

Integrating Virtual Reality, Neurofeedback, and Cognitive Behaviour Therapy for Auditory Verbal Hallucinations (Hybrid): Protocol of an Unblinded Single-Arm Intervention Pilot Study

Jessica Spark, Elise Rowe, Mario Alvarez-Jimenez, Imogen Bell, Linda Byrne, Ilvana Dzafic, Carli Ellinghaus, Suzie Lavoie, Jarrad Lum, Brooke McLean, Neil Thomas, Andrew Thompson, Greg Wadley, Thomas Whitford, Stephen Wood, Hok Pan Yuen, Barnaby Nelson

Submitted to: JMIR Research Protocols
on: June 18, 2024

Disclaimer: © The authors. All rights reserved. This is a privileged document currently under peer-review/community review. Authors have provided JMIR Publications with an exclusive license to publish this preprint on its website for review purposes only. While the final peer-reviewed paper may be licensed under a CC BY license on publication, at this stage authors and publisher expressly prohibit redistribution of this draft paper other than for review purposes.

Table of Contents

Original Manuscript..... 5

Supplementary Files..... 41

 Figures 42

 Figure 1..... 43

 Figure 2..... 44

 Figure 3..... 45

CONSORT (or other) checklists..... 46

 CONSORT (or other) checklist 0..... 47

Integrating Virtual Reality, Neurofeedback, and Cognitive Behaviour Therapy for Auditory Verbal Hallucinations (Hybrid): Protocol of an Unblinded Single-Arm Intervention Pilot Study

Jessica Spark^{1, 2*}; Elise Rowe^{1, 2*} PhD; Mario Alvarez-Jimenez^{1, 2}; Imogen Bell^{1, 2}; Linda Byrne^{3, 4}; Ilvana Dzafic^{1, 2}; Carli Ellinghaus^{1, 2}; Suzie Lavoie^{1, 2}; Jarrad Lum³; Brooke McLean^{5, 6}; Neil Thomas⁷; Andrew Thompson^{1, 2}; Greg Wadley⁸; Thomas Whitford^{1, 9}; Stephen Wood^{1, 2, 10}; Hok Pan Yuen^{1, 2}; Barnaby Nelson^{1, 2}

¹ Orygen Parkville AU

² Centre for Youth Mental Health University of Melbourne Parkville AU

³ School of Psychology Deakin University Burwood AU

⁴ The Cairnmillar Institute Hawthorn East AU

⁵ Centre for Youth Mental Health, The University of Melbourne Parkville, Victoria AU

⁶ Orygen Parkville, Victoria AU

⁷ Centre for Mental Health and Brain Sciences Swinburne University of Technology Hawthorn AU

⁸ School of Computing and Information Systems The University of Melbourne Parkville AU

⁹ School of Psychology University of New South Wales Sydney AU

¹⁰ School of Psychology University of Birmingham Edgbaston GB

*these authors contributed equally

Corresponding Author:

Elise Rowe PhD

Orygen
35 Poplar Road
Parkville
AU

Abstract

Background: Current treatments for schizophrenia and other psychotic disorders have limited efficacy, with high rates of non-response to 'gold standard' treatments. New approaches are therefore urgently required. We have developed a new treatment approach for auditory verbal hallucinations (AVH), a major symptom of psychotic disorders. This treatment ('Hybrid') integrates advances in psychological therapy (cognitive-behaviour therapy for psychosis, CBTp), technology (virtual reality, VR) and neuroscience (EEG-based neurofeedback). Hybrid takes a 'symptom capture' approach using individually tailored VR-based exposure exercises. Participants are progressively exposed to symptom triggers in a controlled environment and develop methods of down regulating neural activity associated with these symptoms (neurofeedback component) while concurrently receiving clinician-delivered CBT for psychosis (CBTp) in-vivo (i.e., during symptom activation). The aims of the current pilot study are to: investigate the feasibility, acceptability, safety and usability of Hybrid treatment (primary aim); explore Hybrid's treatment efficacy and engagement of treatment targets (secondary aims). The treatment targets are self-directed modulation of high-beta band (18-30 Hz) neurophysiological activity (neural target) and progressing upwards through a VR-based symptom-eliciting exposure hierarchy (psychological target). In this paper, we present the background and protocol of the pilot study.

Objective: Primary aim: Investigate the feasibility, acceptability, safety and usability of Hybrid treatment in FEP patients. Secondary aims: Explore Hybrid's treatment efficacy and engagement of treatment targets.

Methods: We will conduct a pilot study of the Hybrid protocol with 10 first episode psychosis (FEP) patients who are currently experiencing AVH. Participants receive the intervention package weekly over 12 sessions. In each session, they are progressively exposed to increasing levels of symptom triggers in a controlled VR environment, while concurrently receiving clinician-delivered CBTp. The neurofeedback, which is integrated into the VR system and based on AVHs-related high-beta band activity, will be used by the FEP participants to downregulate their neural activity in real time, with the aim of enhancing the therapeutic effect and transferring these skills to everyday life.

Results: As of June 2024, this feasibility pilot study recently started recruitment activities. No participants have been recruited yet. We anticipate results of the pilot study to be available towards the end of 2025.

Conclusions: The Hybrid study is piloting a novel approach which has the potential to address the shortcomings of current treatments for psychotic symptoms. If there is favourable evidence for the acceptability, feasibility, safety and usability of Hybrid, the study team will move on to efficacy trials. Clinical Trial: ACTRN12624000136505

(JMIR Preprints 18/06/2024:63405)

DOI: <https://doi.org/10.2196/preprints.63405>

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

Please make my preprint PDF available to anyone at any time (recommended).

Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.

Only make the preprint title and abstract visible.

✓ **No, I do not wish to publish my submitted manuscript as a preprint.**

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✓ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**

Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain visible to all users.

Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in a JMIR publication, my full manuscript will be available to all users.

No. Please do not make my accepted manuscript PDF available to anyone.

Original Manuscript

Integrating Virtual Reality, Neurofeedback, and Cognitive Behaviour Therapy for Auditory Verbal Hallucinations (Hybrid): Protocol of an Unblinded Single-Arm Intervention Pilot Study

Jessica Spark^{1,2*}, Elise Rowe^{1,2*}, Mario Alvarez-Jimenez^{1,2}, Imogen Bell^{1,2}, Linda K. Byrne^{5,8}, Ilvana Dzafic^{1,2}, Carli Ellinghaus^{1,2}, Suzie Lavoie^{1,2}, Jarrad A. G. Lum⁵, Brooke McLean^{1,2}, Neil Thomas⁴, Andrew Thompson^{1,2}, Greg Wadley⁷, Thomas J. Whitford^{1,3}, Stephen J Wood^{1,2,6}, Hok Pan Yuen^{1,2}, Barnaby Nelson^{1,2}

1 Orygen, Parkville, Victoria, Australia

2 Centre for Youth Mental Health, The University of Melbourne, Parkville, Victoria, Australia

3 School of Psychology, University of New South Wales, Sydney, Australia

4 Centre for Mental Health and Brain Sciences, Swinburne University of Technology, Hawthorn, Victoria, Australia

5 School of Psychology, Deakin University, Burwood, Victoria, Australia

6 School of Psychology, University of Birmingham, Edgbaston, UK

7 School of Computing and Information Systems, The University of Melbourne, Parkville, Victoria, Australia

8 The Cairnmillar Institute, Hawthorn East, Victoria, Australia

* Indicates shared first authorship

Corresponding author: Elise Rowe

Corresponding author email: elise.rowe@unimelb.edu.au

Short Running Title: Hybrid: Integrating VR, Neurofeedback and CBT for Treatment of Hearing Voices

Key Words: Psychosis, First Episode Psychosis, Schizophrenia, Virtual Reality, Neurofeedback, EEG, Auditory Verbal Hallucinations, Voices, Cognitive Behaviour Therapy, Youth Mental Health

ABSTRACT

Background

Current treatments for schizophrenia and other psychotic disorders have limited efficacy, with high rates of non-response to 'gold standard' treatments. New approaches are therefore urgently required.

Objective

To address this, we have developed a new treatment approach for auditory verbal hallucinations (AVH), a major symptom of psychotic disorders, that integrates advances in psychological therapy (cognitive-behaviour therapy for psychosis, CBTp), technology (virtual reality, VR) and

neuroscience (EEG-based neurofeedback).

Methods

Hybrid takes a ‘symptom capture’ approach using individually tailored VR-based exposure exercises. Participants (N = 10) will receive the intervention package weekly over 12 face-to-face sessions. Here, participants will be progressively exposed to symptom triggers and develop methods of down regulating neural activity associated with these symptoms (neurofeedback component) while concurrently receiving clinician-delivered CBTp. The aims of the current pilot study are to: investigate the feasibility, acceptability, safety and usability of Hybrid treatment (primary aim); and explore Hybrid’s treatment efficacy and engagement of treatment targets (secondary aims). The primary aim will be assessed via face-to-face user experience surveys on a (self-assessed) 5-point Likert scale (and qualitative open-ended questions) examining (1) acceptability, (2) helpfulness, (3) engagement, and (4) perceived safety. We will also examine consent and completion rates, and the number of sessions attended. Our threshold for moving on to efficacy trials will be at least 70% of our participants ratings 3 and above (which corresponds to Agree or Strongly Agree) that the intervention package was acceptable, feasible and safe. The secondary aims will be assessed by observing whether individuals achieve self-directed modulation of high-beta neurophysiological activity (neural target) and progression upwards through the VR-based exposure hierarchy (psychological target), and by assessing symptom change scores.

