Research Design Protocol

Date: 01/07/2022

Table of Contents

1. Title:

Interoceptive iNsight and Metacognitive Efficacy beliefs (InMe): RCT protocol for a biofeedback-assisted psychological intervention for interoceptive awareness.

2. Expected Duration of Data-Collection Phase:

June 2022-November 2022

3. Abstract

Context: Disruptions in interoception (the sensing, perception and interpretation of one's physiological states) have emerged as a transdiagnostic pathogenic mechanism for several disorders at the mental-physical health interface, such as eating, functional or somatic symptom disorders. However, the interdisciplinary expertise required to identify and therapeutically target psychophysiological mechanisms has limited the efficacy of related therapeutic endeavours.

Objective: We aim to develop and test the efficacy and mechanisms of action of a novel, interdisciplinary (psychophysiological) therapeutic module (InMe) to aid individuals with low interoception awareness.

Design, setting and participants: This is a two-arm parallel group randomised controlled trial comparing InMe intervention to an active control intervention (imagery training without biofeedback). We aim to recruit 120 people experiencing low interoception awareness who will be individually randomised (and stratified by eating disorder symptoms) to receive InMe

intervention or control intervention. INME will use cardiac biofeedback during guided respiration exercises to train individuals to down-regulate their own heartrate under different conditions of stress, while also enhancing related metacognitive beliefs.

Key words: Interoception, Self-efficacy beliefs; Randomised control trials; Heartrate regulation; Biofeedback

4. List of abbreviations

BAQ	Bodily Awareness Questionnaire
BMI	Body Mass Index
BSI-53	Brief Symptom Inventory – 53
EDI-3	Eating Disorder Inventory – 3
EDE-Q	Eating Disorder Examination Questionnaire
GSE	General Self – Efficacy Scale
HRD	Heart Rate Discrimination
HRV	Heart Rate Variability
IUS	Intolerance of Uncertainty Scale
InMe	Interoceptive iNsight and Metacognitive Efficacy beliefs
MAIA	Multidimensional Assessment of Interoceptive Awareness
OC-CDQ	Obsessive-Compulsive Core Dimensions Questionnaire
PANAS	Positive and Negative Affect Scale
PHQ-15	Patient Health Questionnaire
PPI	Public and Patient Involvement
RCT	Randomised Control Trail
STAI	Spielberger Trait Anxiety Inventory
STAI-S	Spielberger Trait-Stait Anxiety Inventory-Short

TAS-20	Toronto Alexithymia scale – 20
TSST	Trier Social Stress Test

5. Research Team:

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6. Scientific background

Interoception refers to the process by which the nervous system senses, integrates and interprets signals originating from within the body, providing a mapping of the body's physiological state. Dysfunctions of interoception, at either conscious or unconscious levels, are increasingly recognized as an important component of different mental health conditions, including anxiety disorders, mood disorders, eating disorders, addictive disorders, and somatic and functional symptom disorders. However, several conceptual and methodological challenges have made it difficult for interoceptive constructs to be broadly applied in mental health research and treatment settings. One such challenge is the interdisciplinary expertise required to identify a mental-physical health interface. On the one end of the disciplinary divide, there are 'interoceptive biofeedback' interventions with precise control of

neurophysiological signals that can be technologically ‘externalised’ and shared with patients to help them improve their interoception or its regulation. However, despite their neurophysiological sophistication, most studies are lacking understanding of the key psychological mechanisms that may contribute to improvements in mental health, for example individual’s beliefs about the meaning of interoceptive sensations or one’s ability to regulate them. On the other end of the disciplinary divide, there is an increasing interest in integrating concepts from research on interoception into mainstream psychological therapies, such as 'mindfulness’, ‘meditation’ or ‘interoceptive exposure’ techniques added to therapies such as Cognitive Behavioural Therapy. The target of these therapies is not the interoceptive sensations themselves, but rather metacognitive beliefs about interoception, i.e. one’s ability to reflect upon, evaluate and regulate our own thoughts and actions. While there is increasing evidence for the efficacy of such therapies, they can target only disturbances in conscious, perceptual levels of interoception, which are not the only critical target in several psychopathologies, such as eating, functional and somatic symptom disorders characterised by poor insight. Such metacognitive therapies are also not effective for all patients, and little is known about the underlying mechanisms of symptom alleviation, particularly in relation to interoception.

7. Research question

This trial aims to answer the question of whether an interoception-based, real-time cardiac biofeedback intervention in people with low interoceptive awareness, compared with an active control intervention (imagery based affective regulation) without biofeedback can significantly enhance interoceptive self-efficacy beliefs under stressful conditions. This heightened interoceptive self-efficacy is in turn expected to raise people’s awareness of their bodily responses in stress and lead to reduction of mental-health symptoms, particularly subclinical disordered eating and somatisation.

8. Aims & Objectives

8.1 Primary objective

To test people with low interoceptive awareness and compare a new interoceptive intervention involving real-time biofeedback with a control intervention (imagery-based affective regulation) without biofeedback, to raise people's awareness of their bodily responses to stress and raise individuals' beliefs about their ability to control their cardiac response using breathing.

