Study of Trauma And Recovery

Efficacy and Mechanism Evaluation (EME) funded Add-On Study Protocol

How does the STAR therapy affect the mind and brain?

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VERSION CONTROL DOCUMENT

PROTOCOL: Therapeutic targets for the effective psychological treatment of trauma sequelae symptoms and psychosis in patients with comorbid Schizophrenia Spectrum Disorder and Post Traumatic Stress Disorder: Psychological and neural mechanisms.

VERSION No.	DATE	DATE APPROVED BY EME	DATE APPROVED BY DMEC/TSC	DATE APPROVED BY R&D	DATE APPROVED BY REC/HRA	DATE IMPLEMENTED	COMMENTS e.g. reason for change, stage of study, status (draft or track changes visible), date sent to co-Is or participating sites, acknowledgement of receipt, etc
1.00	5/10/2020		09/10/2020				Encoding memory task changed to be presented outside the scanner (following PPI feedback); text edited to reduce overlap with STAR protocol; procedural details and ethical considerations added for purposes of ethical review
1.01	3/11/2020						Track changes from original application visible
1.02	9/11/2020						Power calculations reinstated
1.03	20/11/2020	20/11/20		11/12/20	17/12/20	22/01/21	Track changes accepted and added to STAR trial protocol as Appendix
1.04	04.02.21	27/01/21 (by email)	25/01/21 (by email)	23/02/21	23/02/21	23/02/21	Clarification added in relation to temporary closure of scanning facilities due to Covid-19 – **No longer in effect**
1.05	15/03/21	24/03/21	16/03/21	22/04/21	27/04/21	27/04/21	Option added to consent to fMRI procedures only
1.06	28/06/21						Increased participant honorarium for fMRI due to procedures lasting longer than anticipated; added

							option of doing memory encoding task only, without scanning procedures
1.07	18/08/21	07/09/21	21/09/21	24/09/21	29/09/21	05/01/22	Additional scanning site (Newcastle University)
1.08	16/08/22	26/08/22	29/08/22	13/09/22	23/09/22	26/09/22	Memory task in scanner increased by 5 minutes at 9-months follow-up timepoint to include an everyday memories comparison condition; honorarium increased for participants completing follow-up at both timepoints
1.09	31/01/24	27/02/24	20/03/24				Retrospective explanation of the exclusion of the neutral faces condition in the fMRI social threat (emotional faces) task; change in Secondary Hypothesis E3

Title
Therapeutic targets for the effective psychological treatment of trauma sequelae symptoms and psychosis in patients with comorbid Schizophrenia Spectrum Disorder and Post Traumatic Stress Disorder: Psychological and neural mechanisms.

Short title
How does the STAR therapy affect the mind and brain?

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Abstract

Background: Research over the past two decades has shown a strong and consistent association between life trauma and psychosis, with strong evidence that the effect is causal. This finding raises important questions about the mechanisms linking trauma to psychotic symptoms, and has stimulated a number of ongoing clinical trials to determine whether trauma-focused psychological interventions can help psychotic patients. Identifying and measuring trauma-related mechanisms in these patients, and determining the extent to which their amelioration is necessary for effective treatment, is likely to lead to more effective interventions in the future. The STAR trial, in which 300 participants meeting the diagnostic criteria for both schizophrenia spectrum disorder (SSD) and post-traumatic stress disorder (PTSD) will be randomly assigned to Trauma-Focused Cognitive Behaviour Therapy for psychosis (TF-CBTp) in addition to Treatment As Usual (TAU) vs TAU alone, provides an ideal opportunity to do this.

Methods: We will use the Experience Sampling Method (ESM; in which participants use smartphone-based electronic diaries to record their experiences and psychological functioning at regular intervals in everyday life) and functional Magnetic Resonance Imaging (fMRI) to investigate trauma-related mechanisms, for example dysfunctional representation of traumatic memories and hypervigilance to social threat. 200 participants from the STAR trial will be recruited to ESM and 80 will be recruited to fMRI. Both ESM and fMRI will be measured prior to randomization to the STAR arms and 9 months later, corresponding with the end of therapy in the TF-CBTp group. Analyses will determine the relationship between symptoms and hypothesized psychological and neurocognitive mechanisms and whether improvement in symptoms in the treated group is associated with changes in these mechanisms.

Discussion: The proposed investigations have the potential to enhance the scientific value of the STAR trial by identifying those psychological and neurocognitive mechanisms that must change for psychological interventions to be effective in patients with psychosis who have a history of significant psychological trauma.

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Background and rationale

As detailed in the protocol for the STAR (**S**tudy of **Trau**ma **A**nd **R**ecovery) trial, a large volume of research over the past decade has shown that people with schizophrenia spectrum disorder (SSD) report high rates of adversity and trauma, particularly interpersonal victimisation (e.g. emotional, physical, and sexual abuse/assaults) both in childhood and adulthood, with the majority having experienced multiple traumas (75-98% of those reporting trauma [1, 2]. The prevalence rate of Post-Traumatic Stress Disorder (PTSD) in this population is approximately 15%, which is up to five times the general population rates [3]. PTSD is characterised by intrusive memories of the trauma, such as 'flashbacks', hyperarousal, and avoidance of trauma reminders, and post-traumatic symptoms in SSD patients are frequently intertwined with psychotic symptoms, such as delusions and hallucinations [4]. However, the mechanisms leading from trauma to psychosis, and those responsible for the high prevalence of PTSD in SSD patients, are not properly understood.

The STAR trial is a rater-blind, parallel arm RCT comparing an integrated therapy to address post-traumatic stress and psychosis symptoms in SSD patients - trauma-focused cognitive-behaviour therapy for psychosis (TF-CBTp) - in addition to treatment as usual (TAU) to TAU alone, across five sites. The recruitment of a large number of patients to this trial provides an opportunity to understand these mechanisms and, in particular, to understand which mechanisms are required to change in order to treat patients with comorbid psychosis and PTSD. We propose to use two methods to assess potential mechanisms in subsamples of the STAR participants prior to randomisation and as therapy is completed: the experience sampling method (ESM; a smartphone-administered electronic diary system that allows psychological process and symptoms to be monitored in daily life) and neuroimaging.

<u>Potential mechanisms linking PTSD and psychotic symptoms</u>

An influential cognitive model that attempts to integrate findings for PTSD research, proposed by Ehlers and Clark [5], argues that peritraumatic dissociation leads to the encoding of trauma memories that are fragmented, context-independent and easily cued. At the same time negative appraisals of the self ("I am inadequate") and others ("people cannot be trusted") lead to maladaptive coping behaviours (e.g., vigilance for threat, avoidance behaviour and ongoing dissociation) which, in combination, lead to persistent PTSD symptoms. This model has received substantial support from numerous studies, including longitudinal studies of individuals first examined immediately after experiencing trauma (e.g., [6]).

It seems likely that the same mechanisms – the intrusion of dysfunctionally encoded memories, dissociation, negative appraisals and hypervigilance - are responsible for the development of PTSD symptoms in patients with a diagnosis of SSD [7]. However, the evidence that traumatic experience plays a role in schizophrenia spectrum conditions in general (and not only those patients who also experience PTSD), together with the evidence that the onset of PTSD in dual diagnosis patients often precedes the onset of psychosis [8], raises the possibility that these mechanism contribute more directly to positive symptoms of psychosis, such as hallucinations and delusions [4].In fact, there is considerable evidence for this, especially in the case of dissociation and dysfunctional cognitions (for a recent review, see [9]).

For example, the applicants have shown that the hallucinations of psychotic patients often involve trauma-related themes [10], implying that their content can be influenced by intrusive imagery relating to past adverse experiences [4].

