The effects of a novel, transdiagnostic, hybrid ecological momentary intervention for improving resilience in youth (EMIcompass): study protocol for an exploratory randomized controlled trial

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Abstract

Background: Most mental disorders first emerge in youth and, in their early stages, surface as subthreshold expressions of symptoms comprising a transdiagnostic phenotype of psychosis, mania, depression and anxiety. Elevated stress reactivity is one of the most widely studied mechanisms underlying psychotic and affective mental health problems. Thus, targeting stress reactivity in youth is a promising indicated and translational preventive strategy for adverse mental health outcomes later in life and for improving resilience. Compassion-focused interventions (CFIs) offer a wide range of innovative therapeutic techniques particularly amenable to being implemented as Ecological Momentary Interventions (EMIs), a specific type of mHealth intervention, to enable youth to access interventions in a given moment and context in daily life. This approach may bridge a gap in current youth mental health care.

Objectives: The aim of this study will be to investigate the clinical feasibility, candidate underlying mechanisms and initial signals of efficacy of a novel, transdiagnostic, hybrid EMI for improving resilience to stress in youth (EMIcompass).

Methods: In an exploratory randomized controlled trial (RCT), youth aged 14-25 with current distress, a broad Clinical High At-Risk Mental State (CHARMS) or a first episode of a severe mental disorder will be randomly allocated to the EMIcompass intervention (EMI plus face-to-face training sessions) in addition to treatment as usual (TAU) or a control condition of TAU only. Primary (stress reactivity) and secondary candidate mechanisms (resilience, interpersonal sensitivity, threat anticipation, negative affective appraisals, momentary physiological markers of stress reactivity) as well as primary (psychological distress) and secondary outcomes (primary psychiatric symptoms, general psychopathology) will be assessed at baseline, post-intervention and 4-week follow-up.

Results: The first enrolment was in August 2019 and as of May 2021, enrolment and randomization has been completed (n = 92 participants). We expect the end of data collection in August 2021.

Conclusions: The current study is the first to establish feasibility, evidence on underlying mechanisms, and preliminary signals of efficacy of a compassion-focused EMI in youth. If successful, a confirmatory RCT will be warranted. Overall, our approach has the potential to significantly advance preventive interventions in youth mental health provision.

Trial registration: German Clinical Trials Register (DRKS), DRKS00017265; Date of registration: 31.07.2019.

Keywords: Experience Sampling Methodology (ESM); Ecological Momentary Assessment (EMA); mobile intervention; at-risk individuals; smartphone training; blended care; mental health; stress reactivity

1 Introduction

2 Youth is a critical life period as most mental disorders have their onset before the age of 25
3 years [1]. In the early stages of psychopathology, subthreshold expressions of symptoms may
4 occur that reflect an extended phenotype in the general population and are often
5 transdiagnostic in nature, spanning from subthreshold expressions of anxiety, depression and
6 mania to psychotic experiences [2-4]. This extended transdiagnostic phenotype may, in turn,
7 be associated with a range of subsequent psychopathological outcomes or exit syndromes
8 later in life [2, 3]. Based on emerging evidence on transdiagnostic dimensions of
9 psychopathology [5-10], dimensional classification systems with transdiagnostic high-order
10 spectra that place individuals on a continuum of mental ill-health have recently been
11 proposed, including the Hierarchical Taxonomy of Psychopathology (HiTOP [11-14]), and
12 clinical staging models have been posited taking into account the overlapping and nonspecific
13 nature of early psychopathology [15-18]. For example, Hartmann and colleagues [16] in their
14 clinical staging model, distinguish three stages of early mental health problems, i.e., current
15 psychological distress (stage 1a), a broad Clinical High At-Risk Mental State (CHARMS) with
16 attenuated symptoms of psychosis, mania, or depression (stage 1b), and a first episode of
17 severe mental disorder (stage 2). Moreover, mental disorders in youth aged 10-24 years have
18 been reported to be the leading cause of disease burden in high-income countries [19]
19 underlining the importance of early intervention and prevention. However, access to care
20 remains deficient with only one in five youth with mental health problems having accessed
21 mental health services [20, 21]. Thus, there is a strong need for easily accessible, low-
22 threshold, preventive interventions in the provision of youth mental health services.

1 The recent rapid advances in digital technologies have led to the development of novel mobile
2 health (mHealth) assessment and intervention techniques, of which ecological momentary
3 assessment (EMA) [22, 23] and interventions (EMIs) [23-28] are, arguably, among the most
4 powerful [26, 28]. EMIs such as Acceptance and Commitment Therapy in Daily Life [29, 30],
5 recently also referred to as just-in-time adaptive interventions (JITAI [31]), provide a unique
6 opportunity to deliver youth-friendly, adaptive, personalized, real-time transfer of
7 intervention components to individuals' daily life. EMIs enable youth to access interventions
8 that are tailored to what a young person needs in a given moment and context through
9 interactive sampling and administration of specific training components [26, 27, 32]. To this
10 end, EMIs build on real-time data acquired through EMA, a structured digital diary technique
11 that measures moment-to-moment fluctuations in experience, behaviour and – when coupled
12 with Electrocardiography (ECG) and actigraphy sensors - physiological markers in daily life, to
13 offer training components that are adapted to person, moment and context based on EMA
14 data. Therefore, EMIs are amenable to enhancing access to mental health services for youth
15 depending on their needs and preferences. Indeed, youth – as the generation of digital natives
16 - already make regular use of mHealth apps and are more likely to do so when experiencing
17 current psychological distress [33]. However, most mHealth apps that are currently available
18 in major app stores are not evidence-based, often use problematic data sharing and privacy
19 practices, and sometimes contain harmful content [34-36]. As reviewed recently, there is
20 evidence on the effectiveness of mindfulness-based EMI for stress reduction [37] and
21 reduction of psychotic experiences [30, 38, 39]. Furthermore, there is evidence for higher
22 compliance and greater effectiveness of hybrid interventions that include both digital and
23 face-to-face intervention components with research staff or clinicians [40, 41].