Hypothesis 1. "Adaptive interoception" (Desmedt et al., 2022) (primary outcome) will be increased in the InMe arm, versus control arm post-intervention (T1).

8.2. Secondary objectives

Identify mechanisms of action to improve individuals' awareness of their bodily responses.

Hypothesis 2. Elevated belief updating about one's self-efficacy in interoceptive control (as compared to the first prior at T0 and quantified using different computational methods (see https://psyarxiv.com/rntsf/) will mediate the expected primary outcomes change from T0 to T1 in the InMe arm (primary mechanism see secondary outcomes 15.2.1.1).

Hypothesis 3. Core dimensions of Obsessive-Compulsive Disorder (harm avoidance and incompleteness) and Intolerance of Uncertainty will act as moderators of the expected primary outcomes change from T0 to T1 in the InMe arm (secondary mechanism see secondary outcomes 15.2.3). Specifically, individuals with high harm avoidance, incompleteness and intolerance of uncertainty will benefit more from the InMe arm, as the biofeedback can provide increased subjective certainty, agency and perceived control. Measures of cardiac physiology, such as heart rate (HR) and heart rate variability (HRV) as well as self-efficacy and alexithymia traits, will also be used as secondary exploratory moderators following preliminary analyses of their interrelations and the relation with other key variables in the design (see section 17).

Investigate if InMe intervention can reduce mental health symptoms, in particular if it can reduce subclinical symptoms of disordered eating, somatisation and other related difficulties in emotion regulation and mood (see secondary outcomes 15.2.2).

Hypothesis 4. Reduction in eating disorder symptoms at T1 (as compared to T0), will be observed and this effect would be greater in the InMe arm as compared to the control arm.
Hypothesis 5. We also expect a reduction in somatisation, depression and anxiety as well as in difficulties of emotion regulation measures, at T1 (as compared to T0).

Identify mechanisms of action to reduce mental health symptoms, in particular in reducing symptoms of eating disorders or other related difficulties in emotion regulation, such as somatisation.

Hypothesis 6. The above expected mediators (*Hypothesis 2*) and moderators (*Hypothesis 3*) would act as mechanisms of change to reduce mental health symptoms, and in particular symptoms of eating disorders or other related difficulties in emotion regulation, such as somatisation.

Identify maintenance of the treatment effect.

Hypothesis 7. The expected improvement in "Adaptive" interoception and reduction in mental health symptoms in the InMe group versus control arm will be observed in 2-month follow up assessment.

Identify maintenance of the treatment effect in relation to mechanism of actions.

Hypothesis 8. Primary and secondary mechanisms of action, that acted as moderators or mediators of the association between change in "Adaptive interoception" or mental-health symptoms from T0 to T1, will be observed after 2 month-follow up assessment.

Use the expected efficacy and feasibility results and comments and feedback from users participating in the trial, as well as the PPI components of the work (see section 23.0 and 24.0) to develop a protocol for a large, follow-up transdiagnostic RCT targeting key pathogenic mechanisms and feasible determinants.

9. Methods/Design

9.1 Design overview

We aim to recruit 120 people experiencing low interoception awareness (as measured by the BAQ) who will be individually randomised to receive InMe intervention ("InMe arm") or control intervention ("Control arm") for one week (two sessions). Participants have a 50:50 chance of being allocated to receive InMe or Control arm. Data, including the primary and secondary outcomes, will be collected online or at the PI's lab at baseline (T0), post intervention (T1a and T1b) and at Follow-up (T2, 7-9 weeks post the end of T1).

9.1.1 Type of study

This is a two-arm parallel group randomised controlled trial comparing InMe intervention to an active control intervention (imagery based affective regulation without biofeedback).

9.1.2 Setting

Participants will be recruited through SONA system (UCL) or other social media advertisements. The intervention will be delivered at the PI's research lab.

9.1.3 Recruitment

Participants will be recruited to the study by one or more of the following pathways:

a. SONA system UCL
b. Advertisement in social media platforms such as Twitter, Facebook and Instagram

9.2 Participants/target population

Participants will be 120 healthy adults between the ages of 18-30 years.

9.2.1 Inclusion criteria

- 18-30 years old - justification- This is a pilot RCT which does not aim to be fully generalisable but rather give us indications of the mechanisms of action, we wish to recruit a homogeneous sample and hence to restrict our sample age to young adults (18-30 years old).
- Low levels of interoception awareness: Score on the Bodily Awareness Questionnaire (BAQ) <25 percentile*

*Depending on recruitment rate we will need to consider less restrictive criterion of < 30/40 percentile.

