Protocol for a study to investigate Emotions and MOods in a Trans-diagnostic cONtext: the EMOTiON cohort study

Authors: Kristel Klaus, Anna Bevan, Melissa Black, Darren Dunning, Monica Kullar, Jason Stretton, Camilla Nord, Caitlin Hitchcock, Marc Bennett, Chase Antonacci, Kirsty Griffiths, David Johnston, Tim Dalgleish

Abstract

Background: Although current psychiatric classification relies on a disorder-focused diagnostic approach, the limitations (e.g., heterogeneity within and comorbidity between diagnoses, as well as the overlap in symptoms and cognitive-behavioural and biological mechanisms across conditions) are increasingly acknowledged. Consequently, accumulating work is aimed at identifying meaningful symptom clusters, subtypes, and dimensions that may cut across traditional diagnostic boundaries. This study aims to: 1) Develop and validate a novel hybrid measure that provides mental health diagnoses, as well as trans-diagnostic symptom dimensions across mood, anxiety and stress-related conditions; 2) Clarify the structure of affective conditions by investigating the symptom dimensions, subtypes and clusters within and across the presenting conditions; 3) Investigate the underlying biopsychosocial mechanisms impacting on the affective difficulties; 4) Assess the change in affective symptom profiles and the association with underlying mechanisms over time.

Methods and analysis: Four hundred individuals with chronic and/or comorbid affective difficulties and 100 healthy controls (age range 18-70 years) will take part in the main study. The participants will complete a comprehensive set of behavioural and questionnaire measures investigating psychological, psychosocial, physical, cognitive, environmental and biological mechanisms underlying affective difficulties. A number of optional components (MRI scan, medical record linkage, participation in a genetics study, participation in a follow-up session) are also offered to the participants. The follow-up session takes place after approximately 1 year. The primary outcome from most analyses will be the symptom dimensions, subtypes and clusters, and the scores on these measures. However, associations between the various biopsychosocial mechanisms will also be investigated.

Ethics and dissemination: Ethical approval for the study has been obtained from the Cambridge Psychology Research Ethics Committee. Research findings will be disseminated through peer reviewed journals, scientific conference presentations and social media. All participant data will be non-identifiable.

Introduction

Accumulating evidence suggests that there exists marked phenotypical and biological overlap across conditions characterised by mood and emotional difficulties (1, 2), with the vast majority of individuals presenting with such difficulties diagnosable with multiple disorders (3). Additionally, there is tremendous heterogeneity within conditions, whereby two people with the same diagnosis may share few, if any, symptoms in common (4, 5). These difficulties with conventional diagnostic criteria have led researchers to develop novel approaches to mental health disorders by identifying meaningful and more cohesive symptom clusters, subtypes, and dimensions that may cut across traditional diagnostic boundaries (6, 7), therefore delineating the overlap and specificity of the symptoms across conditions (8).

Such novel approaches include, amongst others, quantitative dimensional models that locate individuals on hierarchically nested sets of continua (7), machine learning methods (e.g., support vector machines, neural-network algorithms) to stratify patients into distinct subgroups different to those enshrined in the diagnostic manuals on a data-driven basis, and network analyses that focus on associative and causal patterns of relationships between symptoms (4). In parallel, the Research Domain Criteria (RdoC) initiative (9) focuses on putative trans-diagnostic functional and biological processes that underpin these symptom-level classifications, cutting across multiple psychological domains (negative and positive valence systems, and social, cognitive and arousal systems) and at different units of analysis, from molecules to behaviour.

At the level of psychological processes, numerous trans-diagnostic constructs have been proposed, such as negative and positive affect (10), repetitive negative thinking (11), neuroticism (12, 13), and experiential avoidance (14, 15). More recently, a case has been made for emotion regulation (16) and emotional awareness as trans-diagnostic processes (17). Emotional awareness may be considered a prerequisite for the ability to differentiate between one's emotional states – also known as emotional granularity- which, we believe, deserves further attention as a putative trans-diagnostic process in its own right (18). It has been proposed that poor awareness of one's emotional states and insufficient emotional granularity may lead to generalising across emotional states (19), poorer emotion regulation strategies (18, 20) and over-generalised memory such as that often seen in depression (21). Further, it

should be noted that affective experiences do not only consist of emotions, which tend to be defined as targeted and short-lived affect states. Rather, much affective experience is formed of long-term, milder mood states, such as feeling calm or gloomy (22). Whereas moods and emotions interact dynamically (27), it is unclear to what extent individuals are able to notice, differentiate, and regulate longer-lasting mood states in comparison to emotions, and how individual differences in mood regulation relate to mental health symptoms. There is limited existing work on unpacking the differential contribution to affective states of emotions versus mood, despite the clear impact of the former in the context of mood disorders.

