 score of ≤8.
Social and Occupational Functioning	The clinician-rated Social and Occupational Functioning Assessment Scale[95] assesses social role functioning irrespective of psychopathology.
Quality of life	The WHO Quality of Life Instrument (WHOQOL-BREF)[96]is a short form tool consisting of 26 items divided into four domains (physical health, psychological health, social relationships and the environment) to measure quality of life.
Self-rated depressive and anxiety symptoms	Self-ratings of depressive and anxiety symptoms will be obtained using the Beck Depression Inventory-II[97] and the Beck Anxiety Inventory.[98]
Attachment	The Experiences in Close Relationships-Revised[99]scale assesses attachment in adults.
Body connectedness	Self-ratings of body awareness and bodily dissociation will be obtained using the Scale of Body Connectedness.[100]
Therapeutic alliance	The WAI-SR[91] assesses three key aspects of the therapeutic alliance: (1) agreement on the tasks of therapy, (2) agreement on the goals of therapy and (3) development of an affective bond.
Course of depressive symptoms	Patients will fill out the Patient Health Questionnaire-9[101] before every session to constantly monitor depressive symptom severity as a proxy of therapy progress or deterioration.
Therapeutic Element Checklist	All elements/strategies/components will be recorded immediately after each session including the approximate time the therapist used for applying those interventions using a Therapeutic Element Checklist designed for this feasibility trial.

behavioural activation (eg, identifying and promoting pleasant activities) as the most effective component of CBT.[82] Depending on the selected number of modules, approximately one-third of the time will be spent with basic CBT procedures and two-thirds of the time with the application of modules. Therapists will document the time, which is spent with CBT procedures or with single modules, after each session.

Control intervention: CBT

CBT will be delivered according to the German standard manual by Hautzinger.[83] The main CBT elements are (1) establishing therapeutic relationship, (2) psychoeducation, (3) behaviour activation, (4) cognitive restructuring and (5) maintenance and relapse prevention. CBT has been shown to be efficacious in depressed patients in prior clinical trials,[84 85] but not specifically in this subgroup of depressed and comorbid patients exposed to CM.

Randomisation

The randomisation code will be generated by the Clinical Trials Unit Freiburg (CTU) using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. Randomisation will be performed, stratified by site, in blocks of variable length in a ratio of 1:1. The block lengths will be documented separately and will not be disclosed to the sites. The randomisation code will be produced by validated programmes based on the Statistical Analysis System. This dataset is included in REDCap (Research Electronic Data Capture) so that patients can

		Visits	Pre-screening	Screening	T0 Baseline	*Treatment: MoBa vs. CBT*			T1 Post	T2 Follow-up
		Week(s)	-	-	0	1-4	5-15	16	16	42
THERAPISTS		Sessions per week				2	1	1		
	Questionnaires	Therapeutic Element Checklist				X	X	X		
		AE / SAE				X	X	X		
		PHQ-9				X	X	X		
		WAI-P / WAI-T						X		
RATERS	Interview	telephone screening	(X)							
		SCID-5 (CV/PD)		X						
		HRSD-24		X	(X)				X	X
		SOFAS			X				X	X
		AE / SAE			(X)				X	X
	Questionnaires	CTQ		X						
		RSQ		X					X	X
		IRI		X					X	X
		DERS-16		X					X	X
		MZQ			X				X	X
		BDI-II			X				X	X
		BAI			X				X	X
		WHOQoL-BREF			X				X	X
		PHQ-9			X				X	X
		ECR-RD8			X				X	X
		SBC			X				X	X

Figure 3 Frequency and scope of trial visits. AE, adverse event; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CTQ, Childhood Trauma Questionnaire; CBT, cognitive–behavioural therapy; DERS, Difficulties in Emotion Regulation Scale; ECR, Experiences in Close Relationships; HRSD-24, Hamilton Rating Scale for Depression; IRI, Interpersonal Reactivity Index; MZQ, Mentalisation Questionnaire; PHQ-9, Patient Health Questionnaire-9; RSQ, Rejection Sensitivity Questionnaire; SAE, serious AE; SBC, Scale of Body Connectedness; SOFAS, Social and Occupational Functioning Assessment Scale; WAI,Working Alliance Inventory.

be randomised directly in the electronic case report form (eCRF).