9.2.2 Exclusion criteria

- Self-report of existing substance dependency, moderate to severe cognitive impairment and severe mental health conditions (e.g., psychosis)
- Self-report of exciting severe neurological condition (e.g., epilepsy)
- Self-report of exciting diagnosis of heart-disease
- Self-report on being currently pregnant
- Self-report on current use of neurological, cardiac (e.g., medications that influence blood pressure/cardiovascular functioning) or psychiatric medication (via self-report).
- Self-report on weight and height (to be calculated and exclude BMI ≥ 30, where BMI = kg/m2)
- Self-report on low vision/hearing that cannot be corrected
- Self-reported not-sufficiently fluent English speakers

9.2.3 Withdrawal criteria

Participants will be withdrawn from the study if a psychological or disease-specific issue is identified that prevents the participant to continue with the study procedures. Also, in case of participants not complying to the intervention in T1a/T1b (i.e., would not follow the instruction), they will not be invited to T1b or follow up (T2). Participants are also able to withdraw if they choose, without giving a reason. Reasons for drop-out and withdrawal will be recorded if provided by participants. Exclusion criteria from the analysis are considered below (see section 17.0).

10. Informed consent

Participants will be given a brief explanation about the study including exclusion criteria via the recruitment add. They will be invited to contact the research team by email if they have further questions. Participants who will register to the study (see section 9.1.3) will be able to read the full information sheet and again encouraged to contact the research team if they have any

questions. Full informed consent to take part in this study before the eligibility and screening phase will be obtained via Qualtrics and participants will have the opportunity to write the research team with questions about the research study before signing a consent form. After signing the consent form, they will be asked to verify if they do not answer the exclusion criteria via Qualtrics. Those who are eligible will redirect to the screening questionnaires.

11. Screening process

We will screen 120 healthy adult volunteers to participate in the RCT: 60 in each arm: Screened for low interoception awareness (based on BAQ).

Carried out by:	What the assessment is for	How is the assessment carried out	Instruments, questions
Researcher	1. Screening: Do participants meet inclusion criteria and exclusion criteria? 2. Stratification: Measuring eating disorder symptoms to be used for stratification 3. Feasibility: To be used for future studies targeting somatisation	Self-report online	Age (YOB) Gender Excluding questions on neurological, psychological disorders etc EDE-Q PHQ-15 BAQ

Table 1: Screening process

12. Randomisation

Stratified randomisation with randomly varying block sizes:

1. Gender (If possible at least 15 Males in each group).

2. Subclinical disordered eating based on the EDE-Q norm (Carey et al., 2019)

At ratio of 1:1 to InMe or Control to ensure a balance in the number of participants with different conditions.

Qualtrics' built-in randomiser will be used for random allocation. This will be implemented by an administrator independent (e.g., External researcher) of the trial team to ensure allocation concealment. A separate Qualtrics account will be used to ensure blinding of the data analyst and group allocation will be kept separate from questionnaire data. The external researcher to prepare sealed, signed and numbered envelopes in blocks of 15 for each gender (e.g., F or M) and for High eating disorder separately (e.g., High eating M; High eating F; Low eating M; low eating F). The content of each envelope will be the study arm. When requested by RCT manager (MT) who is in charge of the screening phase, the external researcher opens the envelope (according to instructions – I.e., low M) and lets her know the participant arm. MT to send the experimenters the participant arm (WITHOUT SAYING ANYTHING ELSE). Experimenter to allocate a new ID number to this participant which will be used in all the following testing and to give the external researcher the new ID. The external researcher is the only one who will have access to a file linking the screening id number with the new ID number.

12.1 Design rationale for randomisation

In both arms, participants will receive the intervention designed to regulate their physiological and emotional state at rest and after stress (TSST). This approach will aim to allow individuals in both arms to learn about their interoceptive abilities, to notice the somatic signals and to increase their ability to regulate them in situations that lead to anxiety. In arm1 (InMe group) this will be assisted also by personalised biofeedback which is likely to address also related self-efficacy beliefs (and secondarily, moderators such as compulsivity and 'intolerance of uncertainty' co-morbidities) in these populations. In arm 2 (Control) this will be assisted using guided imagery.

12.2. Design rationale for stratification

Given our future goals to target eating disorders in clinical settings participants with subclinical or clinical disordered eating will be stratified between the two groups in order to balance the

two arms. This has the potential to shed light on feasibility and efficacy measures in eating disorders.

12.3 Blinding

Data files containing participant randomised allocation (see section 12.0) information will be done independently by an independent researcher (AS) and files will be password protected so that they are inaccessible to the blinded individuals.

The nature of the proposed intervention does not allow full blinding, but only a single-blind. Researchers that run the experiments and deliver the intervention (T0 and T1) cannot be blinded to the participants' arm (even though the ones who do the analysis will be blind to group allocation), however participants will not be informed of the use of two arms and which of the expected arm is expected to deliver a greater therapeutic benefit nor which is the active intervention or the control arm. All researchers involved in follow-up collection and statistical analyses will remain blinded to treatment allocation, including the trial data analyst. Statistician and data analyst will always be blinded unless unblinding incidents happen during follow-up data collection facilitated by the data analyst where participants inadvertently reveal their allocation. A record of unblinding incidents will be maintained throughout the duration of the trial.

13. CONSORT diagram

The flow of recruitment though the study will be reported according to Consolidated Standards of Reporting Trials (CONSORT) guidance.