We have also shown that dissociative experiences mediate statistically between traumatic childhood experiences and hallucinatory experiences [11] (a finding that has been replicated elsewhere e.g. [12] and confirmed by meta-analysis [13]). Using ESM we have shown that, in the daily life of patients, episodes of hallucination are often preceded by dissociative experiences [14]. Freeman and colleagues [15] found that, in people who had experienced a physical assault, peritraumatic dissociation predicted hallucinatory experiences six months later. The same researchers showed that negative appraisals also predicted hallucinations at follow-up. In the same sample, negative appraisals also predicted future paranoid symptoms [16].

Aims and objectives

Our overall objective is to test whether TF-CBTp in the STAR trial affects the mechanisms outlined above. If effective, TF-CBTp should bring about changes in these mechanisms and these changes should predict therapeutic response. This additional scientific study is essential for the future development of psychological interventions for psychosis because:

(i) *If it is true* that the amelioration of one or more of these mechanisms is required for effective reduction of PTSD symptoms by TF-CBTp, it follows that therapists can be confident in the use of this intervention with SSD-PTSD patients, and that future developments and enhancements of this therapy should be targeted at the relevant mechanisms with the aim of maximizing this effect.

(ii) *If it is true* that these mechanisms form part of the causal pathway that leads to the occurrence of positive psychotic symptoms, then it follows that trauma-focused interventions are likely to be effective not only in reducing PTSD symptoms in patients who meet the dual diagnosis criteria for SSD and PTSD, but also for reducing psychotic symptoms in these patients and also the much wider group of schizophrenia spectrum patients who do not meet PTSD criteria but nonetheless have a trauma history.

Conversely:

(iii) *If it is **not** true* that the amelioration of mechanisms is required for effective amelioration of PTSD symptoms by TF-CBTp then, if TF-CBTp is effective, other mechanisms will have to be identified to account for its effectiveness in order for the treatment to be enhanced in future research.

(iv) *If it is **not** true* that these mechanisms form part of the causal pathway that leads to the activation of positive psychotic symptoms, then alternative mechanisms will have to be identified to explain the association between traumatic experiences and psychosis.

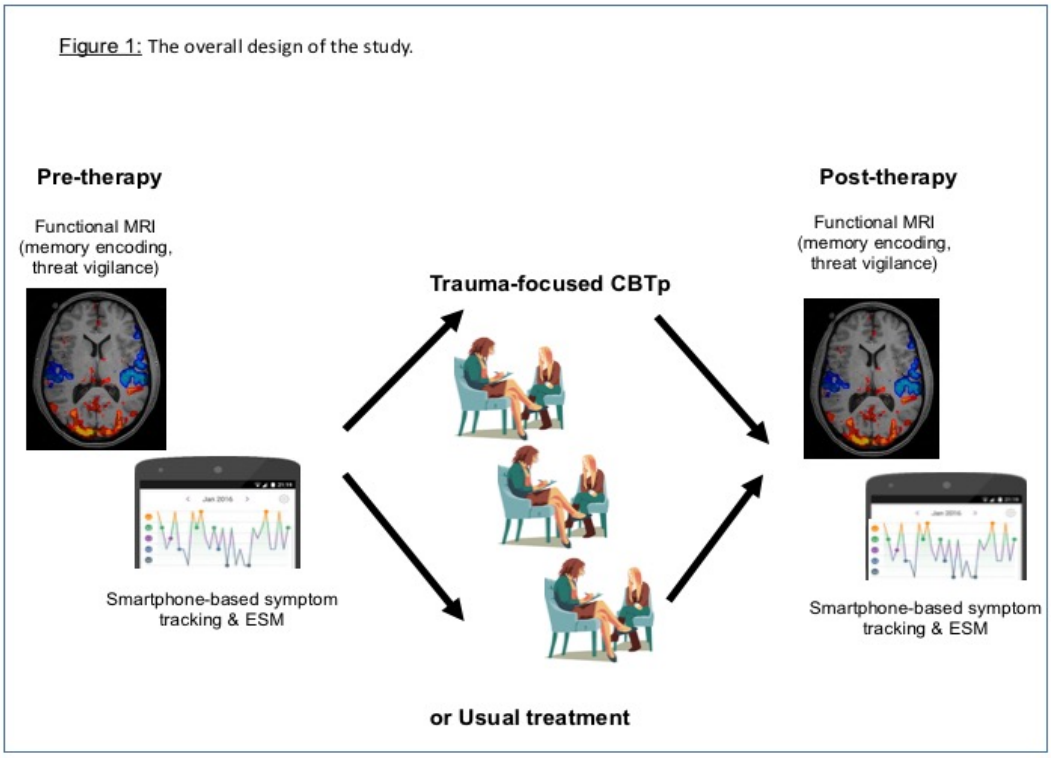
Research plan and methods: General approach

This study will be a longitudinal parallel-group design with psychological (experience sampling) and neuroimaging (fMRI) measures taken at two time points corresponding in the TF-CBTp group to pre-randomisation and end of treatment (see Figure 1).

The participants in the study will be patients meeting dual diagnosis criteria for SSD-PTSD, recruited to the STAR trial (NIHR HTA Reference: NIHR128623).

Assessments will be conducted prior to randomisation and at 9m follow-up which, in the treated group, will coincide with the end of treatment. Hence, the design will allow us to meet our objectives by testing hypotheses about changes in the psychological and neuropsychological processes that result from treatment, while at the same time examining the relationship between involuntary recall of traumatic events and the experience of positive symptoms of psychosis.

The experience sampling protocol we will use to assess changes in psychological processes will be administered to all participants who consent to this sub-study at all five trial sites (South London and Maudsley (SLaM); Greater Manchester Mental Health (GMMH); Cumbria, Northumberland, Tyne and Wear; Oxford Health; Sussex Partnership Foundation NHS Trusts). The neuroimaging assessments will be conducted at three of the collaborating centres, the University of Manchester, King's College London (KCL) and Newcastle University using compatible 3-T scanners that are calibrated across centres. For this element of the study, we will primarily aim to recruit participants from the three nearest trial sites (SLaM; GMMH, CNTW) but, if required in order to meet our recruitment targets, we will have the capacity to recruit participants who are willing to travel from other trial sites (our research costs have been calculated on the assumption that up to 1/3rd of neuroimaging participants will travel from other sites).



The experience sampling method (ESM) and its applicability to psychosis

An important limitation of traditional psychological measures is that they are laboratory-based and typically administered at a single time point. Hence they fail to assess psychological functions in the real life environment and are insensitive to how these functions are affected by contextual factors, such as specific activities the individual is engaged in, the presence of other people or stress. ESM overcomes these limitations by allowing brief psychological assessments to be administered multiple times in a day over several days and in different contexts. This is achieved by using beeps from an electronic device such as a phone app or electronic watch to prompt completion of assessments (usually in the form of a diary or very brief psychological test), which is usually designed to take < 2 minutes per assessment [17].

ESM questions can be of two kinds: those requiring the individual to report their immediate experiences and those asking them to report experiences since the previous beep. It is also possible to include other kinds of brief psychological assessments, such as making judgements about stimuli such as faces. ESM is highly tolerant of missing data [18]. The analysis method therefore does not require a valid assessment to be completed at each beep; typically participants are included in analyses if 20/60 valid reports are recorded over a six day assessment period. This threshold results in high compliance/inclusion rates, even with repeated time points e.g., pre and post-therapy [19]. Therefore, it is a practical and well-tolerated methodology.

Despite its apparent complexity, ESM has been widely used in mental health research, and has been employed in many studies with patients with psychosis over a period of more than two decades [20]. The present applicants have used it in previous studies with patients suffering from severe mental illness that have measured many of the variables of interest in our proposed study such as hallucinations, paranoid beliefs and dissociative experiences [14, 21] [22] [23] [24].