Blinding

All clinical ratings will be completed by trained and independent raters blinded to treatment assignment. Each of the sites implements procedures to mask a patient treatment assignment from the person who will evaluate the results of the clinical ratings through the following: (1) locating the raters at a separate physical location, and (2) reminding the patients at each visit not to mention anything that might reveal their treatment condition to the independent evaluator.

Data management and monitoring

Study data will be entered in pseudonymised form in a study database by authorised and trained members of the study team via eCRF. The data management will be performed with REDCap V.9, a fully web based remote data entry system based on web forms, which is developed and maintained by the REDCap Consortium (redcap@vanderbilt.edu). This system uses built-in security features to prevent unauthorised access to patient data, including an encrypted transport protocol for data transmission from the participating sites to the study database. An audit trail provides a history of the data entered, changed or deleted, indicating the processor and date. Monitoring is performed by CTU. Risk-based monitoring will be done according to ICH-GCP E6 (R2) and standard operating procedures to ensure patient's safety and integrity of clinical trial data.

Statistical analysis

Before the start of the final analysis, a detailed statistical analysis plan will be prepared. This will be completed during the 'blind review' of the data, at the latest. The primary efficacy analysis will be performed according to the intention-to-treat principle and will therefore be based on the full analysis set (FAS) including all randomised patients. Patients are analysed as randomised regardless of any protocol deviations. This analysis corresponds to the analysis of the treatment policy estimand. The effects of CBT and MoBa with respect to the HRSD-24 score after 16 weeks of treatment (primary endpoint) will be estimated within a linear regression model, and the two-sided 95% CI will be calculated for the treatment effect. The model will include treatment and study centre as independent variables, as well as baseline HRSD-24 score. A conservative assumption of the effect size anticipated for the subsequent confirmative trial will be derived from these analyses by a combination of clinical and statistical judgement. Secondary endpoints will be analysed descriptively in a similar fashion as the primary outcome in the FAS, using regression models as appropriate for the respective type of data. Treatment effects will be calculated with two-sided 95% CIs. All secondary analyses are exploratory and are interpreted in a descriptive fashion.