Although many trans-diagnostic psychological processes have been proposed, it is undeniable that individuals within diagnostic categories differ in their symptomatology, which has led some researchers to search for subtypes and the underlying mechanisms within and across mental health conditions. For example, specific depression symptom clusters have been associated with distinct biological markers, including brain regional activity (23), polygenic features, and physiological markers (24). Similarly, specific subtypes of anxiety (including state anxiety, panic, neuroticism/worry, and restlessness/agitation) have emerged in a sample of people with chronic or recurrent depression, suggesting that the different subtypes may benefit from different treatments (25).

To date, approaches exploring trans-diagnostic dimensional constructs and those investigating disorder subtypes have evolved rather separately. Further, much of the research into the various mechanisms - the psychological, biological and environmental underpinnings of mental health difficulties – has remained segregated. We believe there is urgent need to take a multidisciplinary approach by combining the above research strands in order to understand the factors underlying mental health difficulties, which will ultimately aid in developing more effective, person-centred treatment methods. There is a particularly pressing need to gain more insight into populations whose affective difficulties are of chronic/recurrent nature due to the reduced effectiveness of existing pharmacological (26, 27) and psychological (28) treatments in these populations, and the disproportionate burden on health services (29).

Aims of the study

1) Develop and validate a novel hybrid measure that provides mental health diagnoses, as well as trans-diagnostic symptom dimensions across mood, anxiety and stress-related conditions.

2) Clarify the structure of mental health conditions characterised by chronic and recurrent problems with anxiety, stress and low mood by investigating the symptom dimensions, subtypes and clusters within and across the presenting conditions.

3) Investigate the psychological, psychosocial, physical, cognitive, environmental and biological mechanisms that may impact on the affective symptom dimensions, subtypes and clusters.

4) Gain further insight into the mechanisms driving the affective difficulties by investigating the interactions and pathways between the psychological, psychosocial, physical, cognitive, environmental and biological factors.

5) Assess the change in affective symptom profiles over time and investigate how the underlying mechanisms impact on symptom change.

Methods and analysis

Study design

This is a single-centre longitudinal cohort study of people experiencing chronic, complex and/or comorbid difficulties with mood, anxiety and/or stress. All participants will be invited back for a follow-up session in approximately 1 years' time. The study is carried out at the Medical Research Council Cognition and Brain Sciences Unit (MRC CBU), University of Cambridge.

Eligibility criteria

We will recruit 400 participants who meet the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5; 30) criteria for a primary mood, anxiety- and/or stress-related disorder, where these problems have been chronic, recurrent and/or comorbid. Specifically, participants meeting diagnostic criteria for the following conditions, as measured using the Structured Clinical Interview for DSM-5 – Research Version (SCID-5-RV; 31) or clinical records, are deemed eligible: at least two Major Depressive Episodes (MDE) over their lifetime (therefore constituting recurrent depressive episodes), or one MDE if the individual meets criteria for Persistent Depressive Disorder. Participants are also eligible if they meet criteria for Bipolar I or Bipolar II Disorder (duration not specified), Post-Traumatic Stress Disorder (PTSD; duration 1+ month), Panic Disorder (duration 1+ month), Social Anxiety Disorder (6+ months), Agoraphobia (6+ months), Specific Phobia (6+ months), Generalised Anxiety Disorder (GAD; 6+ months) and/or obsessive-compulsive disorder (OCD; duration not specified). As we are interested in current or recent affective difficulties, we will be recruiting participants who have met (or have continued to meet) criteria for the above conditions within the past two years.

We will also recruit 100 healthy individuals, i.e., individuals who report never having experienced long-term affective difficulties and who do not meet diagnostic criteria for any past or current mental health disorder.

All participants will be aged 18-70, literate and fluent in English.

Exclusion criteria for both groups will be current psychosis, current alcohol or substance abuse, current intellectual disabilities, and organic brain damage.

Participant recruitment and selection

Participants will be recruited in three ways. First, we will recruit from the MRC CBU departmental databases. The Cognition, Emotion, and Mental Health Programme (CEMHP) database consists of approximately 600 volunteers with a history of affective difficulties who have agreed to participate in research into mental health. On joining the database, these

participants have completed the SCID-5-RV (31). Another MRC CBU database consists of 3000 members of the community who have joined the database for research purposes and who do not have a history of major mental health difficulties. Secondly, we will use clinical facilities to recruit patients who have consented to be contacted about participation in clinical research. Finally, recruitment will be conducted via advertisements to the local community and social media sites.