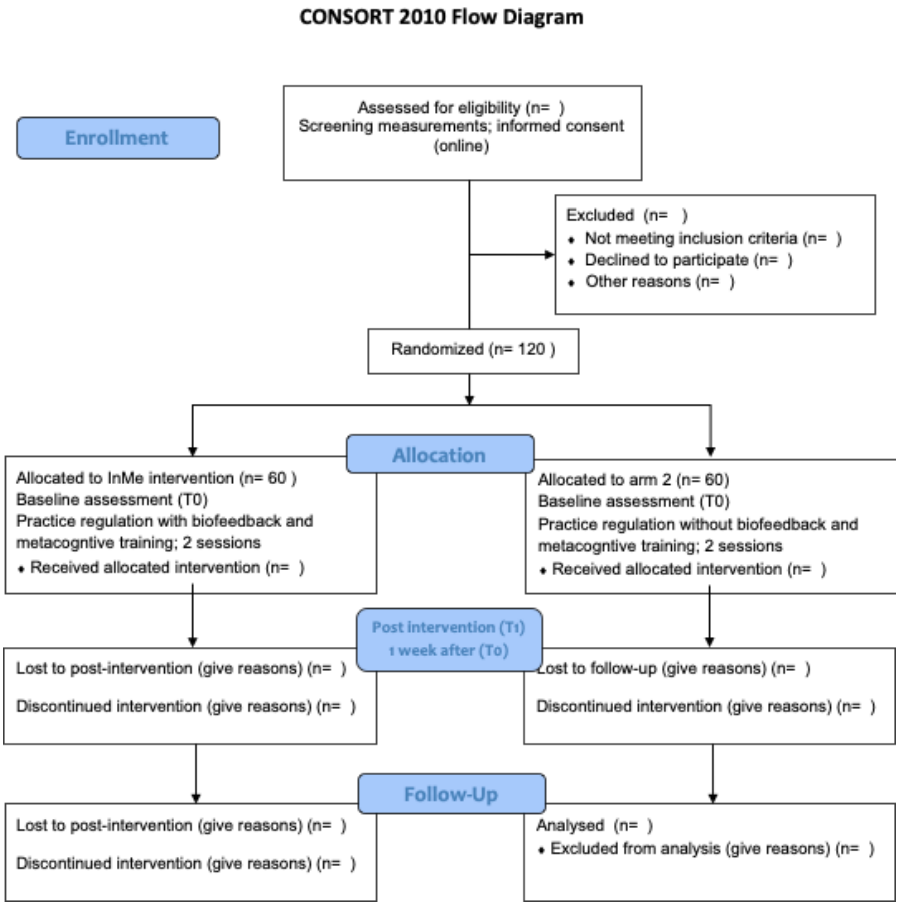

Figure 1: Consort 2010 Flow diagram

14. Data collection

Below we list all the outcomes relevant to this study. Table 2 summarises their schedule of assessment. Specifically, primary, secondary and feasibility outcomes will be assessed either at:

1. T0- Baseline (up to 5 days before first visit/intervention)
2. T1a – At the end of the day of first visit/intervention
3. T1b- At the end of the day of second visit/intervention; scheduled 5-9 days following the first visit.
4. T2- Follow up (7-9 weeks after T0).

14.1 Assessment process

This trial includes several assessment phases. In a Baseline Assessment (T0), participants will fill out a battery of self-report measures on interoception sensibility, mental-health symptoms including depression and anxiety, mood, trait self-efficacy, core dimensions of OCD and tolerance of uncertainty. Baseline assessment will be conducted online, up to 5 days before first visit/intervention before the first intervention (T1a). When participants will come to the first session in the lab, they will also undergo standardized interoception task to assess baseline interoceptive abilities, the heart rate discrimination task (HRD) (with HRV at rest measurement). The task will also include perceptual baseline and global beliefs on self-efficacy and metacognitive measures (see section 15.2). In both visits to the lab, participants will undergo the intervention procedure (see 14.2). After both interventions (T1b second visit), all participants will take part in a post-intervention assessment with all the outcome measures of T0 (see Table 3) with additional measures on feasibility. Finally, in a follow-up assessment (T2), participants will be repeated with all T0 and T1 measures.

Table 2: *Assessment procedures at baseline (T0), post intervention (T1) and 3 months follow-up (T2).*

Visit	Assessment	Carried out by	What the assessment is for	How is the assessment carried out	At what stage is the assessment carried out
1	Baseline (T0)	Researcher	Baseline measures	Self-report either in 1st visit or online	Before training starts, after informed consent is provided
	Intervention (T1a)	Researcher	Intervention measures	In session	intervention
2	Intervention (T1b)	Researcher	Intervention and post intervention measures	In session	Intervention and post intervention

3	2 months follow-up (T2)	Independent Researcher	Follow-up	Self-report either in session or online, all tasks in session	Completion of follow-up testing no more than 7days before the expected due date of follow-up (7-9 weeks from T0) and no more than 10 days after the expected date of follow-up.