24

1 In order to prevent transition to, and incidence of, severe mental disorder, the underlying
2 transdiagnostic mechanisms may be important intervention targets in youth. The most widely
3 studied transdiagnostic mechanisms are i) elevated stress reactivity (i.e., more intense
4 emotional reactions to minor stressors in daily life), ii) heightened interpersonal sensitivity,
5 and iii) enhanced threat anticipation. There is evidence that stress reactivity is elevated in
6 individuals with higher familial or psychometric risk, individuals with an Ultra-High Risk (UHR)
7 state for psychosis, first-episode psychosis (FEP), severe and enduring psychosis [42-45], as
8 well as with depressive disorder [46-48], mania and bipolar disorder [49-51]. Moreover, there
9 is some evidence to suggest that differential reactivity to momentary stressors may reflect a
10 risk and resilience mechanism [44, 52-54]. Heightened interpersonal sensitivity is another
11 putative transdiagnostic psychological mechanism, which has been characterized by an
12 enduring sense of feeling vulnerable in the presence of others [43, 55]. Interpersonal
13 sensitivity has been previously reported to be a relevant psychological mechanism in
14 individuals with UHR, paranoia and psychotic disorder [55, 56] as well as in individuals with
15 affective disturbance, including depression, anxiety and manic bipolar disorder [57-59]. What
16 is more, our recent EMA findings extended beyond elevated interpersonal and socio-
17 environmental sensitivity and, consistent with previous research in psychotic, depressive and
18 anxiety disorders [60-65], also indicated that enhanced anticipation of threat may be an
19 important mechanism in the development of psychosis [43, 44]. These mechanisms have been
20 implicated in a range of adverse mental health outcomes, which we have found to overlap
21 considerably [2, 5, 6, 66] and, as noted above, often manifest at a developmentally early stage,
22 in adolescence. Thus, developing EMIs targeting these candidate mechanisms underlying a
23 dimensional transdiagnostic and extended phenotype of psychosis, mania, depression and
24 anxiety in youth is a promising indicated strategy [67] for preventing transition to, and

1 incidence of, severe mental disorder, which, if effective, will be associated with substantial
2 public health gains.

3
4 Compassion-focused interventions (CFIs) belong to third-wave cognitive behavioural therapy
5 approaches that use a wide range of innovative therapeutic techniques for enhancing
6 emotional resilience through activating emotion regulation systems related to self-
7 compassion, self-acceptance and positive affect rather than those related to stress, threat,
8 anxiety and depression [68-70]. Indeed, there is meta-analytic evidence on CFIs treating
9 various conditions [71-73], such as depression and anxiety [74], psychosis [75] and general
10 distress [76]. CFIs involve the use of techniques that seek to access emotion regulation
11 processes through imagery rather than rational understanding [68, 69]. In doing so, CFIs aim
12 to enhance emotional resilience through developing specific affective regulation patterns and,
13 thereby, reduce reactivity to stress, hypervigilance for threat, interpersonal sensitivity and
14 negative affective appraisals. Experimental evidence indicates that CFI techniques can induce
15 reductions in negative affect and paranoia in moments of high stress [77, 78]. CFIs are,
16 therefore, particularly promising for targeting these putative transdiagnostic mechanisms.
17 Building on this work, we have recently set out to develop a novel, accessible, transdiagnostic,
18 compassion-focused, hybrid intervention for enhancing resilience in youth with early mental
19 health problems, i.e., the EMIcompass intervention [53], which consist of an EMI plus face-to-
20 face training sessions. While there is preliminary evidence on the feasibility and initial
21 therapeutic effects of the EMIcompass intervention from an uncontrolled pilot study [53],
22 robust evidence on the underlying mechanisms, feasibility, and initial signals of efficacy of
23 EMIcompass from an exploratory trial is pending.

Against this background, the aim of this study will be to examine the clinical feasibility, underlying mechanisms, and initial signals of efficacy of EMIcompass for improving resilience in an exploratory, randomized controlled trial of youth with current psychological distress, a broad CHARMS or a first episode of severe mental disorder. The EMIcompass intervention will be administered in addition to treatment as usual (TAU) in the experimental condition as compared to a control condition of TAU only. Specifically, the study aims to:

- 1) establish the clinical feasibility of the trial methodology and delivering the EMIcompass intervention to youth with early mental health problems (based on successful recruitment, assessment of inclusion criteria, randomization, retention in the assessment of outcomes, fidelity of delivering the intervention, compliance with the intervention protocol, satisfaction and acceptability);
- 2) detect initial signals of efficacy of the EMIcompass intervention on reducing psychological distress (candidate primary outcome), primary (i.e., psychotic, manic, anxiety or depressive) symptoms, and general psychopathology (candidate secondary outcomes) at post-intervention and 4-week follow-up;
- 3) test the effects of the EMIcompass intervention on reducing stress reactivity (primary candidate mechanism), threat anticipation, interpersonal sensitivity, negative affective appraisals, resilience, self-compassion, emotion regulation and physiological markers of stress reactivity (secondary candidate mechanisms) at post-intervention and 4-week follow-up;
- 4) explore whether the effects of the EMIcompass intervention on psychological distress, primary (i.e., psychotic, manic, anxiety or depressive) symptoms, and general psychopathology are mediated via pathways through stress reactivity, threat anticipation,

interpersonal sensitivity, negative affective appraisals, resilience, self-compassion, and emotion regulation.

Methods

Study design

In an exploratory randomized controlled trial (RCT), youth aged 14-25 years will be randomly allocated to the EMIcompass intervention in addition to TAU (experimental condition) or a control condition of TAU only, which will include routine mental health care. Participants will be recruited from mental health services in Mannheim, Germany, as well as via online advertisements on the institute's webpage, advertisements via Facebook and Instagram as well as via local registries. Candidate mechanisms and outcomes will be assessed before randomization (at 'baseline'), at the end of the 6-week intervention period ('post-intervention'), and at 4-week follow-up (i.e., four weeks after completing the intervention period) by blinded assessors (see Figure 1). Randomization will be conducted by an independent researcher using a computer-generated sequence. The assessment of outcomes and the statistical analyses will be performed blind to treatment allocation.