Results

As of February 2025, Hybrid has commenced (unblinded) recruitment activities from Orygen clinical services in Northwestern Melbourne, Australia. Seventy-five individuals have been approached and 64 have been pre-screened (41 deemed eligible, 15 ineligible and 8 declined or did not respond to contact attempts) and 5 individuals have been included in the study (however, 1 individual was later deemed ineligible). Of the four individuals who have commenced the Hybrid treatment, two are actively engaged in the program and two have withdrawn (one actively withdrew and one did not respond to contact attempts). We expect recruitment to conclude in July 2025 and for the results to be published in 2026.

Discussion

The Hybrid study is piloting a novel approach which has the potential to address the shortcomings of current treatments for psychotic symptoms. If there is favourable evidence for the acceptability, feasibility, safety and usability of Hybrid, the study team will move on to efficacy trials. Registration: ANZCTR.org.au - ACTRN12624000357550.

INTRODUCTION

Psychosis is the distinguishing feature of schizophrenia spectrum disorders and a frequent manifestation of mood and substance use disorders [1]. It is characterised by alterations in thoughts and perceptions, often taking the form of positive symptoms such as delusions, hallucinations [2] and

disorganised thinking [3], as well as negative symptoms such as blunted affect, poverty of speech, and withdrawal from social and occupational activities [4]. First episode psychosis (FEP) onset most commonly occurs in late adolescence and early adulthood [5], with auditory verbal hallucinations (AVH) being the most prevalent type of positive symptom reported in this clinical population (~80%; [6], [7]). AVH are typically characterized by hearing voices that are perceived as distinct from the person's own thoughts. Such experiences are often a cause of significant distress and disruption to daily functioning [8], making AVHs an important target for treatment. Furthermore, evidence supports the benefits of early intervention following first onset of psychotic symptoms with the duration of untreated psychosis (i.e., the time between first psychotic symptoms to antipsychotic treatment) consistently predicting poorer long-term outcomes in longitudinal studies [9], [10].

Current Treatments for Psychosis

Current treatment recommendations for psychosis include antipsychotic medications, psychosocial support, and psychological treatment, specifically, Cognitive Behaviour Therapy for psychosis (CBTp; [11], [12], [13]. Unfortunately, all currently available treatments are only moderately effective. Firstly, the efficacy of antipsychotic medication for treatment of positive symptoms of psychosis is not optimal. For example, while commonly prescribed antipsychotics can be significantly more effective than placebo, these medications are accompanied by side effects such as weight gain, sedation, and extrapyramidal symptoms which lead to high incidences of patient nonadherence [2]. A 2019 meta-analysis including 16 randomized controlled trials of antipsychotics and >6200 patients with schizophrenia found that 38% of patients met criteria for nonresponse and two-thirds showed only 'minimal improvement' [14]. Secondly, the effect sizes for psychological treatments, such as cognitive behavioural therapy for psychosis (CBTp), tend to be small (~0.4) and limited in long term

efficacy [2]. Both pharmacological and psychological interventions have higher rates of nonresponse [14] and disengagement [15] in patients with earlier onset of illness highlighting the importance of targeting FEP populations and developing effective and reliable treatments for early intervention. New treatment development, both pharmacological and psychological, is therefore urgently required.

“Cold Cognitions”

One of the limitations of psychological therapies such as CBTp may be that they tend to rely on abstract self-reflection (or ‘cold cognitions’) which can be detached from the actual in-vivo experience of symptoms (or ‘hot cognitions’; [16]. This limitation may be particularly relevant for young people in the early stages of psychotic disorder, many of whom find it challenging to engage in this form of self-reflective therapy [17]. Borrowing from the ‘symptom capture’ approach used in other mental disorders, the effectiveness of CBTp may be improved if it is applied *while the symptom is actively occurring* [18] and collaboratively addressing the symptom that has been activated. The benefit of actively eliciting ‘hot’ cognitions has been demonstrated in treatment of anxiety disorders and obsessive-compulsive disorder (OCD; [19]. In these disorders, ‘exposure and response prevention’ (ERP) is a key feature of gold standard psychological treatment [20]. This therapeutic approach involves *actively eliciting* a degree of anxiety by exposing the patient to symptom triggers and addressing the cognitive and behavioural reactions together with the therapist. Once a degree of mastery and tolerance has been achieved over a low-level, anxiety-inducing trigger, the patient and therapist collaboratively proceed to higher levels of an exposure hierarchy.

Virtual Reality (VR)

One advance in technology that may help anchor treatment to the in vivo experience of symptoms is virtual reality (VR). VR is an interactive computer-generated experience in which the user wears a

headset that immerses them in a simulated environment. The VR system is able to create sensory illusions that mimic reality and elicit brain and behavioural responses that parallel those that occur in the real world [21]. VR environments have been found to be useful in the treatment of mental disorders such as social anxiety (for review see [22], phobias (for review see [23], post-traumatic stress disorder (PTSD; for review see [24], and as a treatment of psychotic symptoms such as paranoia [25] and see [26] for review). Similar to CBT for anxiety and OCD, this therapeutic technique is founded on exposure principles, where a person is presented with feared, anxiety-provoking or symptom-inducing stimuli in a graded manner within a controlled environment to enable them to gradually develop strategies to cope when triggers arise in the course of daily life. VR studies for PTSD have found that immersion (i.e., a subjective sense of presence in the VR environment) and personalisation of the VR environment (i.e., tailoring the VR environment to the person's specific and idiosyncratic triggers) may lead to better outcomes, as therapy is more likely to generalise to real world situations [27]. Indeed, a meta-analysis of VR-assisted exposure therapy for anxiety disorders showed a large overall effect size for VR exposure therapy compared to (mostly waitlist) control conditions, Cohen's $d = 1.11$ (S.E. = 0.15, 95% CI: 0.82–1.39) [28]. Furthermore, research on the use of VR for psychosis treatment has indicated the approach can be feasible, acceptable, and effective for improving some symptoms including positive symptoms such as paranoia and hallucinations [29].

For the specific treatment of AVH, the small number of VR trials to date have all involved avatar therapy, a related approach which involves the creation of a computerised, audio-visual avatar that mimics the hallucinated voices normally experienced by participants, either on a computer screen [30] or using a head mounted display [31], [32]. During these sessions, the participant is supported by the therapist to engage in a dialogue with the created personalised avatar, and to develop strategies to respond to the voices. At the same time, the avatar voice and expressions are

gradually adjusted from their normal content/tone (e.g., abusive) to being friendly and supportive controlled by the therapist [33]. A 2020 meta-analysis showed favorable results for avatar therapy in patients with schizophrenia compared to supportive counselling on measures of mental state, level of insight and quality of life [34]. However, whilst avatar therapy involves artificially recreating an analogue AVH experience, the use of the VR environment to elicit symptoms naturally (as is used in traditional ERP treatments) has not yet been explored.

Neurofeedback

Another technological advance, neurofeedback, has proven useful in the treatment of a number of disorders and has shown promising results for psychotic symptoms [35], [36]. Neurofeedback is a technique in which individuals use a brain-computer interface to control their own brain activity by receiving real-time feedback on their neural activity. Neurofeedback has most commonly been provided via electroencephalography (EEG) or real-time functional magnetic resonance imaging (rtfMRI). In an example of EEG neurofeedback, individuals receive real-time information on their brain activity, often presented as a bar graph, where the height of the bar represents power of oscillatory activity in a given frequency band (e.g., alpha or beta) measured in terms of power (i.e., amplitude squared). This visual display allows participants to try to gain control over their brain activity by manipulating the visual feedback. Participants are typically provided with directions or mental techniques to control their brain activity, are encouraged to apply and adapt their own strategies and to use the visual feedback display as a guide [37].

The ability of healthy individuals to manipulate their neural activity using neurofeedback has repeatedly been demonstrated [38], [39], [40] and is suggested to have positive impacts on cognitive and emotional domains, including the improvement of working memory [40], intelligence [38], and identification of emotional prosody [41]. This has led to neurofeedback's clinical

application to a range of psychiatric or neurological disorders, with meta-analyses reporting benefits for attention deficit hyper-activity disorder (ADHD; [42], depression [43], PTSD [44], subclinical OCD [45] and epilepsy [46]. The findings in medication-resistant epilepsy patients are particularly striking, with neurofeedback demonstrating efficacy in averting seizures once patients learn to anticipate their onset, and with a transfer effect evident even years later [42], [46].

The use of neurofeedback in psychotic disorders is increasing in popularity, with a small number of studies published to date (for review see [36]. All studies have found that patients with schizophrenia were able to self-regulate their neural activity, although evidence for a transfer effect (that is, the ability of participants to employ the strategies they have learned during neurofeedback to control their neural activity in the absence of neurofeedback) has yet to be clearly demonstrated. A particularly promising study using rtfMRI indicated a transfer effect for schizophrenia patients with treatment refractory AVH after a two-week training period [47]. Interestingly, the post-training increase in functional connectivity between brain regions associated with AVH (the left superior temporal gyrus and inferior prefrontal gyrus) was associated with a reduction in AVH symptoms over the training period. As Nan and colleagues [48], pp 1) recently concluded, “these positive outcomes suggest that such intensive neurofeedback training may provide new insight into the treatment of schizophrenia and thus deserves further study to fully examine its scope.”