Table 3: Task and questionnaire time points from baseline (T0), post intervention (T1) and 3 months follow-up (T2).

			Visit			
			1		2	3
Data	Measures	Screening	Baseline (T0)	Post Intervention (T1a).	(T1b)	Follow-up (T2)
Demographics	e.g., gender, age, socioeconomic status (education + income), ethnicity and BMI	+	+			
BAQ	Interoception awareness	+				
EDE-Q	Eating disorders	+				
PHQ-15	Somatic symptom disorder	+				
MAIA	Interoception		+		+	+
EDI-3	Subcategories: Eating concern composite; Interpersonal problems composite;		+		+	+

	affective problems composite.					
BSI-53	Psychopathology including somatization		+		+	+
GSE	Self-efficacy		+			+
IUS	Intolerance of Uncertainty scale		+			+
OC-CDQ	Compulsivity motivation; harm avoidance and incompleteness		+			+
STAI_S short+PANAS	Mood			+	+	+
DERS	Difficulties in emotion regulation		+		+	+
HRV			+		+	+
HDT	Global self-efficacy beliefs; interoception accuracy; Interoceptive global Metacognitive sensitivity		+		+	+
Interoceptive self-efficacy belief updating	Belief updating about one's self-efficacy in interoceptive control			+	+	+
TAS-20	difficulty identifying feelings, difficulty describing feelings,		+			+

	and externally oriented thinking					
Menstrual cycles (To be used for another study)			+		+	+

14.2 Main intervention procedure

Participants in both arms will take part in two intervention sessions (see table 3 – in the 1st visit and in the 2ed visit). Each intervention session comprises two blocks:

14.2.1 Training including psychoeducation and familiarisation

Participants will be given brief psychoeducation and task instructions and be told that they will be shown how their heart rate may fluctuate at different points in time and how heart rate changes when one breathes in and out. Participants in arm 1 will be invited to practice the breathing exercises following the Polar app (https://www.polar.com/en/smart-coaching/serene) default practice. Participants in arm 2, will follow guided imagery (see SOP_InMe/SOP_control). In both arms, the psychoeducational component (see SOP) which will teach participants about the importance and role of the autonomic nervous system (in general terms) and explain that heart rate tends to increase when one is stressed and decrease when one is relaxed. Psychoeducation will also stress that one can train oneself to better control one's heart rate, with beneficial effects on one's mood and health. Participants will also be able to ask questions prior to moving on to the main part of the intervention. Throughout the session, heart rate will be recorded using the Polar Ignite 2 watch application. Participants in arm 2 will wear the Polar watch but will not be able to see its screen.

14.2.2 Stressors + interoception self-efficacy beliefs

During the main part of the intervention, we will use the Trier Social Stress Test, which consists of a mock job interview for a high-status managerial position or prestigious university society (order counter-balanced between participants), followed by a verbal mental math task (see details in SOP). All stressors are aimed to enhance heartbeat, and to allow participants to practice their ability to use their breathing (InMe) or imagery (Control) to downregulate their

heartbeat. During the pre- and post-stressor blocks, each participant will be asked to rate their pre-/post- interoception self-efficacy beliefs in their abilities to downregulate their heart rate (see SOP for exact questions).

15. Primary & Secondary Outcome Measures

15.1 Primary Outcome measure

We aim to use a recent identified factor assessing the adaptive relationship with body sensations (i.e., "Adaptive interoception" Desmedt et al., 2022). This factor includes 25 items from the Multidimensional Assessment of Interoceptive Awareness (MAIA) (Mehling et al. 2012) that have been found to capture the capacity to notice bodily signals, to regulate, listen and trust these sensations.

*For other facets and measures of interoception see secondary measures section 15.2.

15.2 Secondary Outcome measures including mechanism of change

15.2.1 Measures of Interoception

1. Interoceptive self-efficacy beliefs updating (as compared to the first prior at T0 and quantified using different computational methods (see https://osf.io/x4ysv). This measure will be tested as a primary mechanism of change.
2. Interoception accuracy (as measured by the HRD) at T1b and T2 (and compared to T0)
3. Interoceptive global Metacognitive sensitivity (as measured by the HRD) at T1b and T2 (and compared to T0).
4. Interoception sensibility measured using the total score of “Multidimensional Assessment of Interoceptive Awareness” (MAIA) and its specific self-regulatory subscale at T0, T1b and T2.

15.2.2 Measures of Mental-health related symptoms

1. Disordered eating symptoms (Sum score calculated based on the EDI-3 subscales (*drive for thinness*, *bulimia* and *body dissatisfaction*) at T1b and T2 (and compared to T0)

2. General Score Index on the BSI-53 at T1b and T2 and its specific subscales on Somatization symptoms, anxiety and Depression (and compared to T0)

3. Affective and Interpersonal problems related to eating disorder (as measured by the score on interoceptive deficits scale (EDI-3) at T1b and T2 (and compared to T0).