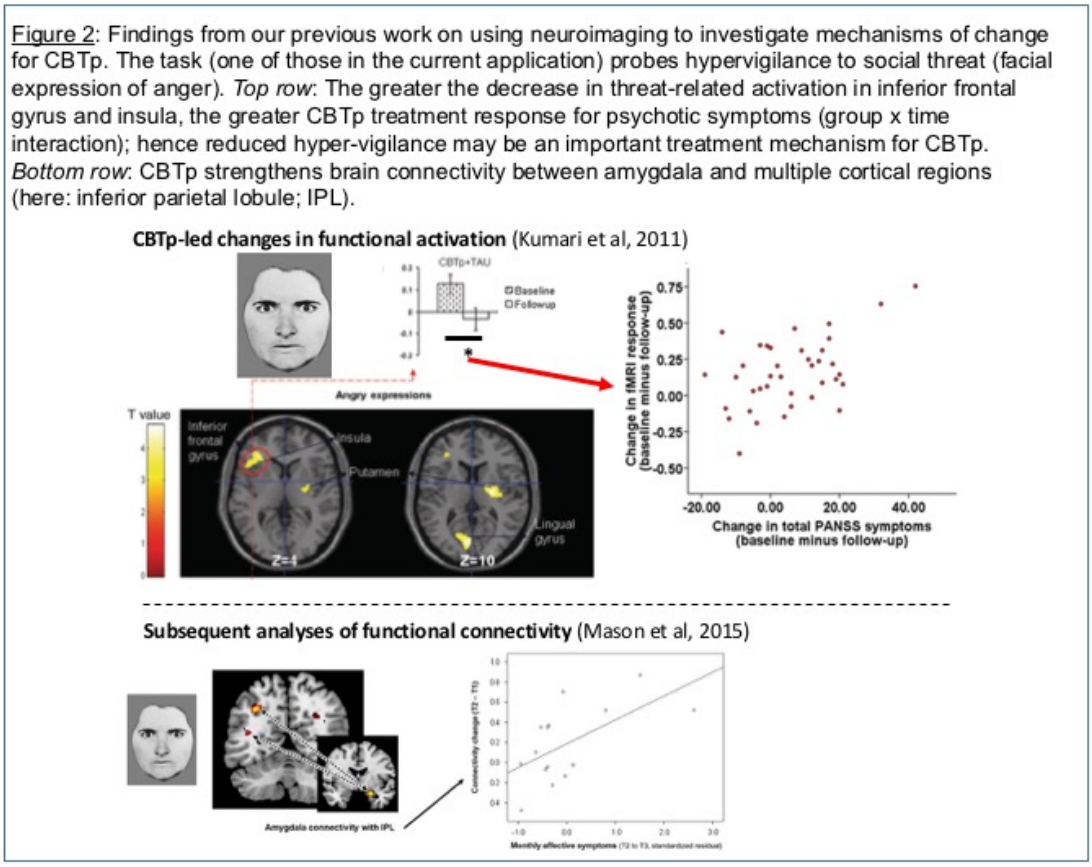
Neuroimaging and its potential for identifying treatment mechanisms

Recent research has harnessed functional neuroimaging to probe the mechanisms of psychological therapies [25, 26]. The field is expanding rapidly – across disorders, there are now over a hundred publications, with over half of these being published in the last three years. These studies have almost exclusively been conducted in mood and anxiety disorders, with only a handful in relation to PTSD [27-29] and even fewer in psychosis [30-32]. To date, our group is the only one to have employed these methods in patients with SSD receiving cognitive behaviour therapy tailored to psychosis (CBTp) (see Figure 2). These studies have demonstrated that functional neuroimaging can be used to better pinpoint mechanisms of therapeutic change [32-34] and can also be used to predict who will respond to treatment [35, 36].

Research on the neurobiology of PTSD points to ways of using neuroimaging to probe the mechanisms of action of TF-CBTp. According to psychological models of PTSD, traumatic memory intrusions occur because the memory is in a 'raw' and incompletely processed form, lacking temporal and contextual detail, which prevents the memory from being stored per typical memory episodes. Trauma-focused psychological therapies are posited to reprocess trauma memories to consolidate the memory in a more complete representation, by updating it with accurate information and meta-memory characteristics; for example, with chronological and contextual information [37].The neurobiology underlying this potential mechanism has only recently received attention. However, disrupted hippocampal memory encoding of the context surrounding traumatic events has been identified as a likely mechanism underlying PTSD [38, 39], a model that draws on evidence that the hippocampus acts as a point of convergence that binds together multi-modal information into a single coherent representation [39, 40].

Practical and ethical reasons make it impossible to examine the live encoding of a real-life traumatic event. Therefore, fMRI studies typically employ negative, emotionally arousing visual stimuli as trauma analogues (see [41]). When encoding trauma analogue items, there was elevated amygdala activity which boosted subsequent memory for these items [42, 43]. However, memory for the associations between trauma analogue items and neutral visual stimuli that were present during encoding was impaired, and the level of this impairment was predicted by the reduction in hippocampal activity during encoding [42]. Moreover, these studies have shown that a 'post-encoding period' shortly after encoding the trauma analogue items is a key marker for the formation of trauma memories, and that amygdala-hippocampal activity predicts subsequent

Figure 2: Findings from our previous work on using neuroimaging to investigate mechanisms of change for CBTp. The task (one of those in the current application) probes hypervigilance to social threat (facial expression of anger). *Top row*: The greater the decrease in threat-related activation in inferior frontal gyrus and insula, the greater CBTp treatment response for psychotic symptoms (group x time interaction); hence reduced hyper-vigilance may be an important treatment mechanism for CBTp. *Bottom row*: CBTp strengthens brain connectivity between amygdala and multiple cortical regions (here: inferior parietal lobule; IPL).



memory bias [43, 44] and level of intrusions experienced on subsequent days (Bisby et al, in preparation) relevant to our hypotheses linking the neuroimaging data to the ESM data.

Specific hypotheses

Based on previous findings, we have a series of hypotheses that we will test using both ESM and in fMRI in STAR trial participants who are willing to undertake the additional protocols, as listed in Table 1 overleaf.

Participants

Participants will be those recruited to the STAR trial and who consent to participate in these additional research procedures. There are no additional exclusion criteria, apart from clinical contra-indications to participating in the fMRI part of the study, which include having received any metal injuries to the eye, had metallic objects (including clips) inserted into the body at an operation, having received a shotgun injury, or having a heart pacemaker.

Sample size calculations

ESM: We will recruit 200 participants across five sites (a total of 40 per site), which corresponds to two-thirds of the full STAR trial sample (N=300). We predict that we will have a 25% attrition rate from the ESM study, which will provide a final sample of approximately n=75 per group completing both of the ESM measurements (i.e., pre- and post- therapy), assuming equal participation across groups. These targets and attrition rates are in line with previous studies using ESM to assess changes in CBTp [19].

For hypothesis E1, a total of 150 participants will be needed to provide 85% power for our therapy vs. control group comparisons. Due to the complexity of sample size estimation for three-level models (which require an unfeasibly large number of unknown parameters to input), the sample size calculation is based on a simple (two-level) multilevel model with random intercepts at the subject level and autocorrelated residuals with an autoregressive structure of the first order at the ESM-beep level. We assume following input parameters: 40 completed data points on average per participant (out of a possible 60), with a standard deviation of 2 for each group, an autocorrelation of 0.3, an intra-cluster correlation of 0.1 and a mean difference of 0.4 (on a 1-7 Likert scale measuring the construct) to be detected at the 0.05 level of significance.