While rtfMRI-based neurofeedback (like that used in the aforementioned study) can be costly and uncomfortable (due to the space restrictions), EEG-based neurofeedback offers the benefits of portability, cost-effectiveness and higher patient acceptability. EEG has the further advantage of capturing oscillatory dynamics associated with neural functioning, which cannot be detected using functional MRI owing to the slow temporal latency of the hemodynamic response [49], [50]. For FEP patients, studies on EEG frequency bands (alpha, 8 to 12 Hz; beta, 13 to 30 Hz; theta, 4 to 7 Hz; delta, 0.5 to 4 Hz; low gamma, 30 to 50 Hz; and high gamma, 50 to 90 Hz) have

reported several abnormalities across all six bands [51]. Oscillations in the high beta band range (approximately 18-30 Hz) are associated with autonomic nervous system hyperarousal and anxiety, which are recognised as one of the most common subjective features of AVH [52], [53]. Previous studies have found that reducing high beta band activity (and hyperarousal) is associated with a decrease in psychotic symptoms in patients with schizophrenia, including AVH [48], [54], [55]. Thus, the use of EEG-based neurofeedback targeting high beta band activity represents an important target for the treatment of AVH.

The Hybrid study

The current study, Hybrid, will investigate the potential of a novel treatment approach to AVH in young people with FEP that, if successful, could be incorporated into an individual's broader health care program. Our integrative model combines psychological therapy (CBTp), new immersive technologies (VR) and neuroscience (neurofeedback) in an individualised symptom capture (or exposure and response prevention) treatment approach. The term 'Hybrid' is used to reflect the integrated approach of treatment where each element has been selected to strengthen the effectiveness of the treatment regime as a whole.

A pilot study is required to investigate the following aims: 1) to determine whether Hybrid is feasible, acceptable, and safe; 2) to examine participants' experience of the intervention package and whether it can be modified to increase probability of clinical utility; 3) to explore if there is a signal of clinical benefit in response to Hybrid treatment; and 4) to examine whether Hybrid engages specific neural (modulating high beta band activity) and psychological (moving up a symptom-eliciting exposure hierarchy) targets (proof of concept).

METHODS

Design

An unblinded single arm pilot intervention study.

Participants

Ten participants with a diagnosed FEP will be recruited via telephone from Orygen's Early Psychosis Prevention & Intervention Centre (EPPIC), headspace youth mental health services and Orygen Clinical Trials Unit database which serve the Northern and Western suburbs of Melbourne, Australia. Help-seeking participants with FEP from the community will also be recruited. Recruitment will involve phone call, email and SMS contact with potential participants. Participants will receive a manually initiated reminder SMS and/or phone call the day before participation sent by the study clinician or research assistant.

Inclusion Criteria:

- Aged 15-26 years inclusive.
- Sufficient fluency in English to engage in psychological therapy with an English-speaking therapist, and to understand the study assessments.
- Ability to give informed consent and adhere to study procedures. Parental or guardian consent will be obtained for participants aged under 18 years.
- Psychotic threshold AVH in lifetime as measured by the Comprehensive Assessment of At Risk Mental States (CAARMS; 5 or 6 on severity and ≥ 4 on frequency for longer than one week; [59])

- A rating in the past year of ≥ 1 on the Psychotic Symptom Rating Scales (PSYRATS) hallucinations scale [60], corresponding to voices occurring at least once/week. The purpose of this is to ensure that participants with reasonably frequent hallucinations are included in the study, as experience of symptoms during Hybrid sessions will optimise the study's test of outcomes of interest.

Exclusion Criteria:

1. Documented history of head injury, seizures, or other significant neurological illness
2. Documented history of intellectual disability
3. Visual impairment precluding ability to view VR scenario

Participants will be reimbursed for their time.

Ethics Approval

Ethics approval for Hybrid has been obtained from The Royal Melbourne Health Human Research Ethics Committee (number 2022.116).

Ethical Considerations

Human subject ethics review approvals or exemptions

The current study has ethics approval via Melbourne Health Human Research Ethics Committee (MHHREC: HREC/76936/MH-2022) for research involving humans and access to patient medical records and information.

Informed consent

Participants (or their carer/guardian if aged under 18) must provide informed consent to participate in the Hybrid treatment. Participants are free to withdraw at any time, with the knowledge that doing so has no impact on their routine treatment.

Privacy and confidentiality

All data from the study is de-identified and only the study investigators have access to this information. This means that each participant's data will have a unique code which only the study team members will have access to.

Compensation details

Each participant will be reimbursed AUD50 per research interview visit as well as AUD20 per EEG recording session.

Data management and imputation strategy

To address attrition or missing values, we will code these as 'N/A'. The current follow-up protocol designed to maximise data collection, however, if the missing data is substantial, we will apply multiple imputation methods.

Key components of the Hybrid treatment model**Psychological Therapy**

The CBTp approach used in Hybrid relies on hierarchical exposure principles in order to trigger cognitive and affective reactions that occur while experiencing symptoms, i.e., 'hot cognitions' during symptom activation [56]. As outlined above, this approach may maximise the impact of psychological therapy, as has been observed in other disorders.

Virtual Reality

The VR paradigm that will be used to elicit AVH is inspired by Stinson and colleagues who used a real-world setting comprising computer generated characters of both sexes and several ethnicities and background sounds simulating the environment [57]. Our VR approach is based in the CBTp framework, beginning with developing a shared understanding (functional analysis) between the participant and therapist of the antecedents of hallucinatory episodes (e.g., presence of other people, lack of meaningful activity) and habitual responses to them (e.g., talking back to voices,

avoidance). The participant and therapist will then select a template scenario from pre-existing VR environments (e.g., supermarket, bedroom) developed in consultation with a small group of current and previous service users. Various aspects of the VR environment will be modified to personalise it for the antecedents the individual has identified and to create a hierarchy of symptom-provoking situations. These will include such aspects as: number of people present, proximity and gaze intensity of people, context (interpersonal interaction, indoors, outdoors, time of day or night), sounds, and presence or absence of 'safety strategies' to manage symptoms (e.g., mobile phone). For each participant, there will be five scaled variants of the personalised scene graded on a 0-100 scale of subjective distress (ranging between 0-20 (low), 21-40 (moderate), 41-60 (high), 61-80 (very high), 81-100 (severe)). There are a number of benefits of the VR approach: 1) It provides a controlled environment which can be stopped at any moment, which is not always feasible in real-life exposure settings; 2) It can be designed in a manner that is highly personalised to the individual, which may maximise therapeutic potential; 3) It is a treatment approach that may be particularly suited to young people, given its engaging and interactive nature 4) It is becoming increasingly feasible for translation into clinical services, given the dramatic reduction in cost of VR equipment and the fact that VR devices are becoming increasingly portable.

Neurofeedback

EEG will be used to provide real-time neurofeedback to participants while experiencing AVH.

EEG will be acquired using the Muse Headband 2 attached to the Oculus Rift S VR headset. The Muse Headband 2 acquires EEG via four electrodes placed over the prefrontal (forehead) and temporal-parietal areas of the brain (electrodes AF7, AF8, TP9, TP10 in the traditional 10-20 electrode system) and collects data at a sampling rate of 500 Hz (with a fifth reference electrode in the position of FPz). The Muse device has been shown to yield frequency based components of the

EEG signal comparable to the research-grade EEG system Biosemi Active Two with the additional benefit of live-streaming capabilities and neurofeedback integration [58]. In Hybrid, the neural target will be the neurophysiological activity associated with autonomic nervous system hyperarousal – specifically, power in the high beta range (18-30 Hz) as discussed above (see below for further details).

Intervention Design

Hybrid consists of a Preparation phase (face-to-face, approximately 2 weeks) followed by an Implementation phase (12 weekly face-to-face sessions based on previous VR study designs [31], [61], [62], [63]). Figure 1 shows a visual representation of the Hybrid intervention design and Figure 2 presents the schedule of assessments.