4. Difficulties in emotion regulation (DERS) at T1b and T2 (and compared to T0).

15.2.3 Measures of Potential Moderators

1. Core dimensions of OCD (harm avoidance and incompleteness as measured by the OC-CDQ) at T0

2. Intolerance for Uncertainty (IUS) at T0

3. Measures of cardiac physiology (as measured by heart rate variability HRV) at T1band T2 (and compared to T0).

4. See section 17.0 (Planned data analysis) for further possible moderators, that will be tested following correlation analyses.

16. Sample size & Power calculations

The sample size was calculated based on a previous RCT that used the MAIA subscales as outcomes Paolucci et al., 2016). In the Paolucci study, the effectiveness of interoceptive intervention showed an effect size of 0.45 (T0 Mean = 2.56; s.d=1.56 T1 Mean=3.4; s.d=1.2) in the MAIA subscales of interest (i.e. noticing, attention regulation, emotional awareness, self-regulation, body listening and trusting comprising the "Adaptive interoception" (Desmedt et al., 2022). A minimal sample size of 53 participants in the InMe arm was found to detect the above effect size using a two-sided dependent t-test with a threshold of significance set at 5%, power set at 90% and a 1:1 allocation ratio. Recruitment will be increased to 120 to allow for ~ 10% drop out.

17. Planned data analysis

Analyses will be conducted following the intention-to-treat principle by a data analyst (blind to treatment allocation) with oversight from a senior statistician (blind to treatment allocation).

All analyses relating to the objectives stated in this protocol will be prespecified in a statistical analysis plan (SAP), which will be finalised and approved by an external trial statistician before data collection is completed.

The data set not containing group allocations for blinded analyses will be provided to the data analyst only after the final SAP has been signed off by the chief investigator, senior statistician and an independent to the trial statistician. All analyses will be conducted using R. Note that before finalisation of the SAP, we will use mock randomisation to verify the plan.
Means/standards deviations and frequencies with percentages will be used to describe the baseline characteristics of the sample and the post-randomisation outcome measures at each time point by group. Initial analysis of the expected heartrate increase/decrease following the intervention will be conducted to ensure that aberrant responses in this respect are taken into account in our final analyses. In addition, Participants who did not respond to the stressor/intervention (I.e., insufficient increase/decrease (2.5sd change below/above the average or change of at least 5 heart beats) of their heart rate during the stressor or following the intervention), will be removed from the analysis and documented.

Intervention effects, as adjusted means between InMe and Control group at each time point, will be estimated using linear mixed-effects models with random effects accounting for repeated observations. Covariates will include baseline level of outcome, age, BMI and gender. Other sociodemographic covariates such as ethnicity, as well as prior experience/practice with biofeedback or other mindfulness techniques will be explored in a post-hoc analysis. Unstandardized and standardised effects estimates will be presented with 95% CIs.
Sensitivity analysis will be conducted for the primary outcome to assess the impact of missing data, using a multiple imputation approach, to deal with missing data due to loss to follow up. In this approach, models are run under a range of plausible scenarios with missing data imputed.

For mediation analysis, the mechanisms of action of the intervention will be examined for the primary outcome and key secondary outcomes (e.g., mental health symptoms see section 15.2.2), using mediator analysis in a structural equation modelling framework using the intention-to-treat sample. Specifically, the mediatory role of interception self-efficacy beliefs

(see 15.2.1), will be assessed to explain any treatment effects at T1 and T2 on the primary outcome and key secondary outcomes (e.g., mental health symptoms see section 15.2.2).
Analyses will estimate the total effect, indirect effect and proportion of the treatment effect on the outcomes that occurs via this putative mediator variable. These effects will be presented with 95%CIs only, as not powered to detect.

For moderation analysis, we will consider the following variables as possible treatment modifiers of our primary and key secondary outcomes: core dimensions of compulsivity, intolerance of uncertainty at baseline.

Following correlation analyses, we will also conduct exploratory moderation analyses with these variables: HRV at baseline, emotion regulation at baseline, general self-efficacy at baseline, perceptual self-efficacy beliefs updating (from HDT) and gender. Analysis for each putative moderator will include the main effect and intervention group by moderator interaction term in the mixed-effects model used to estimate the treatment effect for the primary/secondary outcome, based on the intention-to-treat sample. These effects will be presented with 95%CIs only, as not powered to detect.

Note that analysis for the primary and secondary outcomes will include only those who completed the follow-up testing no more than 10 days before the expected due date of follow-up (7-9 weeks from T0) and no more than 10 days after the expected due date of follow-up.

18. Data handling: collection, entering, coding and checking process

Members of the research team will conduct the data collection. The data will be entered into a csv file as it is collected. Quantitative questionnaire data will be collected using Qualtrics. Notes will be logged on a csv/excel file as it collected.
Data will be monitored weekly, to make sure there are no missing/error values that are due to a technical error, any event will be logged. All members of the research team that are involved in the collection and management of data will be given the necessary training on how to use and administer the clinical measures used in this study. Any statistical analysis that will be

carried out before the end of the trial will be blinded to the study groups. Senior member of the research team will supervise the collecting and processing of the data weekly, allowing regular checks. The senior meet will also meet weekly to discuss pending issues and ensuring that the study runs smoothly. Training will involve weekly meetings with the team who is already experienced in doing the intervention and observing the experienced member of the team. This will be repeated until the new member is confident in their ability to run their part in the intervention/use one of the measures. The senior team will supervise and monitor the training.