When recruiting from databases, an advert detailing the aims and procedure will be sent to potentially eligible participants. The advert will also be distributed in community and on social media sites. The interested individuals are directed to contact the research team. Those expressing interest in participating will complete an initial screening over email or telephone to clarify eligibility. Potentially eligible participants will be emailed the detailed participant information sheets (PIS) with all components of the study and they will be invited to take part.

Any participant who endorses clinical symptoms but has not carried out a prior SCID-5-RV (31) will be invited to join the CEMPH database and the diagnostic interview will be conducted prior to their participation in the EMOTiON study.

Sample size calculation

Many analyses in this study will include a new symptom measure (Trans-diagnostic Measure of Mental Health Symptoms; TraMMHS), and the sample size calculation was largely driven by the aim of validating this measure. Previous studies have suggested that strong factor loadings make the analysis less dependent upon the sample size (32). As a guide, the original validation of a similar measure (Inventory of Depression and Anxiety Symptoms; 33) found factor loadings ranging .23 -.93. Based on the recommendations of Hair and colleagues (34), at least 350 participants are needed to assess the practical significance of a standardized factor loading of .30. We have rounded this number to 400 for the clinical sample in the main study and for the subsequent TraMMHS validation study.

Measures

A summary of the measures used in the study is given in Table 1 and a more detailed overview is given below.

Mental health symptoms

We have developed a hybrid self-report and researcher-administered measure that provides conventional diagnoses of common mental health problems, as well as trans-diagnostic symptom profiles. The measure combines the SCID-5-RV (31), the Inventory of Depression and Anxiety Symptoms-II (IDAS-II; 6), Interview for the Mood and Anxiety Symptoms (35); and The Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS; 36). In compiling the questionnaire, we retained all items from the IDAS-II (6) to allow for the validation of the said measure. We retained the questions covering the DSM-5 (30) diagnostic criteria for mood, anxiety, and stress-related conditions as far as feasible to allow for determining the conventional diagnoses. Finally, the items selected for the measure were selected to cover the following domains: cognitive content, cognitive process, physical feelings, emotional feelings, and behaviour.

The resulting self-report measure (Transdiagnostic Measure of Mental Health Symptoms - Self-Report; TraMMHS-SR) comprises of 278 items that tap the following symptom clusters: depression (56 items), mania (26 items), PTSD (33 items), panic disorder (27 items), agoraphobia (35 items), social anxiety disorder (20 items), specific phobia (20 items), GAD (16 items), and OCD (35 items). Additionally, questions on well-being (10 items) are included. The questionnaire investigates the presence of these symptoms over the past month on a 5-point Likert scale ranging from 1 (Not at all) to 5 (Extremely). The output from the self-report measure generates the likely diagnoses.

TraMMHS-SR also contains a detailed questionnaire on socioeconomic status and demographics, including marital, household, and employment status. The questions are outlined in Table 1.

The second part of the TraMMHS is a researcher-administered interview (TraMMHS-RI), which includes questions on suicidal ideation/behaviour and self-harm, and additional

questions on each TraMMHS-SR module to confirm whether the criteria for DSM-5 (30) diagnoses are met, e.g., questions on the effects of the reported difficulties on everyday functioning.

The researcher-administered interview also includes a life structure interview (LSI) to determine the course of mental health symptoms by mapping the illness episodes across the participant's lifetime. The LSI includes questions on life stressors (e.g. overwork, death of a loved one, separation/divorce) or physical illnesses/injuries/other conditions (e.g. pregnancy/postpartum, heart disease etc.) that may have caused an episode of illness to occur. Finally, the TraMMHS-RI covers any past or current psychological and pharmacological treatments (see Table 1 for further information).

Presence of past difficulties and lifetime psychotic symptoms, alcohol use disorder, substance use disorder, and eating disorders will be assessed using SCID-5-RV (31). These measures will be supplemented by standard mental health questionnaires, outlined in Table 1.

Affective experience

We are further interested in differentiating between the effects of emotions and moods on mental health symptoms. We will be using the circumplex model of affect (37) as the framework for conceptualising affective experiences, whereby emotions and moods vary along the dimensions of valence (pleasant to unpleasant) and arousal (high arousal/energy to low arousal/energy). We define emotions as high-intensity, generally short-lived affective states that have specific, identifiable causes, and are directed at a particular object. Moods are construed as low-intensity, milder affective states that may last for hours or days, brought about gradually by accumulating antecedents (e.g. a model updated by a series of positive or negative experiences) (11). See Supplementary Materials for the specific emotion and mood terms and the methods for selecting appropriate terms.