Figure 1. Hybrid Design

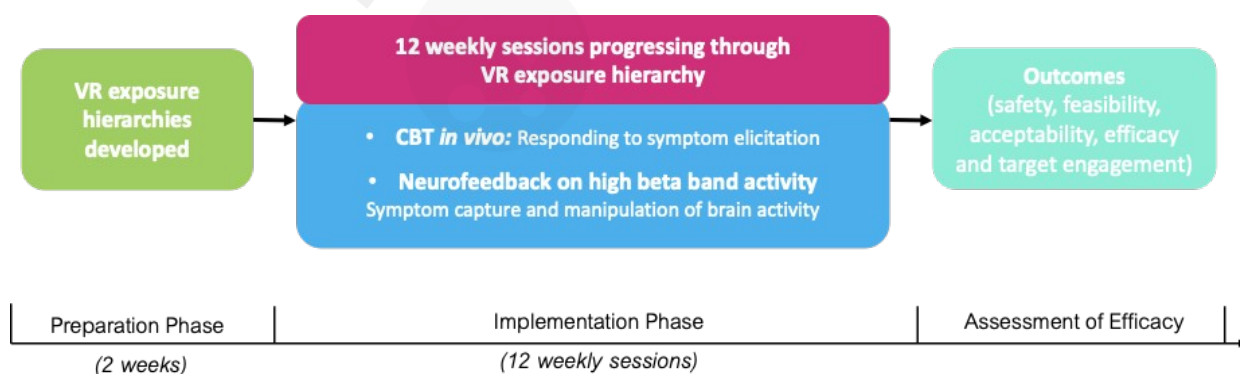
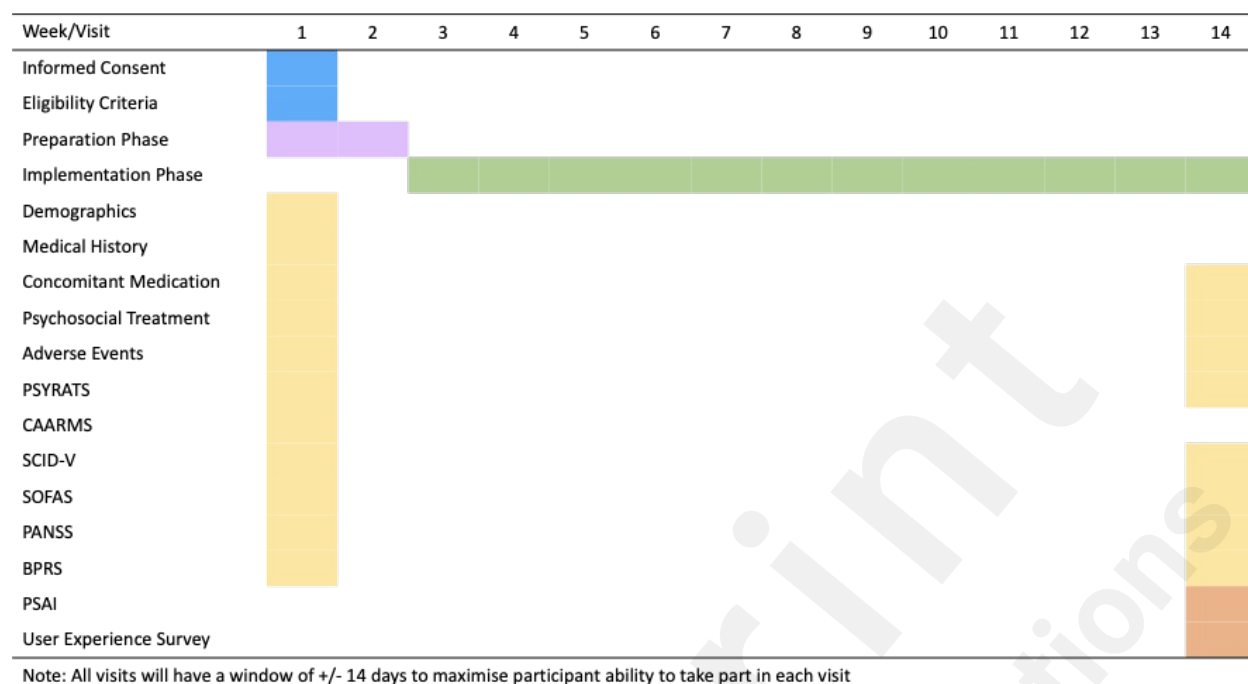


Figure 2 . Hybrid Schedule of Assessments

Note: PSYRATS = Psychotic Symptom Rating Scales, CAARMS = Comprehensive Assessment of At Risk Mental States, SCID-V = Structured Clinical Interview for the Diagnostic and Statistics Manual 5 (DSM-V), SOFAS = Social and Occupational Functioning Assessment Scale, PANSS = Positive and Negative Syndrome Scale, BPRS = Brief Psychiatric Rating Scale, PSAI = Pilot Study Assessment Instrument.

Preparation Phase (Weeks 1-2) Development of the VR Exposure Environment

The preparation of the VR exposure hierarchy will be embedded within a CBT framework by using an adaptation of the standard CBT for voices approach [64]. As mentioned above, the participant and therapist will develop a hierarchy of VR environments personalised for the antecedents identified as symptom-provoking. An example of a VR exposure hierarchy is provided in Figure 3. In developing this hierarchy, the participant will rate the degree of subjective immersion ('presence') they felt in the virtual environment using the Immersive Technology Centre-Sense of Presence Inventory (ITC-SOPI; [65], a widely used measure in this field. VR environments will only be used if they are rated as inspiring at least 'moderate presence', as this has been found to increase

therapeutic effectiveness [27]. Once the VR exposure hierarchies have been developed, participants will commence the Implementation Phase.

Figure 3. Hybrid VR exposure hierarchy example: Shopping centre template

#	Exposure Level	Subjective Distress	VR Environment
5	81 – 100	Maximum	Crowded shopping centre, critical gazes, indistinct noises
4	61 – 80	Very High	Crowded shopping centre, people passing by, looking occasionally
3	41 – 60	High	Interaction with cashier at checkout, people heard in the distance
2	21 – 40	Moderate	Walking in supermarket aisles, passing people, supermarket music playing
1	0 – 20	Low	Leaving shopping centre, in car park, nobody around



Note: Example of VR hierarchy exposure levels (left) based on the shopping centre template. The participant is exposed to the exposure environments via the VR headset while concurrently speaking with their therapist (CBTp) and receiving neurofeedback of high beta band activity via a visual display of a thermometer (right).

Implementation Phase (Week 3-14)

The Implementation Phase will consist of weekly sessions delivered over a 12-week period (+/- 14 days, see Figure 2) and consists of the following two components: (1) cognitive behaviour therapy in vivo (in response to the VR exposure) and (2) neurofeedback simultaneously presented to the participant via the VR device. The VR applications and sessions can only be accessed by the clinician and administered in-person. During these weekly sessions, the therapist will be able to view the VR scenario (via an external monitor) and the neurofeedback thermometer, hear the auditory input and provide guided assistance to the individual.

Cognitive behaviour therapy in vivo (in response to VR exposure)

The participant will start at the lowest level of their exposure hierarchy and progressively work up the hierarchy over the course of the sessions. The standard approach in exposure and response prevention interventions will be adopted, which is to achieve a reduction in subjective units of distress (SUD) to 30/100 before progressing to the next step in the hierarchy. While the participant is exposed to the symptom-eliciting VR scenario, they will engage in CBTp with their therapist (the participant will be wearing 'open backed' headphones, allowing them to hear the therapist as well as sounds coming from the VR environment). The CBT will be standard, manualised CBT for voices [64], [66], [67] dealing with the 'hot' cognition reactions elicited by the VR scenario. Key elements include reassurance regarding lack of threat, challenging appraisals of AVH (e.g., their perceived power, threat, or dominance; reducing submissive or reactive behaviours), actively responding to AVH, and developing a sense of control over AVH by attempting to delay or reduce their volume or distract from them with a variety of strategies (e.g., humming, visualisation). Sessions will last 30-45 minutes and will be stopped at any point if requested by the participant.

Neurofeedback simultaneously presented to participant via the VR device

While the participant is being exposed to the VR scenarios and engaging in CBT with a therapist, they will receive visual neurofeedback of electrophysiological activity (power) in the high beta band (18-30 Hz) range as measured via EEG. The neurofeedback will be provided to the participant via a single visual image of a thermometer in the corner of the VR scene (ranging from 0 to 100 'degrees'). The temperature of this thermometer is based on the individual's 'baseline' neural activity within the high beta band range which is measured at the start of each session prior to entering the VR scenario. The thermometer will increase in 'temperature' if high beta band power increases. The therapist will inform participants that this thermometer is a visual representation of

their current stress levels which will give them a real-time objective indication of how their brains are reacting to the Hybrid therapy. Participants will be instructed to keep their eyes open (so as to remain exposed to the VR scenarios) and to keep the thermometer below the 50-degree reading (i.e., ‘half way’; regulating their neural activity in the desired direction) as an additional motivating goal. In keeping with other neurofeedback studies [18], they will be instructed to devise their own strategy for modulating this neural activity but will be informed that they can discuss different strategies with their therapist. If the thermometer measurement is maintained in the lower half $\geq 50\%$ of the session time, participants will be made aware of the success of their efforts as positive reinforcement at the end of each of their weekly sessions.

Integration of multiple technologies in one innovative treatment package

Combining the treatment components in Hybrid will engage multiple treatment targets and possible pathogenic mechanisms (psychological, neurophysiological, neurobiological) simultaneously. There is also likely to be a synergistic effect through the interaction of the individual treatment components that will make the package more than the sum of its parts. To illustrate, the real-time neurofeedback provided to participants and therapists in response to the VR exposure exercises will feed into the content of the CBT therapy, because the participant and therapist will be able to discuss the direct impact the exposure exercises are having in an immediate, non-retrospective fashion. This preserves the benefits of dealing with ‘hot’ cognitive and affective reactions. In turn, the CBT will assist the young person in developing strategies for modulating their neural activity in response to the VR exposure exercises. Moreover, the neurofeedback will dynamically reinforce and boost the effect of CBT via participants being able to see in real time that the CBT is helping change their brain activity. This will create a salient and durable learning experience, contributing to a ‘real world’ transfer effect and motivate use of CBT skills in the absence of neurofeedback. This tri-directional impact of the treatment components – the way the

individual items work together - will amplify their individual contribution to therapeutic gain.

Measures

Primary outcomes

Feasibility, acceptability, safety and usability of the Hybrid model.

Feasibility and Acceptability

A Pilot Study Assessment Instrument (PSAI) developed by Orygen researchers based on the user experience approach will assess: 1) acceptability, 2) helpfulness, 3) engagement, and 4) perceived safety. Items are rated on a self-assessed 5-point Likert scale. Acceptability and feasibility will also be determined by assessing consent and completion rates; number of sessions attended; number of dropouts; completion rates of measures. A high rate of elicited AVH is required to facilitate “hot” cognitions so that the symptoms are targeted directly rather than through abstract self-reflection.

Safety

Safety will be assessed by recording Adverse Events or Serious Adverse Events.

Usability

Measured using the User Experience Survey, an 18-item questionnaire used for other Orygen VR studies and adapted specifically for this study to evaluate the experience and usability of the VR environments. This measure will be completed at the end of the Hybrid intervention (Week 14 of the study). At this point, participants will also complete a semi-structured interview about their experience of the intervention and suggestions for modifications to the treatment package.