Hypothesis E2, E3 and E4 will use the beep level measures to assess prediction of clinical outcomes (E2) and mediation between the beep level measures themselves. Assuming 40 data points per participant over the two time periods, gives approximately 14,000 unique data points (350 participants at both time points x 40 data points). Although these are not independent data points, the effective sample size will have over 95% power to detect standardised associations between beeps as small as 0.1, and close to 100% power for standardised associations above 0.3.

fMRI: We will recruit 80 participants from the STAR trial, to allow for 25% attrition and allow for a final sample of approximately n=30 per group completing both of the fMRI measurements (i.e., pre- and post- therapy), assuming equal participation across groups. These target and attrition rates are both in line with our previous longitudinal fMRI case-controlled study probing changes following conventional CBTp. Most of these patients will be recruited from the Greater Manchester Mental Health, Cumbria, Northumberland, Tyne and Wear, and South London and Maudsley NHS sites closest to the scanners, but we are assuming that up to a third will travel from other sites; hence we will need to recruit a minimum of 26 participants at each of the two close sites (43% of those potentially available).

At 80% power, we would be able to detect a small effect size of $d \geq 0.37$ in Hypotheses N1a and N1b (group x interaction in fMRI measurements). At 80% power, we could also detect a moderate-sized correlation ($r \geq .43$) between change in fMRI activation and 1) symptom improvement (Hypotheses N1 and N2) and 2) the experience sampling measures (Hypotheses NE1 and NE2).

We anticipate both effects to be larger, based on our past work. Whilst no studies have yet examined change in trauma memory representations following TF-CBTp (Hypothesis N1a), we have previously demonstrated the hypervigilance task used to test Hypothesis N1b is sensitive to

conventional CBTp-led changes in fMRI activation and that the effect size was large in the regions we had predictions for (d = 1.17) [31]. We will have 99.9% power to detect this sized effect with our projected sample size. In addition, we have previously shown that the correlation between CBTp-led changes in fMRI activation and improvement in psychotic symptoms was of large effect size [$r(22)=0.55$] [32]. We would have 90.3% power to detect this sized effect with our projected sample size, and could still detect this sized effect at 80% power even if the final sample size is significantly smaller (N=19).

Recruitment and consent process

The STAR protocol asks participants to consent to be approached about further add-on studies related to the trial. If that consent is given, and once the participant has agreed to take part in the STAR trial, fully informed consent will be sought for the current study. Participants will be able to consent to either or both the ESM and the MRI protocols, or they may refuse consent to both but remain in the STAR trial. Consent for the fMRI protocol will include participants' consent for a summary of their trauma memory assessment to be used to generate stimuli for the fMRI experiment, to avoid burden from repeating this assessment. For the fMRI study there will also be the option of consenting to participating in the memory encoding task only, which is done outside the scanner. All consent process and related materials (PIS and consent forms) will be approved by our service user reference group.

The procedures we will use will fully inform participants of their options with no pressure whatsoever to take part in these additional protocols, with the primary objective of maintaining the integrity of the STAR trial.

<u>Renumeration/compensation</u>

Remuneration for participants' time to complete 6 days of ESM will be £30 at each time point, with an extra £15 for participants who complete both timepoints (i.e., £75 in total). It will be £60 for fMRI procedures at each time point, with an extra £30 for participants who complete both timepoints (£150 in total). Participants choosing to complete the memory encoding task only, without the scanning component, will be remunerated £15 at each time point (£30 in total).

Table 1: Primary hypotheses. Testing these will allow us to achieve our primary objective of determining whether changes in specific psychological mechanisms are required for the efficacy of TF-CBTp.

Hypothesis	**Level and prediction** (E=ESM hypotheses; N=neuroimaging hypotheses)	**Justification**
TF-CBTp will lead to reductions in intrusive trauma memories and related psychopathology	**At symptom level (E1):** The treatment group, compared to the controls, will experience greater reductions in intrusive trauma memories, negative appraisals, avoidance, dissociation and vigilance for threat.	Past research on PTSD shows that these processes play a causal role in PTSD symptomatology and that effective psychological interventions ameliorate these processes, but this has not yet been shown in patients with psychosis. We therefore hypothesize that TF-CBTp must change these mechanisms to be effective.
	At neural level (N1a): The treatment group will show reduced dysfunctional representation of trauma memories as measured by neuroimaging	Dysfunctional representation of trauma memory (increased amygdala and insular activity but reduced hippocampal activity) is the neural mechanism underlying the maladaptive storage of intrusive trauma memories. Hence, if the treatment leads to less dysfunctional memory representations, we should see enhanced hippocampal activity and reduced amygdala and insular activity when retrieving trauma memories.
	At neural level (N1b): The treatment group will show reduced hypervigilance for potential sources of social threat, again measured by neuroimaging	Hypervigilance for threat is a symptom of PTSD. A neural correlate is amygdala response to social threat stimuli. Hence, we will test whether there is a reduction in this amygdala response that is specific to those receiving treatment.
The above reductions in intrusive trauma memories and related psychopathology will correlate with the level of symptom improvement that patients experience following TF-CBTp	**At symptom level (E2):** Changes (between time 1 and time 2) in the experience sampling measures of trauma memory, negative appraisals, avoidance, dissociation and hypervigilance will predict reductions in PTSD symptoms	If these mechanisms are responsible for PTSD symptoms, and if the treatment changes them, then the extent of change should predict the extent to which patients' PTSD symptoms improve.
	At neural level (N2): Changes (between time 1 and time 2) in neuroimaging measures of memory representations and hypervigilance should predict reductions in PTSD symptoms	If these mechanisms are responsible for PTSD symptoms, changes in the neural correlates of these processes should also predict the extent to which patients' PTSD symptoms improve.

Secondary hypotheses. Testing these will meet our broader objective of determining whether trauma-related psychological mechanisms play a causal role in the occurrence of psychotic symptoms

Hypothesis	**Level and prediction** (NE=hypotheses relating to relationships between neuroimaging and ESM)	**Justification**
Measures at the neural level will predict symptom level measures	**Between neural and symptom level (NE1):** At each time point, neural responses measured by fMRI during encoding and recall of trauma memories will predict the frequency and distress of trauma memories in daily life, measured during experience sampling	We have hypothesized specific neural mechanisms associated with intrusive trauma memories (see N1a above). These mechanisms, measured in the scanner, should therefore predict the actual occurrence of intrusive trauma memories in the daily lives of patients, as measured by ESM.
	Between neural and symptom level (NE2): At each time point, neural responses measured by fMRI during a task assessing vigilance to social threat will predict levels of threat hypervigilance and paranoid experiences in daily life measured during experience sampling.	Considerable previous research shows that paranoia is associated with hypervigilance for threat. Hence, we would expect the neural correlates of hypervigilance (see N1b above) to predict hypervigilance for threat and paranoid thoughts in the daily lives of patients, as measured by ESM.
Psychotic symptoms will be mediated by trauma memory intrusions, negative appraisals, avoidance, dissociation, and hyper-vigilance for threat	**At symptom level (E3):** At each time point, the occurrence of intrusive trauma memories, negative appraisals, avoidance, dissociation and vigilance for threat[1], measured in daily life, will predict the subsequent exacerbation of psychotic symptoms (hallucinations and paranoid experiences)	Given previous evidence of the causal role of trauma in psychosis, we hypothesize that trauma memories, negative appraisals, avoidance, dissociation and vigilance for threat will trigger the onset of psychotic symptoms in daily life. We will be able to test the relative contribution of each process[1] using our ESM data.
	At symptom level (E4): At each time point, experiences of dissociation and negative appraisals will mediate between distressing involuntary recall of traumatic experiences and exacerbation of hallucinatory experiences	Given our previous finding that dissociative experiences are associated with hallucinations, and given that dissociative experiences can be triggered by trauma memories, we predict that dissociation measured in daily life will mediate between trauma memories and hallucinatory experiences.