The emotion terms will be harmonised across Positive and Negative Emotion Scale (PANES), Emotion Spatial Arrangement Method (Emotion SPaM), Emotion Valence and Arousal Ratings (Emotion VAR), Emotion Differentiation Task (EDT), and Emotion emBODY tasks. Mood terms will be harmonised across Mood SpAM, Mood emBODY, Mood VAR and Mood Checklist. Each of these measures is detailed below.

Emotion SpAM (38) is a measure of emotional granularity rooted in semantic networks. The participant is presented with 31 emotion terms, and they are instructed to rearrange the items on the screen, such that the inter-item distances reflect the perceived similarity between the words. The resulting data will provide configurations of all combinations of emotion terms which allow for investigating idiosyncratic semantic networks of emotion concepts.

Emotion VAR is another measure of emotional granularity, whereby the participant is asked to rate 31 emotion terms along the scales of valence (ranging from 1=Highly Unpleasant to 9=Highly Pleasant) and arousal (ranging from 1=Low Energy/Arousal to 9=High Energy/Arousal)**.**

EDT is an adapted version of the measure developed by Nook and colleagues (39) to quantify how specifically participants parse their own emotions. Participants view a set of positive and negative images on the computer screen, one at a time, drawn from the International Affective Picture System (40). Along with the images, one of five positive or negative emotion terms will be presented (in line with whether the image is positively or negatively valenced). Participants move a sliding bar along the scale to indicate how much they feel each emotion while looking at the image (0 = not ___ at all, 100 = very ____). Ratings are self-paced and quantified as a percentage of the scale.

In order to map emotion-dependent sensations in distinct bodily regions, we will be using the emBODY (41) tool. The task employs a topographical self-report method, whereby the participants are presented with two silhouettes of a human body and an emotion-related term between them on a computer screen. Participants are asked to inspect the emotion word and use a mouse to paint the bodily regions they typically feel becoming activated (on the left silhouette) or deactivated (on the right silhouette) when feeling this emotion. Painting is dynamic, thus successive strokes on a region increase the opacity of the paint.

The Levels of Emotional Awareness Scale (LEAS; 42) consists of 10 interpersonal scenarios, and the participants are asked to describe the feelings of self and of the other person for each scenario. Answers will be given verbally or via written response and the scoring is aimed at determining the degree of differentiation or specificity in the emotions described, and the range of emotions reported.

Questionnaires on emotional experience will include the PANES to explore the extent to which the participant has been feeling a set of 31 emotions on the current day using a 5-point Likert scale, and the Toronto Alexithymia Scale (43, 44) that measures the difficulties participants may have perceiving, differentiating, and expressing their own emotions.

The procedures involved in the mood tasks (Mood SpAM, Mood VAR, and Mood emBODY) will be identical to those of the equivalent emotion tasks, except that the emotion terms will be substituted with mood terms.

The Levels of Mood Awareness Scale (LMAS) is a novel mood awareness and granularity measure developed by our research group based on the established LEAS (42). It consists of 10 vignettes, with an even spread of 'positive' vs 'negative' scenarios, as well as social vs non-social vignettes of events that took place earlier in the month. Multiple events are described in order to elicit hypothetical background mood states, rather than individual emotional responses to singular events. After reading each vignette, the participant will be asked to verbally or via written response describe their moods over the past hypothetical month of each scenario.

The Mood Checklist will assess the extent to which the participants have experienced a set of 31 moods in the past month on a 5-point Likert scale. Trait Meta-Mood Scale (45) will be used to measure perceived affective intelligence, with the subscales quantifying attention to feelings, clarity of feelings and mood repair.

Affect regulation

Cognitive and behavioural emotion regulation measures are listed in Table 1.

As a novel measure, we have developed the Mood Regulation Questionnaire, which is a self-report measure to investigate mood regulation strategies. In the questionnaire, the participant is asked which strategies they use when in sad/gloomy mood, and secondly, when in anxious/tense mood. The strategies have been chosen based on previous literature (46-48) and broadly fall under the cognitive and behavioural strategies, and further into the

subcategories of diversion (disengagement and distraction), engagement and acceptance. The final item set and structure of the questionnaire will be determined after the measure has been validated.