Participants

We will recruit and randomize 92 individuals with current psychological distress, CHARMS or first episode of severe mental disorder based on a modified version of the clinical staging model by Hartmann et al. [16]. Individuals presenting to mental health services at the Central Institute of Mental Health (CIMH), Mannheim, will be approached by a clinician, who will provide initial information about the study. If the individual agrees, their treating clinician will pass on their contact details to the research team. In addition, individuals from the general

population, who do not seek help from mental health services at CIMH, will be recruited e.g., via social media or local registries. All participants will then be contacted by the research team and initial information about the study will be provided. Following on from this, individuals will be fully informed about the study and written informed consent will be obtained by researchers with a master's degree in psychology (including from parents/legal guardian for minors), which can be withdrawn at any time without any negative consequences. Eligibility will then be assessed in an interview using observer-rated measures (Structured Clinical Interview for DSM-5 (SCID-5 [79]); Comprehensive Assessment of At-Risk Mental State (CAARMS [80]) completed by the researcher as well as self-report measures (Kessler Psychological Distress Scale (K10 [1, 81])). All participants will be reimbursed for their time and travel expenses at the end of the study.

Ethics approval and consent to participate

The study, entitled 'Efficacy of a novel, accessible, transdiagnostic, compassion-focused ecological momentary intervention for help-seeking youth (EMIcompass)' has received ethical approval by the local Ethics Committee of the Medical Faculty Mannheim, Heidelberg University (2017-602N-MA, date: 07.09.2017). Ethical approval was granted before funding was obtained, given this is a requirement for project grants by the German Research Foundation. All participants and, in case of individuals under 18 years of age, parents/legal guardians, will provide written informed consent before inclusion in the study. The sponsor has an insurance, which covers accidents on the journeys to the study appointments but there is no insurance covering harm from study participation, as this is expected to be of low risk.

Inclusion criteria

The inclusion criteria are as follows (see Table 1 for more detail):

- 1) aged 14-25 years;
- 2) meeting criteria for one of the following stages (based on a modified version of the clinical staging model by Hartmann and colleagues [16]: individuals with current psychological distress (stage 1a), i.e., a score of 20 or above on the K10 [1, 81], but no CHARMS (stage 1b) or first episode of severe mental disorder (stage 2); individuals who meet criteria for a CHARMS (stage 1b); individuals, who meet criteria for a first episode of psychotic disorder, bipolar disorder, severe depressive disorder or severe anxiety disorder according to DSM-5 (stage 2);
- 3) high emotional reactivity assessed with a two-item self-report measure (instruction: 'Please think of the most unpleasant event in the last week: A) How sad, disappointed or angry have you been? B) Have you been sad, disappointed or angry because of your feelings?') rated on a 7-point Likert scale (i.e., a score > 3 indicating high reactivity), or by the interviewer-rated CAARMS subscale [80] rated on a 7-point Likert scale (i.e., with a rating of 3 or higher indicating high reactivity);
- 4) reduced positive affect (i.e., a mean positive affect score below 3.19 for men and 3.05 for women, based on normative scores from a representative sample of the German population [82]) or increased negative affect (i.e., a mean negative affect score above 1.81 for men and 1.75 for women [82]), assessed using the Positive Affect and Negative Affect Scale (PANAS [83]);
- 5) willingness to participate in the EMIcompass intervention, and
- 6) ability to provide written informed consent (or consent by parents in case of minors).

Table 1. Inclusion criteria and transdiagnostic sample characteristics based on a modified version of the clinical staging model by Hartmann et al. [16].

[illegible]

Attenuated Hypomanic Symptoms	<p>Elevated, expansive or unusually irritable mood on at least 2 consecutive days <i>and</i> 2 (or in case of only irritable mood 3) additional criteria:</p> <ul style="list-style-type: none"> • inflated self-esteem or grandiosity, • decreased need for sleep, • increased talkativeness, • flight of ideas or subjective experience that thoughts are racing, • distractibility, • increase in goal-directed activity or psychomotor agitation, • unusual ideas, • increased involvement in activities, that are pleasurable in short-time but have a high potential for long-term damage <p>for a duration of max. 3 days, if 3 or more (or in case of only irritable mood 4 or more) additional criteria are met <i>and</i> there are functional disturbances <i>or</i> others notice the mood or functional disturbances</p> <p>for a duration of max. 6 days, if 3 or more (or in case of only irritable mood 4 or more) additional criteria are met <i>or</i> there are functional disturbances or others notice the mood or functional disturbances</p> <p>Exclusion: hospitalization, severe impairment in social or professional functioning, no psychotic elements</p>	SCID-5
Moderate (Attenuated) depression BLIPS ^g	<p>SKID: mild or moderate depression (current or lifetime)</p> <p>At least 1 cardinal symptom, 5 additional symptoms</p> <p><i>And</i> HAM-D > 17 (cutoff)</p> <p>Global rating of 6 on the subscales</p> <ul style="list-style-type: none"> a. unusual thought content b. non bizarre ideas <p>Global rating of 5 or 6 on the subscale perceptual abnormalities</p> <p><i>And/or</i> global rating of 6 on the subscale disorganized speech present for less than a week</p> <p><i>And</i> frequency: 4 - 6 on all above-named scales</p>	<p>SCID-5</p> <p>HAM-D^f</p> <p>CAARMS</p>
Anxiety	<p>SKID: mild - moderate panic disorder /agoraphobia (current or lifetime) <i>or</i></p> <p>SKID: not meeting criteria for GASⁱ, i.e., symptoms for less than 6 months or less than 4 symptoms met <i>or</i></p> <p>Diagnosis of a mild -moderate social phobia (current or lifetime)</p> <p><i>And</i> HAM-A > 9 (cutoff)</p>	<p>SCID-5</p> <p>HAM-A^h</p>
2 (first treated episode)		
	Psychosis	CAARMS
	Severe major depression (current or lifetime)	SCID-5
	Mania/ Hypomania	SCID-5
	Severe anxiety disorder (current or lifetime) e.g. agoraphobia, GAS	SCID-5

^aKessler Distress Scale (K10; [81]); ^bClinical High At-Risk Mental State (CHARMS); ^cSocial and Occupational Functioning Assessment Scale (SOFAS,[84]); ^dStructured Clinical Interview for DSM-5 (SCID-5 [79]); ^eComprehensive Assessment of At-

Exclusion criteria

The exclusion criteria are as follows: 1) a primary diagnosis of alcohol/substance abuse or dependence, assessed with the SCID-5 [79]; 2) evidence that symptoms are precipitated by an organic disease; 3) insufficient command of German so that the intervention cannot be followed and outcomes cannot be reasonably assessed in German; 4) diagnoses of a learning disability according to case records; and 5) current suicidal ideation (indicated by a score > 4 in the CAARMS [80]).