Table 2 Content and implementation of modules

CBASP MODULE ► Corresponding RDoC domain: Negative valence system - Social threat response ► Indicative questionnaire: Rejection Sensitivity Questionnaire (RSQ) ► Objective: 'Retraining' the negative valence system (social threat response) and reducing avoidance behaviour
The CBASP module includes interpersonal discrimination training between abusing and well meaning others based on continued safety signals given by the therapist.[28] As a first step, a so-called 'Significant Other History' (SOH) is conducted, a short procedure listing significant others who left an interpersonal-emotional 'stamp' in the patient's learning history. From the SOH, causal conclusions are derived (eg, 'Growing up with my mother led to the pervasive assumption that I have nothing to expect from others'). Based on the patient's assumptions about relationships the patient experienced in his/her history with abusive significant others, a proactive 'transference hypothesis' is formulated stating the patient's most relevant interpersonal expectation/fear regarding the therapist-patient encounter The transference hypothesis is then systematically contrasted with the therapist's actual behaviour in 'hot spot situations', applying the structured 'Interpersonal Discrimination Exercise'. By means of this exposure procedure, the patient learns to differentiate the abusive significant other (generalised to his/her social environment) from current non-abusive or well-intended persons by discrimination learning. Thus, the patient is enabled to overlearn dysfunctional expectations and reprogram the conditioned social threat systems. In addition, by enriching safety signals in therapists' behaviour and re-establishing the perception of operant interpersonal contingencies, this intervention is designed to provide a secure learning environment to decrease interpersonal threat sensitivity. In addition, teaching the patient the mechanisms of complementary interpersonal processes illustrated by *Kiesler's circumplex model*[102] enables the patient to recognise the consequences of his/her own behaviour on other persons and to develop empathy ('reading others') and social problem-solving skills (element of CBASP). Genuine empathy and theory of mind skills are furthermore facilitated by the therapist's 'Disciplined Personal Involvement' (DPI) and more specifically 'Contingent Personal Reactivity' (CPR), that is, expressing personal emotional reactions to the patients dysfunctional behaviour patterns in a disciplined way (including considering a teachable moment and relating it to the patient's core pathology) and offering alternative behaviour. The key objective of this module is social fear extinction by overlearning conditioned associations and avoidance behaviour.
MENTALISING MODULE ► Corresponding RDoC domain: System for social srocesses ► Indicative questionnaire: Interpersonal Reactivity Index (IRI) ► Objective: Enhancing perception and understanding of self and others (understanding mental states) and social communication
The mentalising module contains modelling and teaching mentalising by learning to 'read' others' behaviour and thereby reconnecting the patient to his/her social environment and creating social competence. To promote mentalised affectivity (ie, mentalising own emotional states as described by MBT), the therapist introduces repetitive sequences to stimulate basic mentalising functions in the patient. Based on empathy, the therapist uses a 'not knowing' stance of exploration of the patients' experiences and identifies context-related emotional reactions, raising 'what-questions' rather than 'why-questions'. Two typical interventions to engage mentalising are the 'Stop and Stand' and the 'Stop, Re-wind, Explore' sequences[68] In the first case, the therapist stops a patient who is stuck in drawing non-mentalising assumptions (eg, 'everybody hates me') by surprise or humour to subsequently help the patient to mentalise about his/her experiences. The second sequence generates a joined attention on the patients past experiences by shifting the focus back and forth within an episodic experience to make it accessible for the mentalising process. Genuine empathy and theory of mind skills are furthermore facilitated by the therapist's 'DPI' (and more specifically 'CPR' as an element of CBASP as well. The key objective of this module is to improve mentalising capabilities in social interactions.
MINDFULNESS MODULE ► Corresponding RDoC domain: Arousal system - hyperarousal ► Indicative questionnaire: Difficulties in Emotion Regulation (DERS-16) ► Objective: Reducing the arousal system (hyperarousal) referring to emotion awareness and regulation
This module integrates mindfulness-based exercises, which focus on (1) observing non-judgmentally internal and external stimuli, (2) shifting attention away from trauma-related inner 'movies' and monitoring skills to (3) overcome hyperarousal and experiential avoidance or being run over by one's emotions. Mindfulness-based interventions aim to change a person's perspective on his or her emotions and cognitions. This process is facilitated through mindfulness meditation (eg, body scan, formal sitting meditation) in which close attention is paid to the present moment while thoughts, feelings and body sensations are noted with an attitude of curiosity, non-judgement, and acceptance of psychological experiences. Mindfulness has been suggested to be effective via four mechanisms: attention regulation, body awareness, changes in perspective on the self, and emotion regulation.[103 104] Mindfulness training enhances positive affect,[105] decreases negative affect, and reduces maladaptive automatic emotional responses[106] being associated with changes in areas of the brain responsible for affect regulation and stress impulse reaction.[103 107] The key objective of this module is to improve emotion awareness and regulation in order to mitigate hyperarousal.

CBASP, Cognitive Behavioural Analysis System of Psychotherapy; DERS-16, Difficulties in Emotion Regulation Scale-16; MBT, Mentalisation-based Psychotherapy; RDoC, Research Domain Criteria.

The safety analysis includes calculation and comparison of frequencies and rates of serious adverse events (SAEs). Furthermore, statistical methods are used to assess the quality of data and the homogeneity of intervention groups. Data should be collected regardless of the patients' adherence to the protocol, especially on the clinical outcome, to obtain the best approximation to the FAS. Data should also be collected on other therapies received post dropout. Patients with missing follow-up will be excluded. As the only available measurement of the patient is taken at baseline and the primary aim is feasibility, this can be considered as an adequate strategy. The reasons for missing postbaseline values will be collected and will be taken into consideration for the subsequent confirmatory trial.

Study results will be reported according to Consolidated Standards of Reporting Trials guidelines. Further details of the statistical analysis will be fixed before data base lock and start of the analysis. The responsible biostatistician will remain blind for treatment allocation throughout the study. For further information regarding the statistical analysis, see the extensive study protocol publicly accessible at https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00022093.

Ethics and dissemination

This study obtained approval from the independent Ethics Committees of the University of Freiburg in August 2020 and the University of Heidelberg in October 2020. Additionally, the administrative department for governance and quality of the University Medical Centre Freiburg verified GCP conformity. All findings will be disseminated broadly via peer-reviewed articles in scientific journals and contributions to national and international conferences.