Psychosocial function

Several of the tasks and questionnaires will focus on psychosocial function, including social status and rank. The Self-Structure Task (49) investigates how self-related information is organised across different self-aspects. In the task, the participants are presented with a set of cue words, i.e. adjectives, on a computer screen and are asked to what extent the word describes them in different social contexts, e.g. self at work, self at party. The Self-Structure task is followed by the MacArthur Scale of Subjective Social Status (50), which presents a "social ladder" and asks individuals to indicate the rung on which they feel they stand, therefore capturing the individual's perceived social status across different contexts. A number of questionnaires covering the topics of social rank, submissive behaviour, social support, loneliness, personality and mindful attention and awareness will also be administered (see Table 1).

Cognitive Function

Non-verbal intelligence will be measured using the Cattell Culture Fair (51), whereby the participant completes a series of timed, visually presented puzzles that require identifying patterns and relationships between novel stimuli. Verbal intelligence will be measured using the National Adult Reading Test (NART; 52), which requires the subject to read aloud a list of 50 irregular words. The accuracy of pronunciation is scored. Working memory will be assessed using the Backward Digit Span task in which participants are asked to recall visually presented numbers in a reverse order using a numeric keypad presented on a computer screen.

As a measure of autobiographical memory, we will use the Good Day-Bad Day task (GDBD), which is based on the paradigm by Dritschel and colleagues (1992). In the task, the participant is asked to recall specific positive and negative events from their past within a limited time. The participant is first instructed to provide one or two words to describe the

event, and is later asked to describe the event in more detail, providing a measure of autobiographical memory fluency, specificity and fading affect characteristics.

Treasure Hunter is a cognitive task that uses a threat conditioning paradigm. Participants navigate around a computer screen using the arrow keys. At the top of the screen is a treasure chest and gemstones of particular shapes. For each trial, participants will decide to approach or avoid the treasure chest. Avoiding omits the possibility of winning 'gold points'. Approaching the chest can be followed by either (1) the delivery of 'gold points' or (2) the explosion of a booby trap. In case of the latter, the avatar adventure makes an aversive ~70dB scream and losses 'health points'.

Stress and Trauma

Traumatic Experiences Checklist (54) will be administered in order to gain a broad overview of potentially traumatising events. The questionnaire asks about the (i) presence of the event; (ii) age at onset (iii) duration of the trauma, and (iv) subjective response on how traumatising this event was for the participant. Questions on daily hassles over the past month will be covered using The Survey of Recent Life Experiences – Short Form (55), and perceived stress over the past month will be measured using the Perceived Stress Scale-10 (56).

Physical Health

Chronic physical health condition assessment covers the presence of 29 chronic conditions, and is based on a subsection of the physical health questionnaire used in the Midlife Development in the United States (MIDUS) survey (57). The Graded Chronic Pain Scale (58) will be used as a self-assessment instrument to assess chronic pain severity, with the subscales measuring pain intensity and pain-related disability.

Additionally, participants will be asked standard questions on height, weight and smoking status, medication intake, menstrual cycle and contraceptive pill use.

Table 1. Measures used in the EMOTiON study.

Topic	Measurement instrument	Method
Demographics		
Basic demographic information	Age, gender, ethnicity	SR
Marital and household status	As in (31), covering marital status, no. and ages of children; no. of people in household	SR
Employment	As in (31), covering employment status (full- or part-time, keeping house or providing care full-time, retired, student/in training, unemployed, disabled); past occupations; reasons for leaving the previous job if current job held for less than 6 months; benefit status; gaps in employment or education history	SR
Socioeconomic status	Standard questions on educational attainment, annual income range, current occupation, postcode	SR
Mental health symptoms		
Presence and severity of current depression, BPD, PTSD, agoraphobia, panic disorder, social anxiety disorder, specific phobia, GAD, and OCD symptoms	Transdiagnostic Measure of Mental Health Symptoms	SR, INT
Presence of past depression, BPD, PTSD, agoraphobia, panic disorder, social anxiety disorder, specific phobia, GAD, OCD	SCID-5-RV (31)	INT, REC
Presence of lifetime psychotic symptoms, AUD, SUD, AN, BN, Binge ED	SCID-5-RV (31)	INT
Course of symptoms and contributing factors	Life structure interview	INT
Treatment history - psychological	Standard questions on type of treatment, frequency, duration, purpose, perceived usefulness	INT
Treatment history - pharmacological	Standard questions on name of medication, dosage/frequency, duration, purpose, perceived usefulness	INT
Depression severity	Patient Health Questionnaire (59)	SR