Threshold

Our decision for moving on to efficacy trials will be based on the User Experience Survey which

utilises a 5-point Likert scale. We will require at least 70% of our participants rating 3 and above (which corresponds to Agree or Strongly Agree) that the intervention package was acceptable, feasible and safe.

Secondary outcomes

Treatment efficacy of Hybrid intervention and its engagement of treatment targets.

Auditory Verbal Hallucinations

The hallucinations scale of the PSYRATS will be used to assess change in AVH severity, frequency, and distress.

General Psychopathology

The Brief Psychiatric Rating Scale (BPRS; [68], Structured Clinical Interview for the DSM-V (SCID; [69], Social and Occupational Functioning Assessment Scale (SOFAS; [70], and the Positive and Negative Syndrome Scale (PANSS; [71] will be used to assess change in general psychopathology and symptoms.

Psychological Treatment Target

The highest level in exposure hierarchies achieved in each session. For each participant, the final target score of each of these measures will be the average over the 12 implementation phase sessions.

Neuropsychological Treatment Target

This will be operationalised as the difference (i.e., change) between the first half and the second half of the VR exposure exercises in average power of high beta band activity. A

mean score will be used for analysis and will be given by the average change ratings over the sessions attended.

Planned Analyses

As this study is a pilot study designed to generate initial data to guide future research, a power calculation has not been conducted. A sample size of 10 participants is consistent with similar proof-of-concept and pilot studies [44], [48].

Primary analyses

Means and standard deviations of acceptability, feasibility, safety and usability measures and percentage of participants showing different levels of ratings on The Pilot Study Assessment Instrument will be reported. Thematic analysis of the semi-structured interviews will also be conducted. The number of adverse events and serious adverse events will be reported and reviewed.

Secondary analyses

1. *Clinical efficacy*: Effect sizes, paired t-tests and Wilcoxon analysis of clinical rating changes pre and post intervention will be computed, which will inform future efficacy trials.

2. *Target scores*: Means, standard deviations and 95% confidence intervals of neural (average beta band power) and psychological (exposure hierarchy level) target scores will be reported. The magnitude of the changes in both scores will reflect the degree of target engagement achieved. A mean score will be used for analysis and will be given by the average change over the first half (mean of weeks 3 to 8) and second half (mean of weeks 9 to 14) of the sessions attended.

Whether greater engagement of neural and psychological targets is associated with greater change in clinical measures will also be explored. This finding would indicate a treatment mechanism that could be systematically tested in future studies.

RESULTS

As of February 2025, Hybrid has commenced (unblinded) recruitment activities from Orygen clinical services in Northwestern Melbourne, Australia. Seventy-five individuals have been approached and 64 have been pre-screened (41 deemed eligible, 15 ineligible and 8 declined or did not respond to contact attempts). Of the 41 individuals who were pre-screened as eligible, 9 have consented (16 declined and 8 did not respond) and 5 individuals were included in the study and completed their baseline assessments (however, we note that 1 individual was later deemed ineligible). The demographic information for these 5 participants are: ages 21 to 27 years ($M = 24$ yrs, $SD = 2$), 5 male sex at birth consisting of gender identity of two cisgender males, one transgender male, one non-binary and one questioning their gender. Of the four individuals who have commenced the Hybrid treatment, two are actively engaged in the program and two have withdrawn (one actively withdrew and one did not respond to contact attempts). We expect recruitment to conclude in July 2025 and for the results to be published in 2026.

DISCUSSION

Hybrid introduces a new treatment approach that integrates CBTp with VR and neurofeedback. This integration of treatment components may augment each individual element in such a way that they maximise the impact of each individual component. We anticipate that this will produce durable skill-building and a 'real world' transfer effect that motivates the use of Hybrid strategies in everyday life. In addition, individuals should see a reduction in AVH distress, severity and frequency as evidenced by symptom change scores at the end of the treatment package.

We predict that Hybrid will be successful in achieving this based on the fact that the treatment package will be: (1) Engaging and acceptable: Previous studies have shown that young people in the early stages of psychosis find neurophysiological assessments highly acceptable and the

neurofeedback and VR components of Hybrid leverage ‘gamification’ [72], [73] (i.e. using game design and mechanics to encourage active participation) in the treatment of mental disorders. (2) Easily implementable. Given the increasingly affordable and portable nature of the tools used in the Hybrid intervention (EEG and VR). 3. Empowering. With young people developing *self-directed control over their symptoms*, as opposed to being an ‘object’ of treatment, which is often how other treatment approaches, such as pharmacotherapy, are experienced [74]. As has been recognised [75] previously, neurofeedback can be a means of ‘taking back control’ of the brain by promoting strategies to manage symptoms that come ‘from the inside’ and can be used at any point in the course of everyday life. 4. Focused on individual symptoms rather than diagnostic categories. This is in keeping with the current trend in psychiatric research away from disorder-bound approaches towards transdiagnostic and symptom-based risk factors [76], [77]. Therefore, Hybrid could represent a breakthrough in clinical research for effective treatments for psychosis and, if successful, would significantly improve clinical outcomes in young people with AVH.

In terms of study limitations, we highlight that our use of the PANSS and SOFAS as measures of symptoms and functioning may be suboptimal for fine-grained assessment of symptomatology (such as for the negative symptoms) and function. We note that the main aim of the current study is to assess the feasibility and acceptability of the Hybrid treatment and we plan to include additional, more fine-grained measures in future studies. We chose to use the PANSS and SOFAS based on many previous studies in early psychosis populations using these measures and increasing our comparability to previous research [70, 71]. Secondly, our clinical assessments are structured to minimise the burden on the individual, therefore, certain features which may be of significance (e.g., past history of trauma or eating disorders) were not assessed, but may affect responsiveness to the Hybrid treatment. In subsequent trials, a more thorough assessment of psychopathology may be included to address this. Finally, by virtue of design, we cannot make inferences about any other

symptoms associated with psychosis (e.g., paranoia, disorganised thinking) as we were targeting AVH in these efficacy trials. Future studies could expand to target other psychotic symptoms.

Conclusion

The current pilot study aims to demonstrate the safety, feasibility and acceptability, as well as establish proof of concept for Hybrid treatment. This initial study will provide valuable information as to whether the Hybrid treatment protocol could be modified and whether moving on to efficacy trials is indicated.

Acknowledgments

We would like to thank Tamar Wong for his significant contribution to the VR component of the Hybrid study. We also extend our gratitude to Hybrid research participants.

Funding Statement

The study is funded by an NHMRC Investigator Grant (2026484) awarded to BN.

Data Availability Statement

Data is available from the researchers upon request.

Author Contributions

JS: Writing original draft, Project administration, Conceptualization, Supervision, Investigation. ER: Writing – review & editing. MA-J: Conceptualization. IB: Conceptualization, Writing – review & editing. LKB: Supervision. ID: Conceptualization, Methodology. CE: Project administration. SL:

Conceptualization. JAGL: Supervision. NT: Conceptualization. AT: Conceptualization. GW: Conceptualization. TJW: Conceptualization. SJW: Conceptualization. HPY: Formal analysis. BN: Conceptualization, Writing – review & editing, Funding acquisition. BM: Project administration, Writing – review & editing, Investigation.

Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder

AVH: Auditory Verbal Hallucinations

BPRS: Brief Psychiatric Rating Scale

CAARMS: Comprehensive Assessment of At-Risk Mental States

CBT: Cognitive Behavioral Therapy

CBTp: Cognitive Behavioral Therapy for Psychosis

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

EEG: Electroencephalography

EPPIC: Early Psychosis Prevention and Intervention Centre

ERP: Event-Related Potential

FEP: First-Episode Psychosis

fMRI: Functional Magnetic Resonance Imaging

rtfMRI: Real-Time Functional Magnetic Resonance Imaging

ITC-SOPI: Immersive Technology Centre-Sense of Presence Inventory

OCD: Obsessive-Compulsive Disorder

PANSS: Positive and Negative Syndrome Scale

PSAI: Posttraumatic Stress Disorder (PTSD) Symptom Assessment Inventory

PSYRATS: Psychotic Symptom Rating Scales

PTSD: Post-Traumatic Stress Disorder

SCID-V: Structured Clinical Interview for DSM-V

SOFAS: Social and Occupational Functioning Assessment Scale

VR: Virtual Reality



REFERENCE LIST

- [1] S. Pini, G. B. Cassano, L. Dell'Ossa, and X. F. Amador, "Insights into illness in schizophrenia, schizoaffective disorder, and mood disorders with psychotic features," *Am. J. Psychiatry*, vol. 158, pp. 122–125, 2001.
- [2] C. Jones *et al.*, "Cognitive behavioural therapy plus standard care versus standard care plus other psychosocial treatments for people with schizophrenia," *Cochrane Database Syst. Rev.*, vol. 11, p. Cd008712, 2018, doi: 10.1002/14651858.CD008712.pub3.
- [3] R. Langdon, M. Coltheart, P. B. Ward, and S. V. Catts, "Mentalising, executive planning and disengagement in schizophrenia," *Cognit. Neuropsychiatry*, vol. 6, no. 2, pp. 81–108, 2001, doi: 10.1080/13546800042000061.
- [4] M. Marshall and J. Rathbone, "Early intervention for psychosis," *Cochrane Database Syst. Rev.*, no. 6, 2011, doi: 10.1002/14651858.CD004718.pub3.
- [5] V. A. Morgan *et al.*, "Psychosis prevalence and physical, metabolic and cognitive co-morbidity: data from the second Australian national survey of psychosis," *Psychol. Med.*, vol. 44, no. 10, pp. 2163–2176, 2014, doi: 10.1017/s0033291713002973.
- [6] S. M. Hare *et al.*, "Disrupted network cross talk, hippocampal dysfunction and hallucinations in schizophrenia," *Schizophr. Res.*, vol. 199, pp. 226–234, 2018, doi: 10.1016/j.schres.2018.03.004.
- [7] N. Sartorius *et al.*, "Early manifestations and first-contact incidence of schizophrenia in different cultures. A preliminary report on the initial evaluation phase of the WHO Collaborative Study on determinants of outcome of severe mental disorders," *Psychol. Med.*, vol. 16, no. 4, pp. 909–928, 1986, doi: 10.1017/s0033291700011910.
- [8] D. B. Arciniegas, "Psychosis," *Contin. Minneap Minn*, vol. 21, no. 3 Behavioral Neurology and Neuropsychiatry, pp. 715–736, 2015, doi:

10.1212/01.CON.0000466662.89908.e7.