Interventions

Control condition: Treatment as usual (TAU)

Participants allocated to the treatment as usual (TAU) control condition will continue to receive all the treatment they received prior to the start of the study. This will include good standard care delivered according to local and national service guidelines and protocols by their general practitioner, psychiatrist and other providers of (mental) health care. Service contacts will be assessed for the duration of the trial using the Client Service Receipt Inventory (CSRI [87]) to monitor variation in delivery of, and engagement with, mental health services.

Experimental condition: EMIcompass intervention + TAU

The EMIcompass intervention will be delivered by trained psychologists within a 6-week period in addition to TAU to individuals allocated to the experimental condition. TAU consists of all the treatment individuals received prior to inclusion to the study, including their general practitioner, psychiatrist, and clinical psychologist, except for treatment using elements of

1 third-wave Cognitive Behavioural Therapy (CBT). The manualized EMIcompass intervention
2 consists of four biweekly sessions (three training sessions, and one review session) with a
3 duration of 45-60 minutes administered face-to-face or using a certified and encrypted video
4 conferencing system, and a 6-week compassion-focused EMI. An optional on demand session
5 will be offered if participants are unable to complete tasks between sessions or report acute
6 psychological distress so that a scheduled session cannot be followed as per manual. The EMI
7 will be administered through a smartphone-based app (movisensXS, movisens GmbH,
8 Karlsruhe, Germany) running on dedicated study smartphones and translates the training
9 from the intervention sessions into individuals' daily lives. The first three sessions are based
10 on elements of compassion-focused therapy (CFT) [68]. In line with our pilot study [53], CFT
11 principles and techniques are introduced in these guided sessions. The first session aims to
12 familiarize participants with the app offering the EMI. Further, practical tasks to activate the
13 soothing system, as a key emotion regulation system in CFT, are presented and trained
14 together with the psychologist, as described elsewhere [88]. The face-to-face sessions also
15 offer the opportunity of reflecting on the progress and problems participants face with the
16 EMI. In the last session, progress with all tasks will be reviewed and subjective improvement
17 in, compliance and satisfaction with, as well as acceptance of, the EMIcompass intervention
18 will be assessed.

19
20 The app will offer EMI tasks according to three types of delivery schemes, i.e., i) enhancing, ii)
21 consolidating, and iii) interactive EMI tasks that aim for ecological translation of therapeutic
22 principles and techniques to daily life. Participants will be asked to complete one 'enhancing
23 task' per week, practicing new compassion-focused tasks such as self-compassionate writing,
24 experiencing emotions as a wave, and discovering their own compassionate self. Furthermore,

1 participants will be offered 'consolidating tasks', covering components of 'enhancing tasks'
2 from previous days. The components of 'consolidating tasks' will be extended each time an
3 'enhancing task' has been presented until all components are covered. Additionally,
4 participants will be offered to complete a brief EMA of momentary stress, affective
5 disturbance, and threat anticipation six times per day on three days per week. Based on these
6 EMAs, 'interactive' tasks will be offered if participants score high on momentary stress or
7 negative affect. The threshold for triggering interactive tasks will be either high momentary
8 negative affect operationalized as a score of 4 or higher (on a 7-point Likert scale ranging from
9 1 to 7) on items of established and validated EMA measures of negative affect (see Table 2)
10 or high momentary stress based on items of established and validated measures of EMA
11 measures of event-related, activity-related or social stress (i.e., a score < 0 on a bipolar scale
12 ranging from -3 to 3). Participants will be instructed in detail in the semantic meaning of the
13 7-point Likert and bipolar scales and encouraged to carefully observe moment-to-moment
14 variation in, and make use of the full range when rating, these scales on EMA items that have
15 been previously used and validated to measure moment-to-moment variation in
16 stress/negative affect. Given a crucial element of compassion-focused therapy is for
17 individuals to use compassionate imagery in moments of high stress or negative affect, these
18 interactive tasks reflect an important component of the EMIcompass intervention.
19 Participants can decline the EMI tasks in each delivery scheme. After completion of the
20 intervention period, participants will return the study devices and will no longer have access
21 to the app.

Clinical feasibility, acceptability, treatment adherence and intervention fidelity

Clinical feasibility will be assessed in relation to 1) the trial methodology and 2) delivering the EMIcompass intervention to youth with early mental health problems. Feasibility of 1) the trial methodology will be assessed based on the following criteria: (a) successful recruitment of at least 96 participants over the study period, (b) assessment of inclusion criteria in 95% of potential participants after written consent obtained, (c) successful randomization of at least 92 participants after completion of eligibility and baseline assessment, (d) a retention rate of at least 85% for assessment of outcomes at least at one of the two time points at post-intervention and 4-week follow-up. In addition, we will assess the following criteria for establishing the feasibility of 2) delivering the EMIcompass intervention including acceptability, intervention adherence and intervention fidelity: (e) satisfaction with the EMIcompass intervention in general, ease of use, accessibility and comprehensiveness of various components of the intervention in a debriefing questionnaire [30, 89] and the subjective quality of EMIcompass using the mobile application rating scale (MARS [90]); (f) compliance with, and adherence to, the EMIcompass intervention protocol based on a satisfactory level of session attendance, an adherence checklist covering all core components [29, 30, 91], and adherence to EMI tasks (i.e., mean number of consolidating/interactive EMI tasks completed per week); and (g) fidelity to the EMIcompass intervention protocol based on independent ratings of a random selection of audio recordings of three face-to-face sessions, including fidelity to session protocol (i.e., independent rating of core components delivered by trained psychologist), ability to model and embody the spirit of compassion as well as use of micro-skills in compassion-focused therapy assessed by the Compassion Focused Therapy-Therapist Competence Rating Scale [92].

Candidate mechanisms and outcomes

All eligible participants will be assessed after obtaining written informed consent on all candidate mechanisms and outcomes before randomization ('baseline', t_0), after the 6-week intervention period ('post-intervention', t_1), and after a 4-week follow-up period ('follow-up', t_2) by blinded assessors (see Figure 1 and Multimedia Appendix 1). Research Electronic Data Capture (REDCap [93]), a secure, web-based software platform hosted at the CIMH servers, will be used for data collection.