Anxiety severity	Generalised Anxiety Disorder Assessment (60)	SR
Impairment in functioning	Work and Social Adjustment Scale (61)	SR
Wellbeing	The Warwick-Edinburgh Mental Wellbeing Scale (36)	SR
Affective experience		
Emotional awareness	Levels of Emotional Awareness Scale (10a) (42)	VER/CT
Alexithymia	Toronto Alexithymia Scale (43, 44)	SR
Emotional granularity	Spatial arrangement method – emotion terms (38)	CT
Emotional granularity	Emotion Valence and Arousal Ratings	CT
Emotional granularity	Emotion Differentiation Task (39)	CT
Emotional state on the day	Positive and Negative Affect Scale	SR
Bodily representation of emotions	EmBODY – emotion terms (41)	CT
Mood awareness	Levels of Mood Awareness Scale	VER/CT
Mood granularity	Spatial arrangement method – mood terms (38)	CT
Mood granularity	Mood Valence and Aarousal Ratings	CT
Attention to, discrimination, and repair of mood states	Trait Meta-Mood Scale (45)	SR
Mood states over the past month	Mood checklist	SR
Bodily representation of moods	EmBODY - mood (41)	CT
Affect regulation		
Cognitive emotion regulation strategies	Cognitive Emotion Regulation Questionnaire (62)	SR
Behavioural emotion regulation strategies	Behavioural Emotion Regulation Questionnaire (63)	SR
Difficulties in emotional regulation	Difficulties in Emotional Regulation Scale-Short Form (64)	SR
Mood regulation strategies	Mood Regulation Questionnaire	SR
Psychosocial function		
Submissive behaviour	Submissive Behaviour Scale (65)	SR
Social rank	Social Comparison Scale (66)	SR
Social rank	Strive to Avoid Inferiority Scale 1 and 2 (67)	SR

Loneliness	de Jong Gierveld Loneliness Scale (68)	SR
Social support	ENRICHD Social Support Instrument (69)	SR
Self-structure	Self-Structure Task (49)	CT
Social status	MacArthur Scale of Subjective Social Status (50)	CT
Personality	Big Five Inventory (70)	
Mindful attention and awareness	Mindful Attention and Awareness Scale (71, 72)	SR
Cognitive function		
Non-verbal intelligence	Cattell Culture Fair (51)	PP, CT
Verbal intelligence	National Adult Reading Test (52)	VER
Autobiographical memory	Good Day-Bad Day task (53)	VER/ PP, CT
Working memory	Backward Digit Span	CT
Threat conditioning	Treasure Hunter	CT
Stress and trauma		
Lifetime traumatic events	Traumatic Experiences Checklist (54)	SR
Current perceived stress	Perceived Stress Scale-10 (56)	SR
Daily hassles	The Survey of Recent Life Experiences (55)	SR
Physical health		
Chronic health conditions	Physical health questionnaire (MIDUS) (57)	SR
Chronic pain	Graded Chronic Pain Scale (58)	SR
Smoking behaviour	Standard questions on smoking status (past/current/ex-smoker), frequency and preferred products	SR
Height	Standard questions	SR
Weight	Standard questions	SR
Current medication intake	Standard questions on type of medication, dosage, purpose	SR
Stage of menstrual cycle	Days since last period started (or whether post-menopausal)	SR
Use of contraceptive pill	Standard questions	SR

AN= Anorexia Nervosa; AUD= alcohol use disorder; Binge ED= Binge Eating Disorder; BPD=Bipolar Disorder; BN= Bulimia Nervosa; CT= computer task; GAD=Generalised Anxiety Disorder; INT= interview; MIDUS=Midlife Development in the United States survey; OCD= Obsessive-Compulsive Disorder; PP= pen and paper; PTSD=Post-Traumatic Stress Disorder; REC= either medical or departmental records; SCID-5-RV= Structured Clinical Interview for DSM-5 – Research Version (31); SR= self-report; SUD= substance use disorder; VER= verbal

Additional optional study components

A number of additional study components are offered to all eligible participants. It is made clear to the participants via the PIS and discussions with the researcher that the participants are free to take part in all, some, or none of the optional parts.

Magnetic Resonance Imaging (MRI) scan

The participants between the ages of 18 and 50 will be offered the option to participate in the magnetic resonance imaging (MRI) scan. Standard MRI exclusion criteria (for instance: pregnancy, irremovable ferromagnetic objects in/on the participant, and implanted medical devices) will be employed. The MRI protocol will involve: (1) a short screening questionnaire to determine suitability according to MRI safety criteria; (2) a series of MRI scans to assess the anatomy and physiology of the participants' brains. These scans are: T1 and T2-weighted anatomical scans (approximately 4.5 minutes each), a diffusion-weighted imaging scan (approximately 10 minutes, assessing white matter tracts), arterial spin labelling (approximately 4 minutes, measuring blood flow), resting-state functional MRI (assessing brain activation at rest), and magnetic resonance spectroscopy (assessing levels of the neurotransmitter GABA in the insula). The MRI session takes approximately 1 hour in total.