[1] We have widened the range of processes to be tested due to recent evidence that processes other than trauma memories are relevant to the link between PTSD and psychotic symptoms (Hardy et al, 2021; Frost, 2023)

	At symptom level (E5): At each time point, negative appraisals and hypervigilance for threat will mediate between distressing involuntary recall of trauma memories and exacerbation of paranoid experiences	Similarly, if negative appraisals and hypervigilance for threat are triggered by trauma memories in daily life, these mechanisms should mediate between trauma memories and paranoid episodes in our ESM data.

Specific ESM protocol

Method of delivery and data security

ESM questions will be delivered on smartphones using an app called M-Path, an ESM app developed by Prof Myin-Germeys at KU Leuven (further information about the app can be found at https://m-path.io/landing/) which has been specifically designed for research with people suffering from severe mental illness. The app is Android and iOS compatible and we will provide participants with an Android smartphone in the event that they do not already own a suitable device.

All data collected with the m-Path app (i.e., questionnaire data) are initially stored locally in a protected folder on the smartphone of the participant which can only be accessed through the m-Path app (it cannot be accessed through other apps). To enhance data security and to prevent data leakage at all times highly secured application-layer encryption is applied. All answers given to questionnaires, all downloaded questionnaires, personal information (i.e. alias), text information, options and notes are stored on the phone using AES 256 bit-encryption with PKCS7 padding. When the user has access to a 3G/4G/5G network, data are transferred to secured university servers located in Leuven and Heverlee. These data will have no identifying data other than project ID numbers. The project team will be able to download the data from the servers on to STAR team computers via a secure and password protected portal. Once downloaded on to the project machines, the data will be encrypted and password protected. In the unlikely event of a security breach, all affected users will be notified. Ethical considerations are considered separately below.

ESM questions

We will ask participants to answer ESM questions 10 times a day over six day periods, each time lasting approximately two minutes. They will complete the ESM procedures once they have completed the main STAR trial baseline assessment, prior to randomization, and at 9th months post randomization (i.e. coinciding with the planned end of treatment in the treatment arm). Completion of the questionnaires will be cued by electronic beeps from the smartphone app on a quasi-random sequence, which will be adapted to individual participants according to their typical sleep-wake patters (e.g. the app will be programmed to notify participants only in hours when they are likely to be awake, to avoid excessive burden and inconvenience).

Our choice of ESM questions has been informed by previous studies and will be subject to piloting, rewording or omitting by the STAR experts by experience reference group, who will give final approval. Twenty-nine questions will cover the following specific topics (unless otherwise stated, responses will be rated 1 – not at all to 7 – very much so):

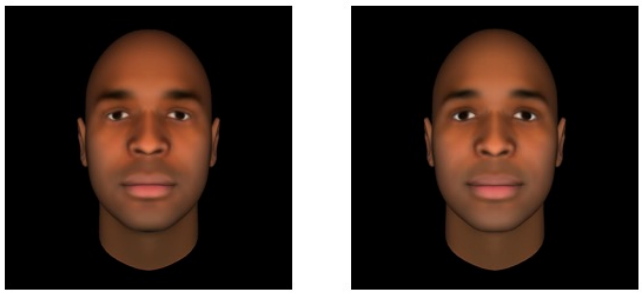
(i) mood (six questions, e.g. “Right now I feel cheerful”); (ii) negative trauma-related cognitions (three questions, e.g. “Right now I believe the world is a dangerous place”); (iii) paranoia (two questions, e.g. “Right now I feel suspicious”); (iv) hallucinations (two questions, e.g. “Right now I can hear a voice or voices that other people cannot hear”); (v) context (two questions, e.g. “Right now I am on my own/with strangers/with people I feel close to”; choose one); (vi) PTSD symptoms (eight questions, e.g. “Since the last beep unwanted memories about the experience popped into my mind”); (vii) dissociative symptoms (three questions, e.g. “Since the last beep I felt like the world around me was not real”); (vii) attachment cognitions (two questions, e.g. “Since the last beep I worried that others don’t’ really want to be close to me”); (ix) emotional impact of the assessment (one question, “This beep has disturbed me”).

In addition to these questions, we will include an experimental measure of ‘vigilance for social threat’, linked to mistrust, a key process in both PTSD and paranoia. Human beings make rapid (within a few hundred milliseconds) judgments about the trustworthiness of unfamiliar faces [45] reflecting the need to make efficient and rapid decisions about individuals we encounter in daily life - given the number of people we typically encounter, we do not have time to ‘think through’ whether each person can be trusted [46]. Recent work by one of the researchers has shown that paranoia is associated with a bias towards judging

unfamiliar faces as untrustworthy [47], reflecting an implicit bias in information processing that cannot be accessed by questionnaires. We will attempt to measure this bias in everyday life.

M-path will be programmed so that, at each beep, participants will be presented with two male faces from the Princeton Social Perception laboratory trustworthiness dataset (http://tlab.princeton.edu/databases/), which have previously been evaluated for normative ratings of trustworthiness (one face from the faces rated +1 SD in trustworthiness and one face from the -1SD faces). Within each beep, the two faces presented will be matched for ethnicity (White, Black or Asian); within each day, 50% of the beeps will be White and 50% will be BAME (Black or Asian). Participants will rate the faces on a 7-point scale of trustworthiness.

Figure 3: Untrustworthy (left) and trustworthy (right) BME faces from the Princeton Social Perception Lab.



ESM analysis plan

We will use multilevel factor analysis to confirm construct validity and factor structure of the constructs; since we will largely use questions employed in previous studies we do not anticipate problems in this regard but, if poorly fitting ESM items are identified, they will be dropped from analyses. As in previous studies, we will define exacerbations of hallucinatory episodes as one or more consecutive moments with a mean score ≥ 3 on the ESM hallucination items. Paranoid intensity at each moment will be defined in terms of mean score on the relevant items.

Multilevel models will be used to examine study hypotheses, taking into account the hierarchal structure of ESM data: beeps nested within days nested within participants. Typically for investigating constructs at the beep level, this requires a random intercept for each participant and for each day within participant to be included in the random effects. Alternatively, for each construct at each time point, summary measures such as variability across the beeps within a participant or the intraclass correlation coefficients (ICCs) can be calculated to estimate the proportion of variability in each level of the data (i.e., assessment, day, and person levels) to be explored as outcomes in further analyses. To test Hypothesis E1 (the treatment group, compared to the control group, will experience greater reductions between time 1 and time 2 in intrusive trauma memories, negative appraisals, avoidance, dissociation and hypervigilance) we will use multilevel models to compare the treatment and control groups at the two time points, using ESM measures of the relevant mechanisms as outcome variables, and including an indicator for treatment group as a covariate, and an appropriate random effect structure.

To test Hypothesis E2 (reductions in intrusive trauma memories, negative appraisals, avoidance, dissociation and hypervigilance between time 1 and time 2 will predict reductions in clinically assessed PTSD symptoms) we will use multilevel models with PTSD symptoms as dependent variable and each of the individual constructs and treatment group as covariates, with an appropriate random effect structure to account for the repeated measures of the covariates.

To test Hypothesis E3 (the occurrence of intrusive trauma memories, negative appraisals, avoidance, dissociation and vigilance for threat, will predict the subsequent exacerbation of psychotic symptoms i.e., hallucinations and the experience of paranoia in daily life), we will use multilevel models with each PTSD symptom score in the interval since the previous moment as the predictor variable and hallucination and paranoia scores at the moment as dependent variables, with an appropriate random effect structure.