- [9] M. Penttilä, E. Jääskeläinen, N. Hirvonen, M. Isohanni, and J. Miettunen, “Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis,” *Br. J. Psychiatry*, vol. 205, no. 2, pp. 88–94, 2014, doi: 10.1192/bjp.bp.113.127753.
- [10] D. O. Perkins, H. Gu, K. Boteva, and J. A. Lieberman, “Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis,” *Am. J. Psychiatry*, vol. 162, no. 10, pp. 1785–1804, 2005, doi: 10.1176/appi.ajp.162.10.1785.
- [11] Early Psychosis Guidelines Writing Group and EPPIC National Support Program, “Australian Clinical Guidelines for Early Psychosis, 2nd edition update,.” Orygen, The National Centre of Excellence in Youth Mental Health, Melbourne., 2016.
- [12] G. A. Keepers *et al.*, “The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia,” *Am. J. Psychiatry*, vol. 177, no. 9, pp. 868–872, 2020, doi: 10.1176/appi.ajp.2020.177901.
- [13] P. McGorry, E. Killackey, T. Lambert, M. Lambert, H. Jackson, and D. Codyre, “Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders,” *Aust. N. Z. J. Psychiatry*, vol. 39, no. 1–2, pp. 1–30, 2005.
- [14] M. T. Samara, A. Nikolakopoulou, G. Salanti, and S. Leucht, “How many patients with schizophrenia do not respond to antipsychotic drugs in the short term? An analysis based on individual patient data from randomized controlled trials,” *Schizophr. Bull.*, vol. 45, no. 3, pp. 639–646, 2019, doi: 10.1093/schbul/sby095.
- [15] G. Haddock, S. Lewis, R. Bentall, G. Dunn, R. Drake, and N. Tarrier, “Influence of age on outcome of psychological treatments in first-episode psychosis,” *Br. J. Psychiatry*,

- vol. 188, no. 3, pp. 250–254, 2006, doi: 10.1192/bjp.188.3.250.
- [16] J. P. Roiser and B. J. Sahakian, “Hot and cold cognition in depression,” *CNS Spectr.*, vol. 18, no. 3, pp. 139–149, 2013, doi: 10.1017/S1092852913000072.
- [17] A. Langman-Levy *et al.*, “Adapting cognitive behavioural therapy for adolescents with psychosis: insights from the Managing Adolescent first episode in psychosis study (MAPS),” *Psychosis*, vol. 15, no. 1, pp. 28–43, 2023, doi: 10.1080/17522439.2021.2001561.
- [18] R. Jardri, A. Pouchet, D. Pins, and P. Thomas, “Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis,” *Am. J. Psychiatry*, vol. 168, no. 1, pp. 73–81, 2011, doi: 10.1176/appi.ajp.2010.09101522.
- [19] M. L. Whittal, D. S. Thordarson, and P. D. McLean, “Treatment of obsessive–compulsive disorder: Cognitive behavior therapy vs. exposure and response prevention,” *Behav. Res. Ther.*, vol. 43, no. 12, pp. 1559–1576, Dec. 2005, doi: 10.1016/j.brat.2004.11.012.
- [20] E. B. Foa and C. P. McLean, “The Efficacy of Exposure Therapy for Anxiety-Related Disorders and Its Underlying Mechanisms: The Case of OCD and PTSD,” *Annu. Rev. Clin. Psychol.*, vol. 12, pp. 1–28, 2016, doi: 10.1146/annurev-clinpsy-021815-093533.
- [21] C. J. Bohil, B. Alicea, and F. A. Biocca, “Virtual reality in neuroscience research and therapy,” *Nat Rev Neurosci*, vol. 12, no. 12, pp. 752–762, 2011, doi: 10.1038/nrn3122.
- [22] I. Chard and N. van Zalk, “Virtual Reality Exposure Therapy for Treating Social Anxiety: A Scoping Review of Treatment Designs and Adaptation to Stuttering,” *Front. Digit. Health*, vol. 4, p. 842460, Feb. 2022, doi: 10.3389/fdgth.2022.842460.
- [23] O. D. Kothgassner, A. Goreis, J. X. Kafka, R. L. Van Eickels, P. L. Plener, and A. Felnhöfer, “Virtual reality exposure therapy for posttraumatic stress disorder (PTSD): a meta-analysis,” *Eur. J. Psychotraumatology*, vol. 10, no. 1, p. 1654782, 2019, doi:

10.1080/20008198.2019.1654782.

- [24] J. L. Maples-Keller, C. Yasinski, N. Manjin, and B. O. Rothbaum, "Virtual Reality-Enhanced Extinction of Phobias and Post-Traumatic Stress," *Neurother. J. Am. Soc. Exp. Neurother.*, vol. 14, no. 3, pp. 554–563, Jul. 2017, doi: 10.1007/s13311-017-0534-y.
- [25] D. Freeman, "Studying and Treating Schizophrenia Using Virtual Reality: A New Paradigm," *Schizophr. Bull.*, vol. 34, no. 4, pp. 605–610, Jul. 2008, doi: 10.1093/schbul/sbn020.
- [26] L. R. Valmaggia, L. Latif, M. J. Kempton, and M. Rus-Calafell, "Virtual reality in the psychological treatment for mental health problems: An systematic review of recent evidence," *Psychiatry Res.*, vol. 236, pp. 189–195, Feb. 2016, doi: 10.1016/j.psychres.2016.01.015.
- [27] B. O. Rothbaum, A. A. Rizzo, and J. Difede, "Virtual reality exposure therapy for combat-related posttraumatic stress disorder," *Ann. N. Y. Acad. Sci.*, vol. 1208, pp. 126–132, 2010, doi: 10.1111/j.1749-6632.2010.05691.x.
- [28] M. B. Powers and P. M. Emmelkamp, "Virtual reality exposure therapy for anxiety disorders: A meta-analysis," *J. Anxiety Disord.*, vol. 22, no. 3, pp. 561–569, 2008, doi: 10.1016/j.janxdis.2007.04.006.
- [29] M. Rus-Calafell, P. Garety, E. Sason, T. Craig, and L. Valmaggia, "Virtual reality in the assessment and treatment of psychosis: A systematic review of its utility, acceptability and effectiveness," *Psychol. Med.*, vol. 48, no. 3, pp. 362–391, 2018, doi: 10.1017/S0033291717001945.
- [30] T. K. Craig *et al.*, "AVATAR therapy for auditory verbal hallucinations in people with psychosis: a single-blind, randomised controlled trial," *Lancet Psychiatry*, vol. 5, no. 1, pp. 31–40, Jan. 2018, doi: 10.1016/S2215-0366(17)30427-3.

- [31] L. Dellazizzo, S. Potvin, K. Phraxayavong, and A. Dumais, “One-year randomized trial comparing virtual reality-assisted therapy to cognitive–behavioral therapy for patients with treatment-resistant schizophrenia,” *NPJ Schizophr.*, vol. 7, p. 9, Feb. 2021, doi: 10.1038/s41537-021-00139-2.
- [32] L. Smith *et al.*, “The CHALLENGE trial: the effects of a virtual reality-assisted exposure therapy for persistent auditory hallucinations versus supportive counselling in people with psychosis: study protocol for a randomised clinical trial,” *Trials*, vol. 23, no. 1, p. 773, 2022, doi: 10.1186/s13063-022-06683-1.
- [33] J. Leff, G. Williams, M. A. Huckvale, M. Arbutnot, and A. P. Leff, “Computer-assisted therapy for medication-resistant auditory hallucinations: Proof-of-concept study,” *Br. J. Psychiatry*, vol. 202, no. 6, pp. 428–433, 2013, doi: 10.1192/bjp.bp.112.124883.
- [34] G. Aali, T. Kariotis, and F. Shokrane, “Avatar Therapy for people with schizophrenia or related disorders,” *Cochrane Database Syst. Rev.*, no. 5, 2020, doi: 10.1002/14651858.CD011898.pub2.
- [35] E. Dudek and D. Dodell-Feder, “The efficacy of real-time functional magnetic resonance imaging neurofeedback for psychiatric illness: A meta-analysis of brain and behavioral outcomes,” *Neurosci. Biobehav. Rev.*, vol. 121, pp. 291–306, Feb. 2021, doi: 10.1016/j.neubiorev.2020.12.020.
- [36] V. Gandara, J. A. Pineda, I.-W. Shu, and F. Singh, “A Systematic Review of the Potential Use of Neurofeedback in Patients With Schizophrenia,” *Schizophr. Bull. Open*, vol. 1, no. 1, p. sgaa005, Jan. 2020, doi: 10.1093/schizbullopen/sgaa005.
- [37] S. Enriquez-Geppert, R. J. Huster, and C. S. Herrmann, “EEG-Neurofeedback as a Tool to Modulate Cognition and Behavior: A Review Tutorial,” *Front. Hum. Neurosci.*, vol. 11, p. 51, Feb. 2017, doi: 10.3389/fnhum.2017.00051.
- [38] A. W. Keizer, M. Verschoor, R. S. Verment, and B. Hommel, “The effect of gamma