Data linkage

The participants will be asked whether they agree for the research team to access their records held at three national databases, such that these records could be combined with the data from the EMOTiON study. The databases include the Cambridgeshire and Peterborough NHS Foundation Trust (CPFT; mental health data), Hospital Episode Statistics database (hospital admissions, A and E attendances and outpatient appointments at NHS hospitals in England), and National Pupil Database (education records). Data processing activities are described on the PIS.

For the purposes of linking the data from different databases, the personal identifiers (e.g. first name, last name, NHS number, date of birth, sex, postcode), together with the participant's Research ID (a local pseudonymised ID) is sent to the respective institutions. These institutions match the identifiers and the Research ID with the records held at their databases, at which point the personal identifiers will be removed from the dataset, retaining only the Research ID. The records will then be combined with the research data from the EMOTiON study based on the Research ID only. The Personal Identifiable Information and Anonymised Research Data will be stored separately and treated according to the standard MRC CBU data management practice and according to the standards set by the respective institutions (CPFT, NHS Digital, the Department for Education and the Office for National Statistics). The protocols for linking the databases have been developed in collaboration with the above-mentioned institutions.

We intend to follow up these records over the next 20 years to obtain up-to-date information on the medical and mental health records. As all participants are over 18 years of age NPD records will only contain historic data.

Genetic Links to Anxiety and Depression (GLAD) study

Participants are invited to take part in the GLAD study, which investigates the role of genetics in the development and treatment of anxiety and depression, and is led by the National Institute of Health Research (NIHR) BioResource Centre Maudsley (part of the NIHR BioResource) and researchers at King's College London. GLAD is a separate research study, but we provide our participants with the GLAD study information sheet and ask them to notify our research group if they decide to take part in GLAD, or if they have done so already. We also ask for the participants' permission to gain access to any genetic data arising from the GLAD study.

Follow-up session

The participants can opt to take part in a follow-up assessment that will be carried out in approximately 1 years' time since the initial assessment. More information on the follow-up session is provided in the next section.

Procedure

After obtaining informed consent for the web-based study, the eligible participants will complete the TraMMHS-SR along with the demographics questionnaire at home, using the Qualtrics platform. This part of the study is estimated to take 30-40 minutes.

The online questionnaire is followed either by: 1) two research sessions at the MRC CBU; 2) remote sessions via online platforms and over the phone. If the participant prefers in-person testing sessions, then upon arrival, PIS will be discussed and written consent for the rest of the study will be elicited. The participant will then complete the TraMMHS-RI in order to determine whether diagnostic thresholds are met, and to collect further information on the participant's mental health history. Participants will then fill in additional mental health self-report symptom measures (e.g. PHQ-9 (59), GAD-7(60)) at their own pace using a computer. The subsequent order of tasks is counterbalanced across participants. All emotion measures are administered on one day, and all mood measures on another day in order to minimise participants switching between both types of affect in similar questionnaires in one session. Before commencing the emotion and mood measures, the difference between these affect states will be explained to the participant in the context of our study (See Supplementary Materials). The remaining questionnaires and tasks on affect regulation, psychosocial function, cognitive function, stress and trauma, and physical health are purposefully interspersed to avoid participant fatigue or boredom. Each of the two daily research sessions takes 2-3 hours depending on the participant's pace. At the end of the study, the participants will be reimbursed, debriefed and thanked for their time.

If the participant chooses the remote testing option, then the web-based TraMMHS-SR will be followed by the TraMMHS-RI and the NART over the phone. The rest of the measures will be administered using online platforms.

The consenting participants who are eligible for MRI scan will come in for a separate testing session.
For the follow-up session, participants will be contacted via email, letter, or phone call, using their provided contact details to schedule the sessions, and study specific PIS and consent forms will be provided. The follow-up session will include the same procedure as that set out in the original study, but measures that are likely to be sensitive to the effects of repeated testing (e.g. LEAS) will not be administered during the follow-up session. Questions regarding the lifetime presence of events/symptoms will be adjusted to cover only the period since the initial session.

Validation of the TraMMHS-SR

In order to validate the TraMMHS-SR, an additional 400 community participants aged 18-65 will be recruited via Prolific Academic or via departmental databases. All participants will have previously agreed to take part in research. A study-specific PIS and consent form will be administered. Using the Qualtrics platform, demographic information (age, ethnicity, educational attainment, occupation, annual income range, marital status), and current receival of treatment (psychological and pharmacological) for mental health will be obtained, followed by the TraMMHS-SR. PHQ-9 (59), GAD-7 (60), WSAS (61) and WEMWBS (36) will also be administered to determine convergent validity. Questions on suicidal ideation and self-harm will be asked only from the departmental database participants. See Ethics and Dissemination for further details.