To test Hypotheses E4 (experiences of dissociation and negative appraisals will mediate between distressing involuntary recall of traumatic experiences and exacerbation of hallucinatory experiences) and E5 (negative appraisals and hypervigilance for threat will mediate between distressing recall of traumatic experiences and exacerbation of paranoid experiences in everyday life) we will run multilevel models and use the difference in coefficients approach for mediation. This involves fitting two separate models for the outcome with and without the mediators as covariates, and an appropriate random effect structure. The difference in coefficient between these models for the distressing recall variable is a measure of the indirect effect through the respective mediators, and non-parametric bootstrapping is used to obtain a standard error for inference testing.

Specific neuroimaging/autonomic measurement protocol

The neuroimaging assessments will be conducted at three of the collaborating centres, the University of Manchester, King's College London (KCL) and Newcastle University using compatible 3-T scanners that are calibrated across centres.

During the scan, participants wear a respiration belt that measures any small changes in breathing and heart rate during the session. This is because these cause small changes to the BOLD response leading to artefacts on the fMRI images, so including these measurements during image processing improves the signal to noise ratio of task-related neural activation.

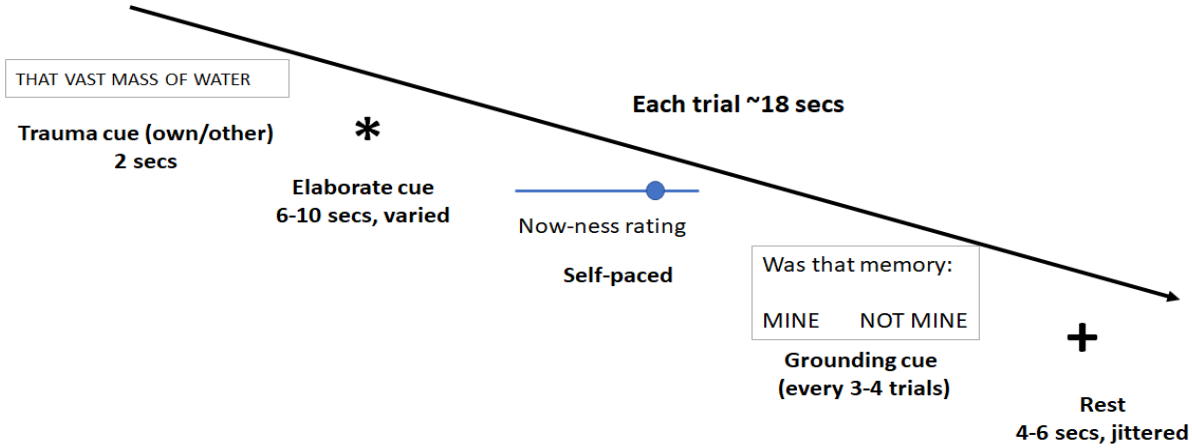
fMRI will be acquired while participants perform tasks probing: 1) retrieval of trauma memories; 2) hyper-vigilance to social threat. This will take place at the same two time points as ESM, described above. The core imaging protocol will last approximately 45 minutes and consist of a structural scan (10 minutes) plus two task-based fMRI tasks (15-20 minutes each). Participants will perform a brief practice of tasks, including a memory encoding task (10 minutes, see below), outside of the scanner, to familiarise themselves with the task instructions and button responses. During fMRI, we will ask participants to give self-report ratings of validated mood state items (happy, sad, anxious, irritable, angry, energetic) and experiences of dissociation chosen from the ESM items (e.g. "I feel spaced out, numb or emotionally shut down") [48] and include these in analyses.

<u>Neuroimaging plan and hypothesis-testing</u>

Retrieval of idiosyncratic trauma memory: *To test Hypothesis N1a* (the treatment group will show improved representation of trauma memories and greater emotional control measured by neuroimaging when prompted to think about trauma), we will examine neural responses during retrieval of the patient's idiosyncratic trauma memory using a previously validated script-driven procedure [49-51], which we will adapt to reduce the potential for patient stress. Prior to the scanning visit, patients will be asked to identify stimuli that remind them of their traumatic experience, already discussed as part of the main STAR trial baseline assessment. At the 9-months follow-up timepoint they will be asked to identify stimuli (short phrases) that remind them of a neutral, non-traumatic experience (e.g. a movie

that you remember seeing in the cinema, or a journey that you used to frequently make) for a 5 minute additional comparison task. Subsequently, during the neuroimaging session, they will be visually presented with key words and phrases relating to these cues, interspersed with those from a thematically distinct trauma account generated from previously published trauma research (see Figure 4). We will identify activity that correlates with subjective ratings of 'nowness' of the trauma memory (i.e. how much the memory feels like it's happening "right now", a measure of how well the memory has been contextualised), sampled by self-report on each trial. We will also periodically ask participants to indicate whether the cue is related to their own trauma experience ("mine") or not ("not mine"), to help participants remain grounded in the here-and-now. We will ask the current study experts by experience reference group to refine this established protocol for the current study context to minimise the potential for participant distress, and there is a separate statement on the consent form for participants to indicate whether they are happy to take part. This may entail adaptations such as dividing the task into multiple shorter blocks.

Figure 4: Idiosyncratic trauma memory trial structure.



Post-encoding rest period: At the end of the trauma memory task, brain activity is measured during rest (5 minutes). Neural activity during this window is used to establish the reconsolidation of trauma memory content, with resting state connectivity of amygdala during this 'offline' period serving as a marker for negative memory biases [43].

To test Hypothesis N1b (TF-CBTp will lead to greater reductions in hypervigilance for social threat) participants will be asked to complete a task probing the processing of facial emotions and ability to regulate their emotional responses to social threat. As per our previous studies examining neural changes following CBTp [32-34], participants are presented with faces displaying potentially threatening (angry) or affiliative (happy) emotions[2]. On half of the trials, participants will view the images and give subjective ratings of the level of threat (automatic threat processing). On the other half of trials, participants are instructed to reappraise the stimuli to a more neutral explanation (e.g., "the person is angry with someone else, rather than with me"; reappraised threat). Neural activation during

[2] It became clear at the piloting stage with the Expert by Experience reference group that the full fMRI procedures took well over an hour, and the group fed back this task was not feasible for inclusion in the scanner in its entirety as it was too long, laborious and time-pressured to present all of the stimuli in the limited amount of scanner time available. This would have been uncomfortable for our clinical population and would have had scanning cost implications. The task was therefore shortened by removing the neutral faces trials, which was the least informative condition. There is emerging consensus that "neutral" facial emotions can be misinterpreted as threatening by psychosis population (Underwood et al, 2015), so there was scientific justification for removing the neutral condition, rather than the reappraised threat condition, which is a better measure of 'neutral' (i.e., non-threatening) emotion (Fitzgerald et al, 2020).

automatic processing of potentially threatening emotion will be contrasted against activity when threat is reappraised as neutral.

To test Hypotheses NE1 and NE2 we will combine the ESM and neuroimaging data to test our prediction that these neural changes are associated with changes in the relevant psychological processes in everyday life. We will also use the clinical data collected in the STAR trial to test the corollary, that the TF-CBTp-led changes in activation are related to the level of improvement in PTSD symptoms.

All neuroimaging analysis will be undertaken using Statistical Parametric Mapping (SPM). To determine effects of treatment on neuronal responses to tasks in hypothesized regions of interest, we will perform repeated measures Analyses of Variance (ANOVAs) to identify significant interactions, with treatment (TF-CBTp vs usual treatment) and time (post vs pre) as between and within-participants variables respectively. To relate neuroimaging findings to ESM and clinical variables, we will perform correlations between signal in significant regions of interest and the ESM and clinical measures.