Primary candidate mechanism

The primary candidate mechanism is a reduction in stress reactivity acquired by EMA from baseline to post-intervention for the experimental condition compared to the control condition. EMA will include eight assessments per day, scheduled at random within set blocks of time, over a period of six consecutive days at baseline, post-intervention and at follow-up [43, 94]. Momentary stress will be assessed using established and validated EMA measures of event-related stress, activity-related stress and social stress (see Table 2, [43, 95]). We will compute a composite momentary stress measure (i.e., the mean score of event-related, activity-related and social stress in line with the literature [52, 96, 97] and the EMIcompass pilot study [53]. Negative affect will be assessed using an established and validated EMA measure of negative affect [43]. Stress reactivity as the primary candidate mechanism will be computed in linear mixed models with composite momentary stress as independent variable and negative affect as outcome variable [43, 94, 95].

Secondary candidate mechanisms

Secondary candidate mechanisms (see Multimedia Appendix 1 and Table 2) measured using EMA include threat anticipation, negative affective appraisals, emotional resilience to stress (operationalized as attenuated recovery in positive affect in response to minor stressors), and elevated stress reactivity (i.e., increased negative affect) in response to event-related, activity-related and social stress using subscale scores of the EMA stress measure. Threat anticipation will be additionally assessed using the Threat Anticipation Measure (TAM [62]) asking participants to estimate the future likelihood of a list of negative, neutral, and positive events happening to themselves and to other people [61-63]. Interpersonal sensitivity will be assessed using the Interpersonal Sensitivity Measure (IPSM [98]) in addition to EMA. Resilience will be measured using the Connor-Davidson Resilience Scale (CD-RISC [99]) and the Resilience Scale (RS-13 [100]). Further, the Self-Compassion Scale (SCS [101]), the Five Facet Mindfulness Questionnaire (FFMQ-sf [102]) as well as the Cognitive Emotion Regulation Questionnaire (CERQ [103]) will be used to assess self-compassion and emotion regulation. Additionally, we will assess physiological markers of stress reactivity using a sensor for ambulatory Electrocardiography (ECG) and actigraphy (movisens ECGmove4) during the 6-day EMA at baseline, post-intervention and at follow-up.

Candidate primary outcome

The candidate primary outcome of this exploratory RCT is psychological distress measured with the well-validated Kessler Psychological Distress Scale (K10 [81]). The ten items are rated on a 1 (never) to 5 (always) Likert-scale focusing on psychological distress in the last month. Strong psychometric properties have been reported with a reliability of Cronbach's alpha > 0.90 [81].

Candidate secondary outcomes

Secondary outcomes include primary (i.e., psychotic, manic, anxiety or depressive) symptoms and general psychopathology. These will be assessed using the following observer-rated measures: the Brief Psychiatric Rating Scale (BPRS [104]), including, the Comprehensive Assessment of At Risk Mental State (CAARMS [80]), the Young Mania Rating Scale (YMRS [105]), the Hamilton Depression Rating Scale (HAM-D [85]), and the Hamilton Anxiety Rating Scale (HAM-A [86]). Based on these measures we will assess transition to another clinical stage (according to a modified version of the clinical staging model by Hartmann et al. [16]; see above). In addition the following self-report measures will be used: the Brief Symptom Inventory (BSI [106]) and the Beck Depression Inventory (BDI [107]), and the Prodromal Questionnaire (PQ [108]). Secondary outcomes further include quality of life measured with the WHO-Quality of Life assessment (WHOQOL-BREF [109]).

Other measures

Other study parameters will include basic socio-demographic characteristics, familial risk factors for psychopathology and other parameters (including age, sex, alcohol/substance use, and childhood trauma (CTQ [110]). The Client Service Receipt Inventory (CSRI [87]) will be used to record patients' contacts with mental health services, monitor variation in delivery of TAU and model economic outcomes for a definitive trial. The Working Alliance Inventory (WAI-P, WAI-T [111, 112]) will be used to assess the relationship between practitioner and patient.

Table 2. EMA measures.

Domain	EMA measure
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Momentary stress	Momentary stress was operationalized as unpleasant events, activities and social situations in daily life. In line with previous research, we distinguished three different types of stress, i.e., event-related stress, activity-related stress and social stress [43, 95]. Participants will be asked to report the most important event that happened in the time since the last assessment. This event will be subsequently rated on a 7-point Likert scale (-3 = very unpleasant, 0 = neutral, 3 = very pleasant) comprising the event-related stress measure. Activity-related stress will be assessed by asking participants to report their current activity and then judge the valence of the activity ('This is ...') using a 7-point Likert scale (1 = very unpleasant, 7= very pleasant). Further, social stress will be measured by asking participants to evaluate the social context when other people were present as well as when they were alone by answering the items 'I am taking care of myself' / 'I am taking care of somebody' and 'I would rather be alone' / 'I would prefer to have company' using two 7-point Likert scales and the item on social valence ('This is..' rated on the 7-point Likert scale from 1 = very unpleasant to 7= very pleasant) .
Negative affect	Six items will be used to assess negative affect (anxiousness, loneliness, insecurity, anger, annoyance and feeling down), using 7-point Likert scales ranging from 'not at all' (rating of 1) to 'very much' (rating of 7).
Negative affective appraisals	In case participants report negative affect (ratings >3), two items on how they cope with their negative affect will be displayed: 'I want to change my negative feelings' and 'I would like to get rid of my negative feelings' using two 7-point Likert scales .
Positive affect	Positive affect will be assessed by four items (cheerfulness, satisfaction, enthusiasm and feeling relaxed) using 7-point Likert scales ranging from 'not at all' (rating of 1) to 'very much' (rating of 7).
Aberrant salience	The EMA measure comprises three items in line with [43]. The items will be rated on a 7-point Likert scale (ranging from 1 ['not at all'] to 7 ['very much']): 'Everything grabs my attention right now', 'Everything seems to have meaning right now', and 'I notice things that I haven't noticed before'.
Self-esteem	Three items will be rated on a 7-point Likert scale ranging from 'not at all' (rating of 1) to 'very much' (rating of 7): 'I feel guilty', 'I doubt myself', 'I feel disappointed about myself'.
Self-compassion	Three items will be rated on a 7-point Likert scale ranging from 'not at all' (rating of 1) to 'very much' (rating of 7): 'I like myself', 'I feel safe', 'I feel benevolent'.
Psychotic experiences	Psychotic experiences will be assessed using eight items on thought problems and hallucinations ('I see things that aren't really there', 'I hear things that aren't really there', 'I feel suspicious', 'It's hard to express my thoughts in words', 'I feel unreal', 'My thoughts are influenced by others', 'I can't get these thoughts out of my head', 'I feel like I am losing control') that will be rated on 7-point Likert scales ranging from 'not at all' (rating of 1) to 'very much' (rating of 7).
Resilience	If participants indicate that there was a negative event (valence -3 or -2), then the item 'I had difficulties to recover' will be rated on a 7-point Likert scale.
Threat anticipation	In line with previous research we will ask participants to rate the likelihood of negative events happening to them in the future [43]. They will be asked to think of what might happen in the next few hours and to rate the item "I think that something unpleasant will happen" on a 7-point Likert scale from 'not at all' (rating of 1) to 'very much' (rating of 7).
Disturbance	'This prompt disturbed me' will be rated at the end of each assessment on a 7-point Likert scale from 'not at all' (rating of 1) to 'very much' (rating of 7).