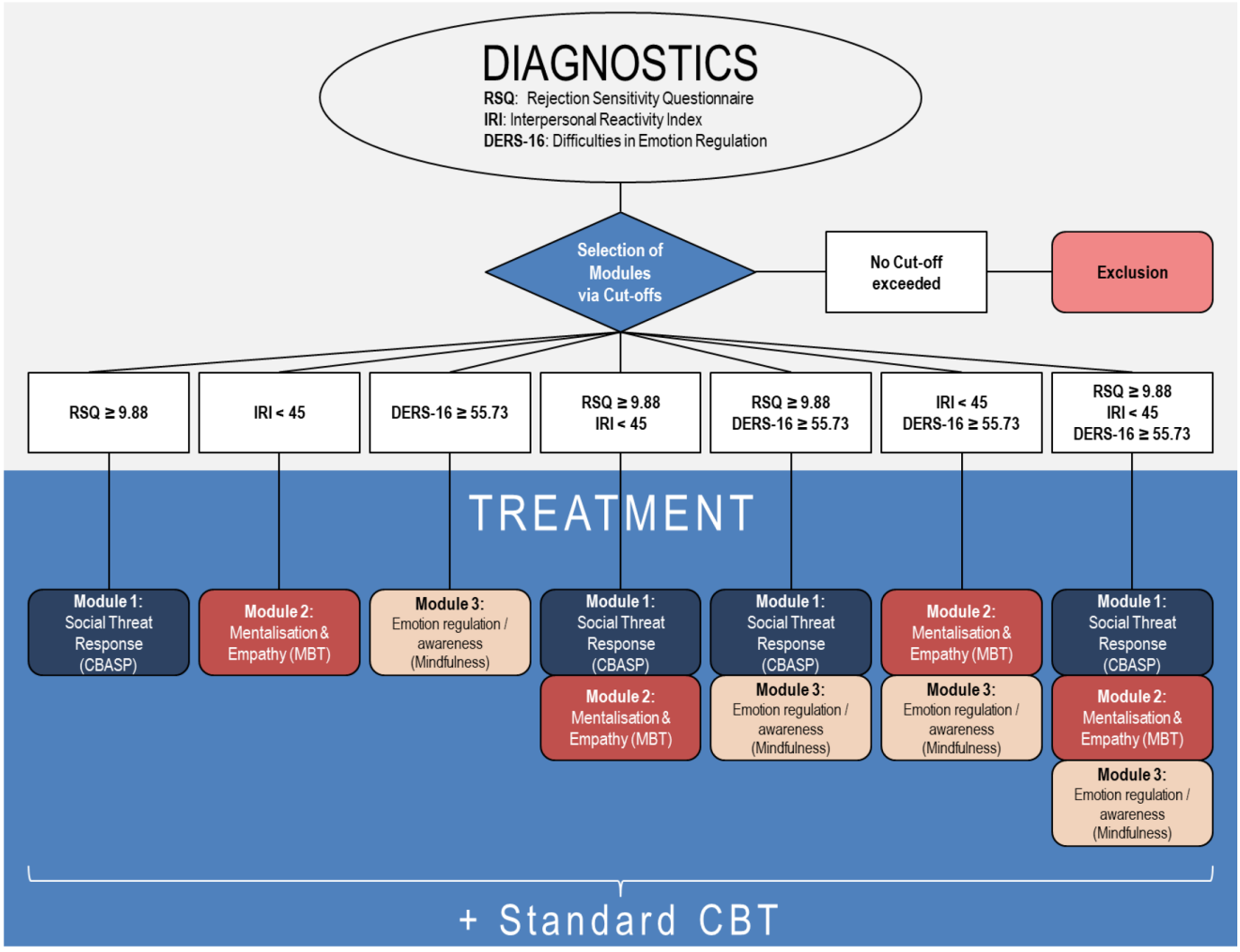

Figure 4 Decision tree algorithm for modular-based psychotherapy. CBASP, Cognitive Behavioural Analysis System of Psychotherapy; CBT, Cognitive–behavioural Therapy; MBT, Mentalisation-based Psychotherapy.