- enhancing neurofeedback on the control of feature bindings and intelligence measures,” *Int. J. Psychophysiol.*, vol. 75, no. 1, pp. 25–32, 2010, doi: 10.1016/j.ijpsycho.2009.10.011.
- [39] T. Ros, M. A. Munneke, D. Ruge, J. H. Gruzelier, and J. C. Rothwell, “Endogenous control of waking brain rhythms induces neuroplasticity in humans,” *Eur. J. Neurosci.*, vol. 31, no. 4, pp. 770–778, 2010, doi: 10.1111/j.1460-9568.2010.07100.x.
- [40] D. Vernon *et al.*, “The effect of training distinct neurofeedback protocols on aspects of cognitive performance,” *Int. J. Psychophysiol.*, vol. 47, no. 1, pp. 75–85, 2003, doi: 10.1016/s0167-8760(02)00091-0.
- [41] G. Rota *et al.*, “Self-regulation of regional cortical activity using real-time fMRI: the right inferior frontal gyrus and linguistic processing,” *Hum. Brain Mapp.*, vol. 30, no. 5, pp. 1605–1614, 2009, doi: 10.1002/hbm.20621.
- [42] M. Arns and U. Strehl, “Evidence for efficacy of neurofeedback in ADHD?,” *Am J Psychiatry*, vol. 170, no. 7, pp. 799–800, 2013, doi: 10.1176/appi.ajp.2013.13020208.
- [43] D. E. Linden *et al.*, “Real-time self-regulation of emotion networks in patients with depression,” *PLoS ONE*, vol. 7, no. 6, p. e38115, 2012, doi: 10.1371/journal.pone.0038115.
- [44] M. Gapen, B. A. van der Kolk, E. Hamlin, L. Hirshberg, M. Suvak, and J. Spinazzola, “A Pilot Study of Neurofeedback for Chronic PTSD,” *Appl. Psychophysiol. Biofeedback*, vol. 41, no. 3, pp. 251–261, 2016, doi: 10.1007/s10484-015-9326-5.
- [45] D. Scheinost *et al.*, “Orbitofrontal cortex neurofeedback produces lasting changes in contamination anxiety and resting-state connectivity,” *Transl. Psychiatry*, vol. 3, no. 4, p. e250, 2013, doi: 10.1038/tp.2013.24.
- [46] G. Tan *et al.*, “Meta-analysis of EEG biofeedback in treating epilepsy,” *Clin. EEG Neurosci.*, vol. 40, no. 3, pp. 173–179, 2009, doi: 10.1177/155005940904000310.

- [47] N. D. Orlov *et al.*, “Real-time fMRI neurofeedback to down-regulate superior temporal gyrus activity in patients with schizophrenia and auditory hallucinations: a proof-of-concept study,” *Transl. Psychiatry*, vol. 8, no. 1, p. 46, 2018, doi: 10.1038/s41398-017-0067-5.
- [48] W. Nan, F. Wan, L. Chang, S. H. Pun, M. I. Vai, and A. Rosa, “An Exploratory Study of Intensive Neurofeedback Training for Schizophrenia,” *Behav. Neurol.*, vol. 2017, p. 6914216, 2017, doi: 10.1155/2017/6914216.
- [49] M. X. Cohen, “Where does EEG come from and what does it mean?,” *Trends Neurosci.*, vol. 40, no. 4, pp. 208–218, 2017, doi: 10.1016/j.tins.2017.02.004.
- [50] N. K. Logothetis and J. Pfeuffer, “On the nature of the BOLD fMRI contrast mechanism,” *Magn. Reson. Imaging*, vol. 22, no. 10, pp. 1517–1531, 2004, doi: 10.1016/j.mri.2004.10.018.
- [51] A. Perrottelli, G. M. Giordano, F. Brando, L. Giuliani, and A. Mucci, “EEG-Based Measures in At-Risk Mental State and Early Stages of Schizophrenia: A Systematic Review,” *Front. Psychiatry*, vol. 12, p. 653642, 2021, doi: 10.3389/fpsyt.2021.653642.
- [52] P. Delespaul, M. deVries, and J. van Os, “Determinants of occurrence and recovery from hallucinations in daily life,” *Soc. Psychiatry Psychiatr. Epidemiol.*, vol. 37, no. 3, pp. 97–104, Mar. 2002, doi: 10.1007/s001270200000.
- [53] M. Ratcliffe and S. Wilkinson, “How anxiety induces verbal hallucinations,” *Conscious. Cogn.*, vol. 39, pp. 48–58, 2016, doi: 10.1016/j.concog.2015.11.009.
- [54] A. S. Bolea, “Neurofeedback Treatment of Chronic Inpatient Schizophrenia,” *J. Neurother.*, vol. 14, pp. 47–54, 2010, doi: 10.1080/10874200903543971.
- [55] T. Surmeli, A. Ertem, E. Eralp, and I. H. Kos, “Schizophrenia and the efficacy of qEEG-guided neurofeedback treatment: a clinical case series,” *Clin. EEG Neurosci.*, vol. 43, no. 2, pp. 133–144, 2012, doi: 10.1177/1550059411429531.

- [56] P. O'Brien and L. Johns, "A graded exposure intervention for distressing visual hallucinations in schizophrenia," *Behav. Cogn. Psychother.*, vol. 41, no. 4, pp. 495–499, 2013, doi: 10.1017/s1352465812001130.
- [57] K. Stinson, L. R. Valmaggia, A. Antley, M. Slater, and D. Freeman, "Cognitive triggers of auditory hallucinations: an experimental investigation," *J. Behav. Ther. Exp. Psychiatry*, vol. 41, no. 3, pp. 179–184, 2010, doi: 10.1016/j.jbtep.2009.12.003.
- [58] C. Cannard, H. Wahbeh, and A. Delorme, "Validating the wearable MUSE headset for EEG spectral analysis and Frontal Alpha Asymmetry." Accessed: Sep. 05, 2024. [Online]. Available: <https://ieeexplore.ieee.org/document/9669778>
- [59] A. R. Yung *et al.*, "Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States," *Aust. N. Z. J. Psychiatry*, vol. 39, no. 11–12, pp. 964–971, 2005, doi: 10.1080/j.1440-1614.2005.01714.x.
- [60] R. Drake, G. Haddock, N. Tarrier, R. Bentall, and S. Lewis, "The Psychotic Symptom Rating Scales (PSYRATS): Their usefulness and properties in first episode psychosis," *Schizophr. Res.*, vol. 89, no. 1, pp. 119–122, Jan. 2007, doi: 10.1016/j.schres.2006.04.024.
- [61] R. M. C. A. Pot-Kolder *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*, vol. 5, no. 3, pp. 217–226, Mar. 2018, doi: 10.1016/S2215-0366(18)30053-1.
- [62] N. Liang *et al.*, "Visual P300 as a neurophysiological correlate of symptomatic improvement by a virtual reality-based computer AT system in patients with auditory verbal hallucinations: A Pilot study," *J. Psychiatr. Res.*, vol. 151, pp. 261–271, Jul. 2022, doi: 10.1016/j.jpsychires.2022.04.027.
- [63] O. Percie du Sert *et al.*, "Virtual reality therapy for refractory auditory verbal