The research team will meet weekly to monitor the trial conduct and recruitment. In case recruitment rate is low (less than 10% people eligible in a week) the team will discuss the possibility of reducing the inclusion criteria based on the BAQ (see section 9.2.1). Frequent contact via Teams and email will ensure the trial runs smoothly in line with the protocol. The core team includes the principal investigator, project lead, PhD students and research assistants. An external trial statistician will cross-check the SAP. Any issues with raised by the research team who is running the study will be dealt in case-by-case matter. In case of adverse events reported by the research team, participants or identified by the senior team, the senior team will respond according to the risk procedures protocols.

18.1 Missing data policy

Attrition rate, i.e., withdrawal from T1/T2 will be reported overall and by intervention group. Missing values of participants for each variable either due to withdrawal or exclusion and reasons for withdrawal/exclusion will be summarized for each treatment group at each time point. Sensitivity analysis will be conducted for the primary outcome to assess the impact of missing data, using a multiple imputation approach, to deal with missing data due to loss to follow up.

18.2 Data security

Participant names will not be used at any point during the collection of research data. With regards to data collection, participants will be identified using a unique numerical code. The quantitative data collected using computers (i.e. assessment data collected using Qualtrics)

will be downloaded from the secure online Qualtrics database as soon as it is complete. All of the data collected on computers will be anonymous and non-identifiable, and protected by a password (i.e. a password will be required to download the Qualtrics data, and a password will be required to access the data collected from computerised tasks). Only members of the research team will know the passwords and will therefore be able to access the electronic data. The password-protected computers that data will be stored on will be situated in the Department of Clinical and Health Psychology at UCL.

18.3 Data sharing

Anonymised data may be shared outside of the research team for research purposes only. Only anonymised data will be shared. This will be made explicit to participants on the study consent form. The participants' personal details will not be shared with anyone outside of the research team.

19. Ethical considerations

The study has been approved by the departmental UCL ethics (CEHP/2019/577, Title: Body to Mind Awareness, Exp:30.09.2024, PI: Aikaterini Fotopoulou.

20. Confidentiality

All of the data collected within the research study will be kept confidential and personal information will not be released outside of the research team. Participants will be identified during data collection using a unique participant identification code (ID code). A separate document will be kept that links participants identifiable information to their ID code – this document will be kept securely in an electronic format, in line with the data storage and security policies set out in this protocol.

21. Risk procedures and Potential for distress

21.1 Risk to participants

Risk to participants is expected to be low. InMe is a non-invasive intervention based on a CBT and biofeedback approach. Participants are healthy volunteers. In a feasibility audit work prior to this trial, none of the participants raised concerns about the content of the treatment being too distressing.

In addition, while we did not identify any risk with the above protocol as all experimental tasks and intervention are not accepted to trigger any major, or lasting stress or somatic reaction and do not involve any deception, we do want to emphasise two ethical considerations that might be raised:

21.1.1 RCT design

It should be noted that due to the nature of RCT design not all participants will be receiving the same feedback procedures. However, all participants will be receiving the same breathing training and we may see improvements in both groups. The aim of the study is to test the mechanism of action of these improvements. Moreover, given that this study is focusing on healthy individuals and is not offering treatment for a clinical condition no further ethical issues should arise from this randomisation, but if any of the 'control' arm participants wishes to try out the task of the other arm, they would be invited in the lab for this purpose. This possibility will be made known to them on the information sheet.

21.1.2 Questionnaires (sensitive content)

Although our study does not involve sensitive content such as questions on trauma, we take into consideration that answering questions about mental status and related traits and behaviours and can cause some people mild concern or discomfort. For example, reflecting on their experiences in a formal context may draw their attention to things that were not previously of concern. We will take several precautions to ensure that participants do not experience undue concern or distress, including specific explanations in the Information sheet

and the offer to discuss with the more senior members of research team, two of which are qualified counselling psychologists with extensive experience working with people experiencing mental health difficulties. If information is shared that presents risk to the participant or someone else, if needed, students will be given information on UCL counselling services and further resources will be given to all participants including 24-hr mental health services such as SANE and the Samaritans and website links to Beat eating disorders and Seed eating disorder support service. In emergency situations, the emergency services will be contacted.

21.2 Adverse events

All adverse events will be documented and will be reported first to the senior team and if needed to the departmental ethical committee. In the case participants will experience a distress, they will be offered the opportunity to take a break. Participants will be reminded of their right to withdraw, and where there is evidence of significant distress, participants will be explicitly offered the opportunity to withdraw from a specific aspect of the study (i.e. not complete a particular assessment), or withdraw from the study as a whole. In the rare case that a participant will experience difficulties in breathing or panic attack due to the stressors, the experimenter will follow a risk procedure (see SOP) to help the participant to downregulate their stress reaction.