Consent to participate

At first contact, all prospects will be informed about the study in detail and will receive standardised participant information sheets. At screening, voluntary written informed consent for study participation and storage, evaluation and transfer of study-related data will be obtained from each study participant by research associates of the respective study centre. Withdrawal of written consent is possible at any time, without giving reasons. In the event of a withdrawal of the informed consent, patients can decide whether their data should be deleted or destroyed or whether they can be used in anonymised form for this research project.

Safety/harms

Side effects of evidence-based psychotherapies are fortunately rather rare (eg,[86 87]). According to the most recent meta-analysis, only approximately 5% of patients deteriorate while in psychotherapeutic treatment.[3] AEs (eg, private/occupational stress or conflicts in the patient-therapist relationship) and SAEs (eg, severe events requiring stationary medical treatment or with potential permanent damage) are screened for at every assessment or therapy session. AEs have to be reported to the principal investigators (ES, SH) and SAEs to the independent experts. In addition, on-site data monitoring will be regularly conducted by a clinical monitor from CTU to ensure patients' safety and integrity of the clinical data in adherence to the study protocol, as well as to check data quality and accuracy. Individual trial participation will be stopped if one of the following discontinuation criteria occurs:

- Active suicidality
- The physical health of the patient is at risk according to clinical judgement
- Occurrence of an AE/SAE with therapeutic implications incompatible with the study
- Newly occurring exclusion criteria (demanding further procedures not compatible with the continuation of the study participation)
- Withdrawal of the informed consent

If the study principal investigator or the coprincipal investigator have serious ethical concerns because of the performance at one of the sites or severe safety concerns become apparent to the independent experts, the whole trial will be discontinued.

Trial status

Official study begin was in May 2020. The first patient was included in December 2020. Within the first months of recruiting, there were no difficulties regarding the recruitment and inclusion of eligible patients, or the implementation of the MoBa and CBT treatments. Due to the ongoing COVID-19 pandemic, all in person contacts (assessments as well as psychotherapy sessions) are done while wearing appropriate face masks (surgical or FFP2) according to the national guidelines and the respective guidelines of the University Medical Centres in Freiburg and Heidelberg. The end of treatment is expected for August 2022 and data collection aims to be completed in April 2023.

DISCUSSION

Most evidence-based treatment protocols are single-disorder-specific manuals disregarding common comorbidities and transdiagnostic clinical phenomena as sequelae of early trauma and childhood adversities. This leaves a mismatch between the available disorder-specific manuals and the clinical reality. Many clinicians consider the use of evidence-based manuals as challenging or even inadequate for their daily work and report resistances to the 'oversimplified', 'rigid', 'inflexible' or 'flawed' rationales and the 'extensive efforts' needed to maintain up-to-date knowledge by ongoing training.[88] Even attending evidence-based workshops has little impact on clinicians' decisions to use evidence-based treatment protocols in their practice resulting in the well-known underutilisation in community settings.[89 90] In contrast to conventional evidence-based treatment protocols, a MoBa supports the eclectic approach of most clinicians by providing them with an evidence-based treatment algorithm to combine and integrate available treatment modules as independent but combinable sets of functional units systematically. This reduces the perceived challenges of using evidence-based approaches by ensuring a high flexibility and goodness-of-fit within a systematic framework for personalised treatments. By optimally tailoring module selection and application to the specific needs of each patient, MoBa has great potential to improve the currently unsatisfying results of psychotherapeutic treatments in research and clinical practice as a bridge between disorder-specific and personalised approaches. Due to the limited sample size of this feasibility study, statistical analyses will be limited exclusively to comparisons of MoBa versus CBT, since tests between different modules within the MoBa intervention arm are not sufficiently powered. While the modules are selected based on our evidence-based algorithm, the selection of specific treatment strategies or techniques within a specific module and the sequencing between modules are based on individual case conceptualisations, since there is no reliable evidence to implement a data-driven decision algorithm for sequencing yet.

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Competing interests ME received minor book royalties. SH received minor royalties for books with chapters on modular psychotherapy. MH received book royalties from several publishers. ES received book royalties and honoraria for workshops and presentations relating to Interpersonal Psychotherapy and CBASP.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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