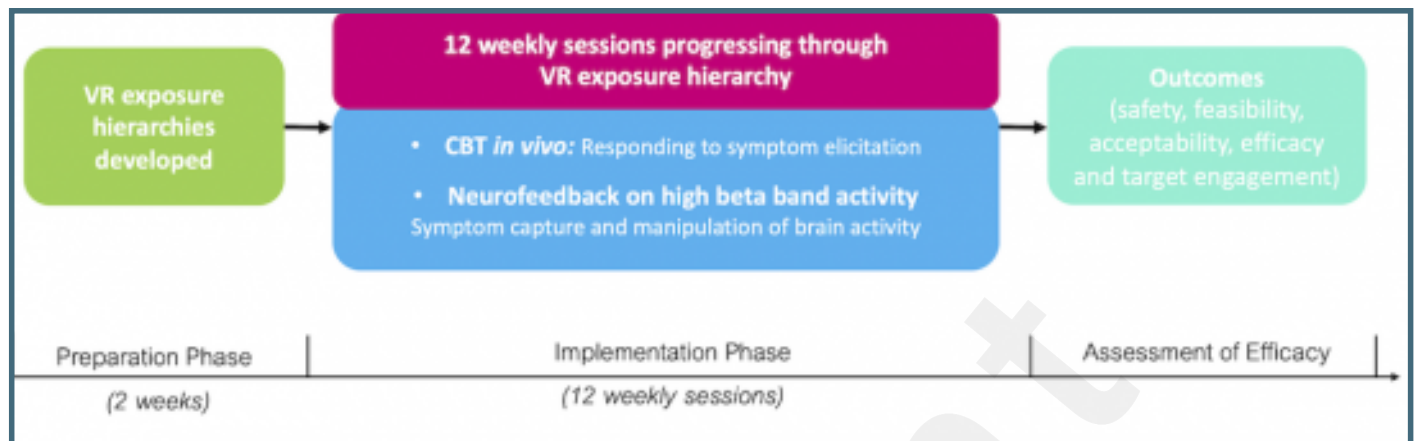
- hallucinations in schizophrenia: A pilot clinical trial,” *Schizophr. Res.*, vol. 197, pp. 176–181, Jul. 2018, doi: 10.1016/j.schres.2018.02.031.
- [64] N. Thomas, S. Rossell, J. Farhall, F. Shawyer, and D. Castle, “Cognitive behavioural therapy for auditory hallucinations: effectiveness and predictors of outcome in a specialist clinic,” *Behav. Cogn. Psychother.*, vol. 39, no. 2, pp. 129–138, 2011, doi: 10.1017/S1352465810000548.
- [65] J. Lessiter, J. Freeman, E. Keogh, and J. Davidoff, “A Cross-Media Presence Questionnaire: The ITC-Sense of Presence Inventory,” *Presence*, vol. 10, pp. 282–297, 2001, doi: 10.1162/105474601300343612.
- [66] M. Birchwood, M. Michail, A. Meaden, and others, “Cognitive behaviour therapy to prevent harmful compliance with command hallucinations (COMMAND): a randomised controlled trial,” *Lancet Psychiatry*, vol. 1, no. 1, pp. 23–33, 2014, doi: 10.1016/S2215-0366(14)70247-0.
- [67] N. Thomas *et al.*, “Psychological therapies for auditory hallucinations (voices): current status and key directions for future research,” *Schizophr. Bull.*, vol. 40, no. Suppl 4, pp. S202–S212, 2014, doi: 10.1093/schbul/sbu037.
- [68] J. Overall and D. Gorham, “The Brief Psychiatric Rating Scale.” Accessed: Sep. 05, 2024. [Online]. Available: <https://journals.sagepub.com/doi/10.2466/pr0.1962.10.3.799>
- [69] J. Williams, R. Karg, and R. Spitzer, *Structured Clinical Interview for DSM-5, Clinician Version*. 2016.
- [70] B. Rybarczyk, “Social and Occupational Functioning Assessment Scale (SOFAS),” in *Encyclopedia of Clinical Neuropsychology*, J. S. Kreutzer, J. DeLuca, and B. Caplan, Eds., New York, NY: Springer, 2011, pp. 2313–2313. doi: 10.1007/978-0-387-79948-3_428.
- [71] S. R. Kay, A. Fiszbein, and L. A. Opler, “The positive and negative syndrome scale

- (PANSS) for schizophrenia,” *Schizophr. Bull.*, vol. 13, no. 2, pp. 261–276, 1987, doi: 10.1093/schbul/13.2.261.
- [72] T. Von Bargen, C. Zientz, and R. Haux, “Gamification for mHealth - A Review of Playful Mobile Healthcare,” *Stud. Health Technol. Inform.*, vol. 202, pp. 225–228, 2014.
- [73] M. D. Lee, “Gamification and the Psychology of Game Design in Transforming Mental Health Care,” *J. Am. Psychiatr. Nurses Assoc.*, vol. 22, no. 2, pp. 134–136, 2016, doi: 10.1177/1078390316636857.
- [74] B. J. Deacon, “The biomedical model of mental disorder: a critical analysis of its validity, utility, and effects on psychotherapy research,” *Clin. Psychol. Rev.*, vol. 33, no. 7, pp. 846–861, Nov. 2013, doi: 10.1016/j.cpr.2012.09.007.
- [75] S. McCarthy-Jones, T. Trauer, A. Mackinnon, E. Sims, N. Thomas, and D. L. Copolov, “A New Phenomenological Survey of Auditory Hallucinations: Evidence for Subtypes and Implications for Theory and Practice,” *Schizophr. Bull.*, vol. 40, no. 1, pp. 231–235, Jan. 2014, doi: 10.1093/schbul/sbs156.
- [76] B. Nelson *et al.*, “Improving treatments for psychotic disorders: beyond cognitive behaviour therapy for psychosis,” *Psychosis*, vol. 13, no. 1, pp. 78–84, 2021, doi: 10.1080/17522439.2020.1742200.
- [77] J. Spark *et al.*, “Distinguishing schizophrenia spectrum from non-spectrum disorders among young patients with first episode psychosis and at high clinical risk: The role of basic self-disturbance and neurocognition,” *Schizophr. Res.*, vol. 228, pp. 19–28, Feb. 2021, doi: 10.1016/j.schres.2020.11.061.

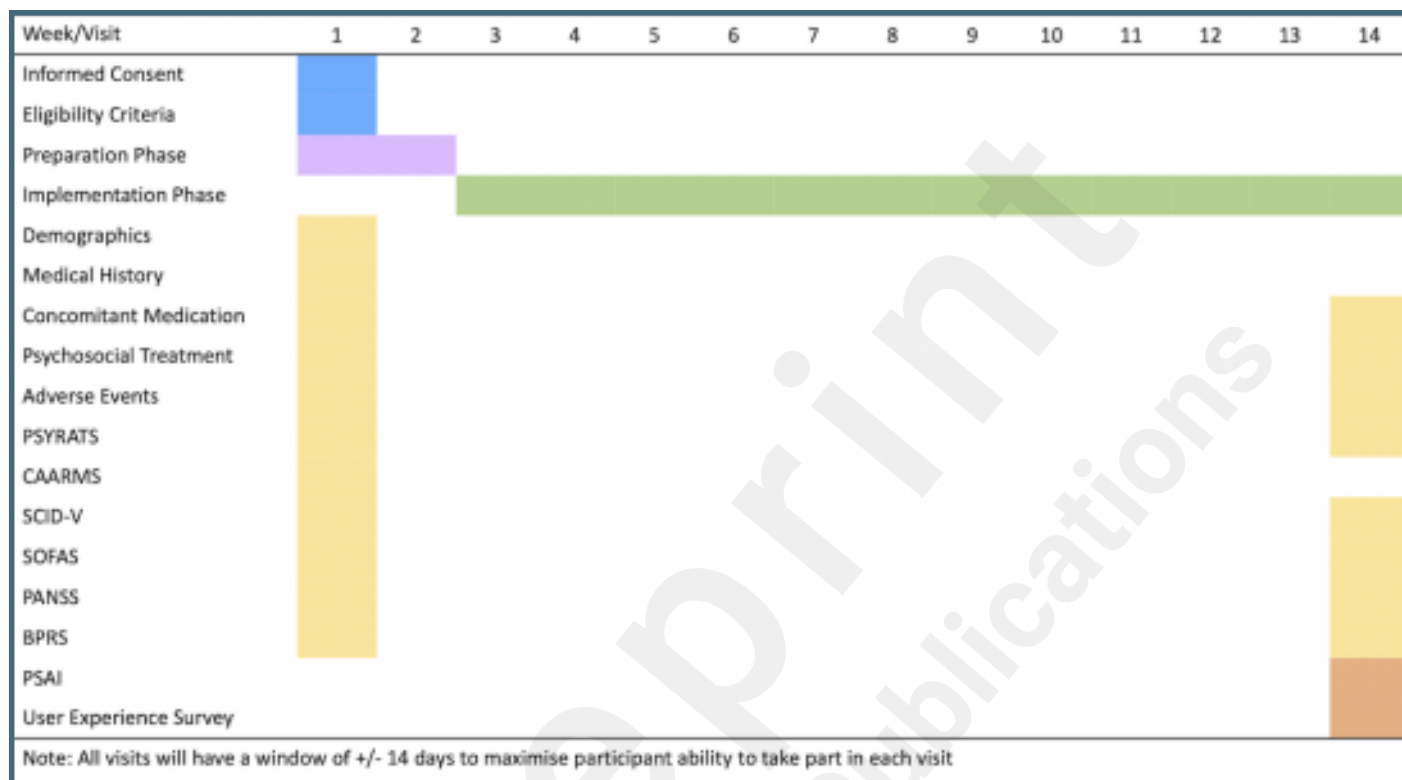
Supplementary Files

Figures

Hybrid Design.



Hybrid Schedule of Assessments. Note: PSYRATS = Psychotic Symptom Rating Scales, CAARMS = Comprehensive Assessment of At Risk Mental States, SCID-V = Structured Clinical Interview for the Diagnostic and Statistics Manual 5 (DSM-V), SOFAS = Social and Occupational Functioning Assessment Scale, PANSS = Positive and Negative Syndrome Scale, BPRS = Brief Psychiatric Rating Scale, PSAI = Pilot Study Assessment Instrument.



Hybrid VR exposure hierarchy example: Shopping centre template Note: Example of VR hierarchy exposure levels (left) based on the shopping centre template. The participant is exposed to the exposure environments via the VR headset while concurrently speaking with their therapist (CBTp) and receiving neurofeedback of high beta band activity via a visual display of a thermometer (right).

#	Exposure Level	Subjective Distress	VR Environment
5	81 – 100	Maximum	Crowded shopping centre, critical gazes, indistinct noises
4	61 – 80	Very High	Crowded shopping centre, people passing by, looking occasionally
3	41 – 60	High	Interaction with cashier at checkout, people heard in the distance
2	21 – 40	Moderate	Walking in supermarket aisles, passing people, supermarket music playing
1	0 – 20	Low	Leaving shopping centre, in car park, nobody around



CONSORT (or other) checklists

CONSORT checklist.

URL: <http://asset.jmir.pub/assets/35601e8b51be42f89e59ee937e091cf2.pdf>