Sample size

A formal sample size calculation is not essential for this exploratory trial that primarily seeks to establish feasibility, effects on candidate mechanisms, and initial signals of efficacy. In planning, we aimed to determine the sample size in such a way as to establish the feasibility of the methodology for conducting a randomized controlled trial and delivering the EMIcompass intervention to youth with early mental health problems as well as initial signals of efficacy of EMIcompass on reducing psychological distress as candidate primary outcome (see Statistical Analysis Plan for further detail [113]) as a basis for a future definitive trial. For the latter, previous studies of third-wave CBT [72, 114] including compassion-focused interventions [68, 77], suggest that these types of interventions may yield clinically meaningful reductions in psychological distress of moderate to large effect size. This is consistent with initial findings from an uncontrolled phase I pilot study [53]. However, even if the effect size for the main effect of condition on psychological distress (primary outcome) in this exploratory RCT is small, a power simulation in the R environment indicated that a sample size of $n = 80$ participants ($n = 40$ experimental, $n = 40$ control condition) will be sufficient to detect a small effect size of 0.3 across post-intervention 4-week follow-up with a power of 81% when testing at $\alpha = 0.05$ for the effect of condition (experimental vs. control condition) on psychological distress using linear mixed modelling, which will be tested using a Wald-type test of no difference between the two conditions across both timepoints against the two-sided alternative hypothesis that the conditions are, on average, a different across the two follow-up timepoints (given the exploratory nature of this trial), while controlling for baseline psychological distress and group status. At 4-week follow-up, we expect an attrition rate of 15%, resulting in a loss to follow-up of around 6 individuals per condition on average (see Figure 1). Therefore, we will randomize a total of $n = 92$ participants at baseline, which leaves

n = 80 participants at follow-up to detect a small effect size of 0.3 at this time point. This sample size is also sufficient to test criteria for establishing feasibility. Simulation studies on power and accuracy for multilevel mediation models with continuous variables [115] and our recently completed multilevel moderated mediation analysis of EMA data [42] suggest further very little bias in parameter estimates with samples of this size (and 40 repeated measures, on average, per participant).

Randomization and blinding

Participants will be randomized at a 50:50 ratio to the experimental or control condition at the level of the individual participant after completion of the baseline assessment. Block randomization in blocks of four will be performed by an independent research assistant through a computer-generated sequence, with stratification for the three stages (i.e., stage 1a, stage 1b, stage 2). The assessors will be blind to the allocation of participants when assessing outcomes at post-intervention and follow-up. Any data specific to the intervention group (e.g., on clinical feasibility) will be stored in a separate database. Breaks in masking will be documented and another (blinded) researcher will repeat the assessment to maintain masking.

Assessment of safety

Serious adverse events (SAE) will be monitored throughout the entire study period and reported to the accredited Medical Ethics Review Committee, the Data Monitoring and Ethics Committee (DMEC) and, where required, the Trial Steering Committee (TSC). SAE are any serious incidents that result in death, persistent or significant disability or incapacity, that require hospitalization or are life threatening. SAE are not expected to occur as a result of the

1 intervention. In case there are any doubts on safety or ethical concerns the TSC will terminate
2 the trial. The DMEC will advise on safety and ethical concerns, monitor evidence for harm by
3 the intervention (e.g., SAEs) in the experimental condition and review whether these events
4 are in line with expectations. If deemed necessary, the DMEC can recommend to the Principal
5 Investigator (PI) and TSC for interim analyses to be conducted and the trial to be terminated
6 prematurely.

8 [Statistical analysis](#)

9 The primary interest of this exploratory RCT is to establish the feasibility of trial methodology
10 and intervention delivery and initial signals of efficacy on the candidate primary outcome (i.e.,
11 psychological distress) as a basis for a future definitive trial. In addition, this trial seeks to
12 obtain parameter estimates (95% confidence intervals) for the effects on primary and
13 secondary candidate mechanisms and on candidate secondary outcomes. A detailed
14 Statistical Analysis Plan [113] has been agreed with the DMEC and the TSC and has been
15 preregistered and published on the Open Science Framework. It was registered while
16 collecting the data, prior to study completion and accessing the locked database. Descriptive
17 statistics will be used and confidence intervals will be constructed as appropriate to compute
18 basic sample characteristics and address the primary aim of establishing feasibility of trial
19 methodology and intervention delivery based on the criteria described above and in further
20 detail in the Statistical Analysis Plan using three categories (in line with a traffic light system)
21 of (i) feasibility fully established (green), (ii) feasibility established, but study procedures need
22 modifying (yellow), and (iii) feasibility not established (red) [113]. The analysis on candidate
23 mechanisms and initial signals of efficacy has been described in detail in the Statistical Analysis
24 Plan [113] and will be an intention to treat analysis or an available case analysis following