After the above questionnaires, the participants are given the option to leave the survey or continue to the following optional tasks: LEAS, Emotion VAR, PANES, LMAS, Mood VAR, and Mood Checklist.

Study outcomes and data analysis plan

The data analysis plan follows from the main aims of the study. The primary outcome from Aim 1 is the hybrid self-report and interview measure of mental health symptoms. In order to clarify the structure of TraMMHS-SR as a trans-diagnostic measure, we will conduct a

principal factor analysis. In selecting the factors, we aim to: a) identify the maximum number of factors that are psychologically meaningful and b) focus on factors that are generalisable and robust across different samples (6, 33). Items with the clearest factor markers will be retained, which will maximise discriminant validity. Additional correlational analyses will help to minimise redundancy and retain item clusters that are maximally distinct and informative. Convergent validity will be tested by carrying out correlational analyses between the emerging symptom dimensions/clusters and conceptually similar disorder-specific measures, such as PHQ-9 (59) and GAD-7 (60). Criterion validity of the scales will be investigated by relating the scores from the scales to the DSM-5 (30) diagnostic thresholds as determined by SCID-5-RV (31). For the latter analyses, we will likely be using polychloric and logistic regression analyses. The TraMMHS-SR will further be validated in the community sample described above.

In line with Aim 2, to clarify the structure of the affective conditions, the wealth of information collected here will allow for using various methods, such as machine-learning methods, network analyses, structural equation modelling, and factor analyses, with the goal of determining meaningful overarching symptom dimensions, subtypes or clusters,.

In order to investigate the mechanisms impacting on affective symptom clusters and dimensions (Aim 3), we will conduct regression models with the psychological, psychosocial, physical, biological, cognitive, and environmental measures as predictors, and the mental health symptom scales inserted as variables of interest. The outcomes relating to this aim will therefore allow for investigating symptom severity in relation to underlying mechanisms.

Regression analyses, as well as pathway, mediator, and moderator analyses, and the approaches described above will be used in order to investigate the more complex interactions and pathways between the multitude of variables in line with Aim 4. The outcome variables may include scores on any of the symptom-related, psychological, psychosocial, cognitive function, stress or trauma-related measures, or outcomes from the MRI scans.

The longitudinal design of this study will allow for repeated measures analyses on variables of interest to investigate symptom change over time.

The healthy participants recruited in this study enable carrying out between-group comparisons, although these comparisons will likely stay at the level of descriptive statistics due to the modest sample size of the healthy population.

The analyses permitted by the optional parts of the research study remain to be determined, depending on the number of participants willing to take part in these aspects of the study.

Ethics and dissemination

Ethical approval for the study has been obtained from the Cambridge Psychology Research Ethics Committee (REC; PRE.2019.040). All participants recruited via clinical route are members of the Affective Disorders Research Database, which has received an approval from the NHS REC (15/EE/0305). Participants are fully informed of the purposes of this study via PIS and consent is obtained for each part separately (online, in-person testing sessions, optional parts, online TraMMHS validation study). For the data linkage projects and the genetics study, which involve exchanging information between institutions, the consent form gives granular options to consent to each step of the data processing activities. It is made clear via the PIS and consent forms that the participant has the right to refuse or withdraw consent to participate at any point without detriment and without having to give a reason.

As we will be recruiting participants with varying levels of mental health difficulties, any changes in mood that occur in-session are monitored and, if necessary, repaired. We will follow an adverse events protocol to ensure the wellbeing of the participants, with the following steps taken if necessary:

1. Provide a safe space
2. Offer a confidential consultation with a clinical psychologist
3. Ensure safe transport home and further follow up if necessary

For the online portions of the study, disclaimers are added, which advise the participants to contact their GP, local mental health services, or other support services if they have any concerns about their mental health, and to carefully consider their participation in the study.

If suicidal ideation with a plan or intent is identified, a Clinical Psychologist will complete a risk assessment and link the individual with mental health services to ensure immediate and ongoing support, in line with the MRC CBU Safeguarding Policy. MRI procedures follow the standard MRC CBU MRI Adverse Events Protocol.

All participant data will be de-identified and stored in accordance with the applicable security standards. After de-identification, the data will be made freely available to other researchers, subject to relevant data usage agreements. Research findings will be disseminated through peer reviewed journals, scientific conference presentations, and via social media.

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