Memory encoding task (outside of scanner)*:* To measure memory abilities, we have adapted an established task [42] to be significantly briefer (10 mins). Participants encode target memory items (pictures) that are each presented alongside either a negative image (e.g. spider, crashed car) or neutral image (e.g. chair, banana)**.** ***Retrieval:*** Participants complete a retrieval test (5 mins, also outside of the scanner), consisting of previously seen images (66%) and new images (33%) which they asked whether they have seen before or not, to measure memory accuracy.

Acceptability and ethical considerations

All of our tasks have been or will be piloted with our experts by experience reference group to ensure acceptability and user-friendliness of our procedures. Specifically, feedback will be elicited with regards to content of ESM items, to trauma memory words for the fMRI task, and to the photographs used for the memory task.

ESM is a method that has been widely used in research with patients suffering from psychosis, beginning in the 1990s; a search in Google scholar with the search terms ‘ESM’ and ‘psychosis’ led to 1,890 hits. Several features of the method make it highly tolerable. First, the assessments are designed to be very brief (typically < 2 minutes per administration); second, participants can miss completing assessments and are told that they should do so if completing them interferes with ongoing activity (e.g. when driving).

We have considerable experience with this methodology. One of the applicants, Varese, has recently published an edited book on ESM methodology [52]; another, Emsley, has extensive experience of analysing ESM studies and wrote the chapter on the statistical analysis of ESM data in Varese’s book; another, co-CI Bentall, has published ESM studies of paranoid symptoms [21] and auditory hallucinations [14]. The method has recently been adapted for use in clinical trials [19]; 116 patients with psychosis) and is proving to be acceptable in the ongoing ReProcess trial of trauma-focussed therapies for patients with a dual diagnosis of schizophrenia and PTSD (the same group of patients we will be studying) that is currently being conducted in the Netherlands (ISRCTN56150327), on which applicant Hardy is a co-applicant; of the 29 people recruited to that trial so far (trial sample aim is 200), all have consented to participate in the ESM protocol. Hence we believe that the acceptability of ESM has been demonstrated in precisely the circumstances in which we propose to employ it.

Neuroimaging is more demanding for participants because it involves a longer time commitment from participants (4 hours in total on two occasions: approximately 1.5 hours eliciting and rating trauma reminder stimuli prior to scanning visits, then around 2.5 hours per visit, with approximately 1 hour in the scanner itself (45 minutes of scanning, 15 minutes to settle in and out of scanner), 1 hour to do safety checks with the radiographer, receive instructions, practice tasks, and 30 minutes for debrief and feedback). People will be able to choose not to take part in the scanning, and complete the memory encoding task only, if

they think they would find the scanner environment uncomfortable or claustrophobic. However, we know of no evidence that psychotic patients are less able to tolerate the scanner environment and numerous (many hundreds) studies have conducted neuroimaging with this patient group over a period of thirty years, including studies led by Co-PI Peters and Co-I Mason in a similar investigation of the mechanisms of action of CBTp [31, 32. 34]. The locations where the neuroimaging will take place have excellent track records for acceptability to patients experiencing psychosis. We use a "mock scanner" environment prior to scanning to help with acclimation, and we typically achieve well over 80% revisits of our patient populations.

Neuroimaging has been increasingly used to investigate processes involved in therapeutic change. Across disorders, there are now over a hundred such publications. In our studies investigating the mechanisms of change in psychotic patients receiving cognitive-behaviour therapy [32-34] we found no evidence that imaging impacted on recruitment or retention into the main intervention being evaluated. Nonetheless, we recognise the importance of taking steps to reduce the probability of adverse reactions to our neuroimaging protocol that would affect participation in the STAR trial. First, as with our previous studies, participation in the neuroimaging protocol will be entirely voluntary and all potential participants will be made aware that they can decline to take part if they anticipate that it will be stressful; it is for this reason that we are seeking to recruit only a subsample of STAR participants into the neuroimaging study (n=80 out of a possible 300). Second, we are utilising protocols previously used successfully with PTSD patients [50, 51] which we have modified to ensure it is briefer, and less arousing for our patients. Finally, of course, participants will be free to terminate the scanning sessions any time they wish without affecting their involvement in other aspects of the trial.

We will elicit feedback from participants on their experience of taking part in the study to ensure acceptability throughout, with a view to adapting our research procedures should concerns arise or barriers be identified. We will have the same standard protocol as the STAR trial for managing any distress potentially elicited by the study procedures, which has been developed in collaboration with experts-by-experience. This will include a debrief at the end of the scanning procedures with the RWs to enable participants to feedback any potential distress, and to 'take a breather' before leaving the scanning facility. We will also offer telephone contact within 48 hours of completing the study procedures to check on participant well-being, and a summary of support and crisis numbers. All appointed RWs will have a psychology background and have experience of working with populations with severe mental health problems. They will receive training in interviewing skills and how to respond sensitively and empathically to any distress that arises. There will be close supervision of RWs throughout the trial (by experienced Research Clinical Psychologists) and regular review both within the main trial team (at monthly meetings) and at the TSC and DMEC.

References

1. Read, J., et al., *Childhood trauma, psychosis and schizophrenia: A literature review and clinical implications.* Acta Psychiatrica Scandinavica, 2005. **112**: p. 330-350.
2. Varese, F., et al., *Childhood adversities increase the risk of psychosis: A meta-analysis of patient-control, prospective and cross-sectional cohort studies.* Schizophrenia Bulletin, 2012. **38**: p. 661-671.
3. de Bont, P.A.J.M., et al., *Predictive validity of the Trauma Screening Questionnaire in detecting post-traumatic stress disorder in patients with psychotic disorders.* British Journal of Psychiatry, 2015. **206**(408-416).
4. Hardy, A., *Pathways from trauma to psychotic experiences: A theoretically informed model of postraumatic stress in psychosis.* Frontiers in Psychology, 2017. **8**: p. 697.

5. Ehlers, A. and D.M. Clark, *A cognitive model of posttraumatic stress disorder.* Behaviour Research and Therapy, 2000. **38**: p. 319-345.
6. Beierl, E.T., et al., *Cognitive paths from trauma to posttraumatic stress disorder: A prospective study of Ehlers and Clark's model in survivors of assaults or road traffic collisions.* Psychological Medicine, 2019.
7. Hardy, A., I. van de Geissen, and D.P.G. van den Berg, *Trauma, posttraunatic stress, and psychosis*, in *A clinical introduction to psychosis*, J.C. Babcock and G. Paulik, Editors. 2020, Academic Press: London. p. 223-243.
8. Okkels, N., et al., *Traumatic stress disorder and risk of subsequent schizophrenia spectrum disorder or bipolar disorder: A nationwide cohort study.* Schizophrenia Bulletin, 2016. **43**: p. 180-186.
9. Williams, J., et al., *Psychological mediators of the association between childhood adversities and psychosis: A systematic review.* Clinical Psychology Review, 2018. **65**: p. 175-196.
10. Hardy, A., et al., *Trauma and hallucinatory experiences in psychosis.* Journal of Nervous and Mental Disease, 2005. **193**: p. 501-507.
11. Varese, F., E. Barkus, and R.P. Bentall, *Dissociation mediates the relationship between childhood trauma and hallucination-proneness.* Psychological Medicine, 2011. **42**: p. 1025-1036.
12. Perona-Garcelán, S.P., et al., *Dissociative experiences as mediators between childhood trauma and auditory hallucinations.* Journal of Traumatic Stress, 2012. **25**(3): p. 323-329.
13. Pilton, M., et al., *The relationship between dissociation and voices: A systematic literature review and meta-analysis.* Clinical Psychology Review, 2016. **40**: p. 138-165.
14. Varese, F., et al., *The relationship between dissociation and auditory verbal hallucinations in the flow of daily life in patients with psychosis.* Psychosis, 2011. **3**: p. 14-28.
15. Geddes, J., A. Ehlers, and D. Freeman, *Hallucinations in the months after a trauma: An investigation of the role of cognitive processing of a physical assault in the occurrence of hallucinatory experiences.* Psychiatry Research, 2016. **246**: p. 601-605.
16. Freeman, D., et al., *Paranoia and post-traumatic stress disorder in the months after a physical assault: a longitudinal study examining shared and differential predictors.* Psychological Medicine, 2013. **43**: p. 2673-2684.
17. Myin-Germeys, I., P. Delespaul, and J. van Os, *The experience sampling method in psychosis research.* Current Opinion in Psychiatry, 2003. **16, supp 2**: p. 33-38.
18. Carter, L.-A. and R. Emsley, *The analysis of experience sampling data*, in *A guide to experience sampling in mental health research and practice*, J. Palmier-Claus, G. Haddock, and F. Varese, Editors. 2019, Routledge: London. p. 18-37.
19. Pot-Kolder, R., et al., *Virtual-reality-based cognitive behavioural therapy versus waiting list control for paranoid ideation and social avoidance in patients with psychotic disorders: A single-blind randomised controlled trial.* Lancet Psychiatry, 2018. **5**: p. 217-226.
20. Myin-Germeys, I., et al., *Experience sampling methodology in mental health research: new insights and technical developments.* World Psychiatry, 2018. **17**: p. 123-132.