1 intention to treat principles, with data from all participants entered into the analysis including
2 those who have low adherence to, or who will drop-out from, the intervention. We will make
3 every effort to assess all participants at post-intervention and 4-week follow-up. Linear mixed
4 modelling in Stata 16 will be used to compare candidate mechanisms and outcomes between
5 experimental and control condition at post-intervention and 4-week follow-up. The primary
6 candidate outcome of psychological distress measured at post-intervention and 4-week
7 follow-up will be entered as the dependent variable and psychological distress measured at
8 baseline, group status (3-level factor), time (2-level factor), and condition (2-level factor) as
9 independent variables. The main effect of condition on psychological distress will be
10 parameterized so that it reflects the difference between the two conditions at the two follow-
11 up timepoints (i.e., post-intervention, 4-week follow-up), which will be tested (at $\alpha = .05$) by
12 a Wald-type test with $df = 1$, which tests the joint null hypothesis of no difference at both
13 follow-up timepoints against the alternative hypothesis that there is, on average, a difference
14 across the two follow-up timepoints. In addition, given the exploratory nature of this trial,
15 with the main goal to establish feasibility and obtain parameter estimates for a future
16 definitive RCT, 95% confidence intervals for the two time-specific contrasts of a time $\times$
17 condition interaction term will be inspected to obtain estimates for the differences across
18 conditions at each of the two timepoints, with a time $\times$ condition interaction and a baseline
19 psychological distress $\times$ time interaction added as independent variables to the previous
20 model. Within-subject clustering of repeated measures (post-intervention, 4-week follow-up)
21 will be taken into account by including a level-2 random intercept and by allowing the models'
22 level-1 residuals to be correlated with a completely unstructured error variance-covariance
23 matrix. The model will be fitted using restricted maximum likelihood (REML) estimation. The
24 analysis of secondary candidate outcomes as well as primary and secondary candidate

mechanisms will in principle follow the same steps, focusing on 95% confidence intervals (rather than p-values at $\alpha < 0.05$). Multilevel moderated mediation analysis of EMA data will be used to explore whether effects of condition on primary (i.e., psychotic, manic, anxiety or depressive) symptoms are mediated via stress reactivity, threat anticipation, negative affective appraisals, and interpersonal sensitivity [42]. As participants will be randomly assigned to experimental and control condition no differences across conditions are expected in other study parameters (socio-demographic characteristics, alcohol/substance use, and childhood trauma). No statistical tests will be done on these study parameters at baseline.

Results

The trial is ongoing. The trial started recruitment on 15th July 2019. The first enrolment was in August 2019. We are currently working with trial protocol version 5 (24th June 2020). The last changes to the protocol were related to adaptations due to the COVID-19 pandemic, such as introducing the option of using video conferencing systems. As of May 2021, enrolment and randomization has been completed ($n = 92$ participants). Assessment of outcomes at post-intervention and follow-up is still ongoing, with the last assessment for the last participant being scheduled for August 2021. Data will then be entered, checked and the database locked (by September 2021). We expect results to be published in 2022.

Research governance

The CIMH is the trial sponsor. The study has received ethical approval by the local Ethics Committee (EC) of the Medical Faculty Mannheim, Heidelberg University (2017-602N-MA). Amendments to the study protocol will be submitted to the EC and sent to the DMEC, TSC, and sponsor of the study. The trial is registered at the clinical trials register and changes to

the protocol will be updated. Deviations from the protocol will be documented in the study folder using a breach report form and will be reported to the TSC. The trial does not involve the collection or storage of biological samples. All data will be handled confidentially and will be coded using a number according to the order of study entry. Data will be securely stored in line with the European General Data Protection Regulation (GDPR). Personal data will be kept separately from pseudonymized data. The PI has overall responsibility for the trial. The trial research team will meet on a regular basis and will be chaired by the PI. It will manage the day-to-day running of the study, monitor progress of the trial (i.e., recruitment, assessment) and oversee preparation of presentations and reports to EC, TSC and DMEC. The TSC will meet biannually and provide independent overall supervision, monitor progress of the trial (e.g. recruitment, data completion rates and adherence to the protocol), and approve the protocol and any amendments. The DMEC will meet at least once per year, advise on ethical or safety concerns, monitor SAEs and other evidence of intervention harm and whether this is in line with expectations. If deemed necessary, the DMEC can recommend to the PI and TSC to be granted access to all trial data, to perform interim analyses and to terminate the trial prematurely.

Discussion

Transdiagnostic mechanisms implicated in the development of severe mental disorders are important targets for prevention and early intervention. Ecological translation of compassion-focused intervention components to individuals' daily life through an EMI offers new avenues for tangible, indicated prevention strategies delivering real-world and real-time interventions that are easy accessible by youth [116]. In fact, findings from a recent, nationally representative survey suggest that psychological distress, social isolation, lack of company,

1 and worrying during the COVID-19 pandemic were highly prevalent in youth and, interestingly,
2 associated with the current use of, and a positive attitude toward, digital interventions [33].
3 EMIs are also amenable to enhancing access to mental health services for youth depending
4 on their needs and preferences, for instance, by delivering low-threshold interventions by
5 frontline mental health staff [117-119], as one component that can be rolled out across
6 adolescent and adult mental health services and link in with what is urgently needed, i.e., a
7 wider youth mental health reform that aims to provide a seamless coverage of mental health
8 care with smooth transitions from adolescence to mature adulthood at around 25 years of
9 age[20]. Further, EMIs allow for investigating the strength of the evidence in support of
10 several causal criteria (i.e., association, temporality, sole plausibility, ecological validity) as
11 part of the ecological interventionist causal model approach that targets candidate underlying
12 psychological mechanisms in daily life in order to achieve sustainable change under real-world
13 conditions [27]. However, robust, trial-based evidence on EMIs and other mHealth
14 interventions remains very limited [26, 27, 29, 116, 117, 120] and a key next step is to examine
15 the efficacy of youth-friendly, accessible, interactive, real-time interventions targeting
16 candidate mechanisms underlying the transdiagnostic phenotype of psychosis, mania,
17 depression and anxiety and, thereby, help preventing adverse outcomes later in life. While, in
18 the current study, we use EMA items that have been previously used and validated to measure
19 moment-to-moment variation in stress/negative affect, with considerable within-person
20 variability having been observed for these items in several EMA studies [43, 95, 121] , inter-
21 individual differences in within-person variability as well as general response tendencies may
22 influence the number of triggered EMI tasks and, hence, further research is needed to
23 optimize and personalize the assignment of EMI components, e.g., by using methods of
24 artificial intelligence, recurrent neural networks (RNNs) in particular [122]. So for example, we

1 currently aim to apply RNNs in an ongoing study personalized digital mental health promotion
2 and prevention in youth [33]. In addition, clinical staging models of severe mental disorder
3 require further scrutiny, including heterogeneity in phenomenology, course and outcome
4 within individual stages [5, 123, 124].