21.3 Risk to research staff

There are not believed to be any likely risks to members of the research team in conducting this study. Risk procedures will be put in place in the event of any adverse events. The study will be restricted to office hours. Furthermore, the 24-hour security staff based at the University can be contacted.

22. Projected outputs and Dissemination

Findings will be published in high-impact peer-reviewed journals and will be presented at different international conferences. In addition, we will ensure to disseminate our findings to

a wider audience of patients, organisations, professionals and clinicians through different social media platforms.

23. Patient and Public Involvement (PPI)

23.1 Past PPI

Our involvement plan is to ensure that the InMe study protocol including, methods, design and study information are a coproduct and sensitive to service users' needs and priorities.

For this aim we established a Lived Experience Advisory Panel (LEAP) and a Clinical-Academic Trial Steering Committee (CATS). Members were recruited based on their 'experiential knowledge' (i.e. relevant experience of living with eating disorders or somatisation, clinical or academic direct experience or service). Members recruited using advertisement (Flyer sent to relevant groups and Twitter) as well as through personal/professional contacts and word-of-mouth.

The members of the two committees were consulted on the design and feasibility of the trial. Specifically, both LEAP and CATS members attended two PPIs events that were 1.5 hours long (with some participants joining only to one event). In the first PPI the research team consulted with the members before conducting an audit in Edinburgh, on the design and feasibility of the audit. Feedback from this audit was used for the initial develop of the current protocol, and for our ethics application. In the second PPI event the research team presented preliminary results from the audit, and the suggested InMe protocol (e.g., hypotheses, trial design, trial materials including information sheet). After discussion, the protocol and trial's procedures were adapted according to the feedback of the committees. Key examples of such changes include: (a) a risk procedure was developed after a committee member suggestion, in the event of a panic attack during the breathing training, facilitating the participant to downregulate their stress reaction. In addition, (b) after discussion, questions relating to participant's experiences with mindfulness practices and health tracking devices were also added to the study's battery of questionnaires. Lastly, (c) after a panel's member feedback it was agreed to add questions relating to the participant's view on the effectiveness of the breathing training and stressor exposure.

23.2 Future PPIs

According to our PPI timeline we are planning to organise a third PPI event in December 2022, by which our recruitment and participant assessment are expected to finish. In this future PPI we will give the opportunity to the committee members to comment on our progress and discuss next steps such as analysis. Additionally, in March 2023 we will carry a further PPI event giving the opportunity to PPI committee members in contributing and providing feedback to our analysis and dissemination of our study results.

24. Feasibility and acceptability outcomes

The main feasibility outcomes will include the feasibility of the recruitment process and the measurement tools, the acceptability of the intervention in the InMe and guided imagery group. Participants responses will be recorded and analysed using quantitative and qualitative questions. Specifically:

24.1. Feasibility of the recruitment process:

1. Percentage of people that were screened for the study from the total number of people that enrolled.
2. Percentage of people that reported to have subclinical symptoms of eating disorder or somatisation symptoms from the total number of people that were screened to the study (i.e., scoring less than the cut-off of the BAQ).
3. Percentage of people that did not agree to be randomised to the two arms
4. Percentage of people that withdrew following screening
5. Percentage of people that were willing to randomise.

24.2. Feasibility of the measurement tools

1. Time taken to fill in questionnaires
2. Missing data from questionnaires
3. Missing physiological data from the Polar watch
4. Retention rate from T1b to T1a and from T2 to T1
5. Missing data or floor performance in the HRD task

6. Adverse effects associated with the any of the studies measures

24.3. Feasibility of the stressors and intervention

1. Number of adverse events (including minor events such as individuals reporting on dizziness or headache while doing the breathing/guided imagery practice).
2. practicality of delivering the intervention (in terms of number of length of each session, resources, people and training required, mistakes made; a log will be kept)
3. Percentage of people who could not/would not practice the breathing/guided imagery correctly (Adherence to the breathing/guided imagery intervention as measured by the observational report of the experimenters and participants' self-report)
4. Percentage of people who refuse to take part in/withdraw from the stressor tasks
5. Percentage of people who did not show the expected up and down regulation of their HR by the stressor/breathing.
6. Percentage of people who did not trust the biofeedback (as measured by these two questions: How accurate did you find the watch feedback about your decreasing/increasing heart-rate? (only in the InMe group)
7. Two intervention feasibility questions (watch comfort and watch future use)

24.4. Acceptability of the intervention (including the stressor, breathing/guided imagery, and biofeedback components)

1. Reasons for not taking part in the study (from the screening phase; i.e., participants that were eligible but didn't what to take part).
2. Practice intervention and biofeedback use (i.e., retrospective self-report on the intervention/biofeedback at home in between the sessions and prospective reports on their practice).
3. Individuals' self-report on the acceptability of the stressor (i.e., "The stressor tasks were appropriate and proportional to the aims of the study").
4. Qualitative questions and three quantitative questions on acceptability of the intervention (to be asked at T1b and T1a).