21. Thewissen, V., et al., *Instability in self-esteem and paranoia in a general population sample.* Social Psychiatry and Psychiatric Epidemiology, 2007. **42**: p. 1-5.
22. Sitko, K., F. Varese, and R.P. Bentall, *Paranoia and attachment in daily life: An experience sampling study.* Psychiatry Research, 2016. **246**: p. 32-38.
23. Oorschot, M., et al., *Temporal dynamics of visual and auditory hallucinations.* Schizophrenia Research, 2012. **140**: p. 77-82.
24. Peters, E., et al., *Appraisals, psychotic symptoms and affect in daily life.* Psychological Medicine, 2012. **42**: p. 1013-1023.
25. Clark, D.A. and A.T. Beck, *Cognitive theory and therapy of anxiety and depression: Convergence with neurobiological findings.* Trends in Cognitive Sciences, 2010. **14**: p. 418-424.
26. Holmes, E.A., et al., *The Lancet Psychiatry Commission on psychological treatments research in tomorrow's science.* Lancet Psychiatry, 2018. **5**: p. 237-286.
27. Cisler, J.M., et al., *Amygdala response predicts trajectory of symptom reduction during Trauma-Focused Cognitive-Behavioral Therapy among adolescent girls with PTSD.* Journal of Psychiatric Research, 2015. **71**: p. 33-40.
28. Shou, H., et al., *Cognitive behavioral therapy increases amygdala connectivity with the cognitive control network in both MDD and PTSD.* Neuroimage: Clinical, 2017. **14**: p. 464-470.
29. Schlumpf, Y.R., et al., *Functional reorganization of neural networks involved in emotion regulation following trauma therapy for complex trauma disorders.* Neuroimage: Clinical, 2019. **23**.
30. Aguilar, E.J., et al., *Emotional fMR auditory paradigm demonstrates normalization of limbic hyperactivity after cognitive behavior therapy for auditory hallucinations.* Schizophrenia Research, 2018. **193**: p. 304-312.
31. Kumari, V., et al., *Neural changes following cognitive behaviour therapy for psychosis: A longitudinal study.* Brain, 2011. **134**: p. 2396–2407.
32. Mason, L., et al., *Cognitive behavioral therapy normalizes functional connectivity for social threat in psychosis.* Schizophrenia Bulletin, 2016. **42**: p. 684-692.
33. Kumari, V., et al., *Dorsolateral prefrontal cortex activity predicts responsiveness to cognitive–behavioral therapy in schizophrenia.* Biological Psychiatry, 2009. **66**: p. 594-602.
34. Mason, L., et al., *Brain connectivity changes occurring following cognitive behavioural therapy for psychosis predict long-term recovery.* Translational Psychiatry, 2017. **7**: p. e1001.
35. Kumari, V., et al. *Beyond dopamine: functional MRI predictors of responsiveness to cognitive behaviour therapy for psychosis*. Frontiers in Behavioral Neuroscience, 2010. **4**, DOI: 10.3389/neuro.08.004.2010.
36. Tolmeijer, E., et al., *Using fMRI and machine learning to predict symptom improvement following cognitive behavioural therapy for psychosis.* Neuroimage: Clinical, 2018. **20**: p. 1053-1061.
37. Ehlers, A., et al., *Cognitive therapy for post-traumatic stress disorder: Development and evaluation.* Behaviour Research & Therapy, 2005. **43**: p. 413-431.
38. Brewin, C.R., et al., *Intrusive images in psychological disorders: Characteristics, neural mechanisms, and treatment implications.* Psychological Review, 2010. **117**: p. 210-232.

39. Bisby, J.A. and N. Burgess, *Differential effects of negative emotion on memory for items and associations, and their relationship to intrusive imagery.* Current Opinion in Behavioral Science, 2017. **17**: p. 124-132.
40. McClelland, J.L., B.L. MnNaughton, and R.C. O'Reilly, *Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory.* Psychological Review, 1995. **102**: p. 419-457.
41. James, E.L., et al., *The trauma film paradigm as an experimental psychopathology model of psychological trauma: Intrusive memories and beyond.* Clinical Psychology Review, 2016. **47**: p. 106-142.
42. Bisby, J.A., et al., *Opposing effects of negative emotion on amygdalar and hippocampal memory for items and associations.* Social Cognitive and Affective Neuroscience, 2016. **11**: p. 981-990.
43. Kark, S.M. and E.A. Kensinger, *Post-encoding amygdala-visuosensory coupling Is associated with negative memory bias in healthy young adults.* Journal of Neuroscience, 2019. **39**: p. 3130-3143.
44. Tambini, A. and L. Davachi, *Persistence of hippocampal multivoxel patterns into postencoding rest is related to memory.* Procedings of the National Academy of Science, 2013. **110**: p. 19591-19596.
45. Todorov, A., P. Mende-Siedlecki, and R. Dotsch, *Social judgments from faces.* Current Opinion in Neurobiology, 2013. **23**: p. 373-380.
46. Sutcliffe, A., et al., *Relationships and the social brain: Integrating psychological and evolutionary perspectives.* British Journal of Psychology, 2012. **103**: p. 149-168.
47. Martinez, A.P., et al., *Mistrust and negative self-esteem: Two paths from attachment styles to paranoia.* Psychology and Psychotherapy: Theory, practice, research, in press.
48. Watson, D., L.A. Clark, and A. Tellegren, *Development and validation of a brief measure of positive and negative affect.* Journal of Personality and Social Psychology, 1988. **54**: p. 1063-1070.
49. Lanius, R.A., et al., *Recall of emotional states in posttraumatic stress disorder: An fMRI investigation.* Biological Psychiatry, 2003. **53**: p. 204-210.
50. Osuch, E.A., et al., *Regional cerebral blood flow correlated with flashback intensity in patients with posttraumatic stress disorder.* Biological Psychiatry, 2001. **50**: p. 246-253.
51. Whalley, M.G., et al., *An fMRI investigation of posttraumatic flashbacks.* Brain and Cognition, 2013. **81**: p. 151-159.
52. Palmier-Claus, J., G. Haddock, and F. Varese, eds. *Experience sampling in mental health research*. 2019, Routledge: London.