5 The present exploratory RCT is the first to establish feasibility, evidence on underlying
6 mechanisms, and preliminary signals of efficacy of a compassion-focused, hybrid EMI for
7 reducing stress reactivity (EMIcompass) in youth at different clinical stages. Preliminary
8 evidence from a pilot study of the EMIcompass intervention in help-seeking youth showed
9 reductions in clinical symptoms and stress reactivity [53]. If the current exploratory trial is
10 successful, a confirmatory RCT will be warranted. Overall, our approach has scalable potential
11 to contribute to preventing transition of early mental health problems to severe and enduring
12 mental disorder, not only in individuals at-risk for developing psychosis, but
13 transdiagnostically and across clinical stages and, thereby, significantly advance preventive
14 interventions in youth mental health provision.

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Authors' contributions

UR designed the study, is PI and has managerial responsibility for the successful completion of the study. JRB is the trial statistician. BB provides supervision for the trained psychologists delivering the intervention. AS, UR, CR and IP drafted the manuscript. All authors were involved in writing, have read, and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Abbreviations

CAARMS: Comprehensive Assessment of At-Risk Mental State

CBT: Cognitive Behavioural Therapy

CHARMS: Clinical High At-Risk Mental State

CIMH: Central Institute of Mental Health

CFI: Compassion-focused intervention

DMEC: Data Monitoring and Ethics Committee

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

ECG: Electrocardiography

EMA: Ecological Momentary Assessment

- 1 EMI: Ecological Momentary Intervention
- 2 FEP: First-Episode Psychosis
- 3 K10: Kessler Psychological Distress Scale
- 4 mHealth: Mobile Health
- 5 PANAS: Positive Affect and Negative Affect Scale
- 6 PI: Principal Investigator
- 7 RCT: Randomized Controlled Trial
- 8 RNN: Recurrent Neural Network
- 9 SAE: Serious Adverse Event
- 10 SCID-5: Structured Clinical Interview for DSM-5
- 11 TAU: Treatment As Usual
- 12 TSC: Trial Steering Committee
- 13 UHR: Ultra-High Risk
- 14
- 15
- 16

1 Figure 1. Study flow chart.

2
3 Note: Multimodal EMA, Ecological Momentary Assessment (incl. self-report, activity/ ECG sensor) collected 8
4 times per day on 6 consecutive days; n denotes the total number of participants.

1 Multimedia Appendix 1: SPIRIT figure.

		STUDY PERIOD		
	Enrolment	Allocation	Post-allocation	
TIMEPOINT	$-t_1$	0	t_1 Post measurement	t_2 4 week Follow-up
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Randomization		X		
INTERVENTIONS:				
<i>EMIcompass + TAU</i>
<i>TAU</i>
ASSESSMENTS:				
SCREENING				
<i>SCID-5</i>	X		X	X
<i>CAARMS past 4 weeks</i>	X			
<i>BPRS</i>	X			
<i>SOFAS</i>	X			
<i>HAM-D</i>	X			
<i>HAM-A</i>	X			
<i>YMRS</i>	X			
<i>Fam. Risk</i>	X			
<i>K10</i>	X			
<i>PQ-SV</i>	X			
<i>SPQ</i>	X			
<i>Stress reactivity</i>	X		X	X
<i>PSRS</i>	X		X	X

PANAS	X		X	X
PRIMARY CANDIDATE MECHANISM				
<i>EMA: stress reactivity</i>		X	X	X
SECONDARY CANDIDATE MECHANISM				
<i>EMA: threat anticipation</i>		X	X	X
<i>EMA: negative affective appraisals</i>		X	X	X
<i>EMA: resilience to stress</i>		X	X	X
TAM		X	X	X
IPSM		X	X	X
CD-RISC		X	X	X
RS-13		X	X	X
<i>ECG markers of stress sensitivity</i>		X	X	X
PRIMARY OUTCOME				
K10		X	X	X
SECONDARY OUTCOME				
<i>CAARMS since last assessment</i>			X	X
BPRS			X	X
SOFAS			X	X
HAM-D			X	X
HAM-A			X	X
YMRS			X	X
PQ			X	X
BDI-II		X	X	X
BSI		X	X	X
WHOQOL-BREF		X	X	X

	FFMQ		X	X	X
	SCS		X	X	X
	CERQ		X	X	X
	ACCEPTABILITY MEASURES				
	EMA debriefing		X	X	X
	Debriefing intervention			X	
	WAI-T			X	
	WAI-P			X	
	OTHER				
	CSRI	X		X	X
	WPAI	X		X	X
	Medication use	X			
	CTQ		X		

Notes: Structured Clinical Interview for DSM-5 (SCID-5 [79]); Social and Occupational Functioning Assessment Scale (SOFAS [84]); Comprehensive Assessment of At Risk Mental State (CAARMS [80]); Brief Psychiatric Rating Scale (BPRS; [104]); Brief Symptom Inventory (BSI-18 [106]); Hamilton Depression Rating Scale (HAM-D [85]); Hamilton Anxiety Rating Scale (HAM-A [86]); Young Mania Rating Scale (YMRS [105]); Kessler Distress Scale (K-10 [81]); Positive Affect Negative Affect Scale (PANAS [83]); Stress reactivity assessed using two items; Threat Anticipation Measure (TAM [62]); Interpersonal Sensitivity Measure (IPSM; [98]); Connor-Davidson Resilience Scale (CD-RISC [99]); Self-compassion Scale (SCS [101]); Five Facet Mindfulness Questionnaire (FFMQ [102]); Working Alliance Inventory – Short form (WAI-SF [111, 112]); Beck Depression Inventory-II (BDI-II [107]); Childhood Trauma Questionnaire (CTQ [110]); Prodromal Questionnaire – Short version (PQ-SV [108]); Schizotypal Personality Questionnaire (SPQ [125]); Cognitive Emotion Regulation Questionnaire (CERQ [126]); Client Service Receipt Inventory (CSSRI [87]); Work Productivity and Activity Impairment questionnaire (WPAI [127]); WHO-Quality of Life (WHOQOL-BREF [109]); Ecological Momentary Assessment (EMA); Electrocardiography (ECG).

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