IDENTIFYING ELECTROENCEPHALOGRAPHY (EEG) BIOMARKERS IN INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS IN AN INTERNATIONAL MULTI-SITE STUDY

STUDY PROTOCOL

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ABSTRACT

Background: The clinical high-risk for psychosis (CHR-P) paradigm was introduced to detect individuals at risk of developing psychosis and to establish preventive strategies. While current prediction of outcomes in the CHR-P state is based mostly on the clinical assessment of presenting features, several emerging biomarkers have been investigated in an attempt to stratify CHR-P individuals according to their individual trajectories and refine the diagnostic process. However, heterogeneity across subgroups is a key challenge that has limited the impact of the CHR-P prediction strategies, as the clinical validity of the current research is limited by a lack of external validation across sites and modalities. Despite these challenges, electroencephalography (EEG) biomarkers have been studied in this field and evidence suggests that EEG used in combination with clinical assessments may be a key measure for improving diagnostic and prognostic accuracy in the CHR-P state. The PSYSCAN EEG study is an international, multi-site, multimodal longitudinal project that aims to advance knowledge in this field.

Method: Participants at 6 international sites take part in an EEG protocol including EEG recording, cognitive and clinical assessments. CHR-P participants will be followed up after two years and subcategorised depending on their illness progression regarding transition to psychosis. Differences will be sought between CHR-P individuals and healthy controls and between CHR-P individuals who transition and those who do not transition to psychosis using data driven computational analyses.

Discussion: This protocol addresses the challenges faced by previous studies of this kind to enable valid identification of predictive EEG biomarkers which will be combined with other biomarkers across sites to develop a prognostic tool in CHR-P. The PSYSCAN EEG study aims to pave the way for incorporating EEG biomarkers in the assessment of CHR-P individuals, to refine the diagnostic process and help to stratify CHR-P subjects according to risk of transition. This may improve our understanding of the CHR-P state and therefore aid the development of more personalised treatment strategies.

1- INTRODUCTION

Clinical high-risk for psychosis (CHR-P) designation (Fusar-Poli, 2017) has the goal of altering the course of psychotic disorders through indicated prevention strategies (Fusar-Poli et al., 2017d). CHR-P individuals accumulate several risk factors for psychotic disorders (Fusar-Poli et al., 2017c; Oliver et al., 2019) and the majority display attenuated psychotic symptoms (Fusar-Poli et al., 2017b), in addition to a decline in functioning (Fusar-Poli et al., 2013) and help-seeking behaviour (Falkenberg et al., 2015). Because of these features, their risk of developing a psychotic disorder within two years is 22% (Fusar-Poli et al., 2020), although this rate varies across different CHR-P subgroups (Fusar-Poli et al., 2016a; Fusar-Poli et al., 2016b; Fusar-Poli et al., 2017a). Despite these achievements, some key challenges have limited the impact of the CHR-P prediction strategy. Firstly, we cannot detect all individuals who will later develop psychosis (Fusar-Poli et al., 2019) or formulate a prediction of their outcomes beyond group-level prognostication (Fusar-Poli et al., 2018). Secondly, current prediction of outcomes is generally based on the clinical assessment of presenting features and may not be reliable (Fusar-Poli et al., 2015). Thirdly, prediction does match for the underlying neurobiological processes that trigger the onset of psychosis (Millan et al., 2016). To overcome these barriers, over the recent decade, extensive research has investigated the underlying neurobiological abnormalities in CHR-P individuals (Fusar-Poli et al., 2020; Schmidt et al., 2017).

Several emerging neuroimaging biomarkers have been investigated to stratify CHR-P individuals according to their individual trajectories (Reilly et al., 2018) and may therefore be suitable as diagnostic markers to forecast the probability of a certain condition to be present and prognostic markers to forecast the probability of a certain outcome to occur (Schmidt et al., 2017).

Although electrophysiological (Lavoie et al., 2012), neuro-anatomical (Anticevic et al., 2014; Koutsouleris et al., 2009) and blood markers (Cannon et al., 2015) have been considered as predictors in this group, their clinical validity is limited by a lack of external validation across sites and modalities, despite attempts to do so. Due to this lack of validation, their use has been limited in precision psychiatry compared to other predictors such as clinical or socio-demographic predictors (Salazar de Pablo et al., 2020).

Among these biomarkers, electroencephalography (EEG) used in combination with clinical assessments (Nieman et al., 2014) has been investigated with promising results (Mathalon and Sohal, 2015). EEG is an investigational technique that has excellent temporal resolution, directly measures electrical neuronal activity, is relatively inexpensive and easy to implement without major training, and is therefore an ideal modality for use in clinical practice. More specifically, reduced gamma band responses, at around 40Hz, are a robust EEG alteration in established schizophrenia (Thuné et al., 2016), and a proposed mechanism exists linking dysfunction in such high frequency neural oscillations (>20Hz) with psychotic symptoms (McNally and McCarley, 2016). According to previous research, gamma band activity may also have predictive properties to inform individual risk assessment in CHR-P subjects (Tada et al., 2016). In addition to such high frequency oscillations, theta (4-7Hz) and delta (1-4Hz) are also promising EEG biomarkers for CHR-P individuals, since resting state theta and delta are increased in chronic psychosis (Ranlund et al., 2014). Increased frontal theta has been reported in CHR-P individuals (Sollychin et al., 2019), and theta and delta alterations may also have predictive properties in this population (Jhung et al., 2013; van Tricht et al., 2014).

PSYSCAN is an international, multi-site, multimodal and longitudinal project which uses machine learning techniques to analyse imaging, clinical, cognitive, and biological data to facilitate the prediction of psychosis onset and outcome (Tognin et al., 2020). To test the potential utility of gamma band oscillations as diagnostic and prognostic biomarkers in CHR-P individuals, while at the same time controlling for the current limitations of research, large scale studies including CHR-P and healthy controls are required and this is one of the PSYSCAN project´s core objectives. The current manuscript describes the PSYSCAN EEG protocol, which investigates oscillatory and event related activity in CHR-P individuals. It is hoped that this study will pave the way for incorporating EEG biomarkers in the assessment of CHR-P individuals, to refine the diagnosis process and improve the prognosis of mental health outcomes.

2- METHODS

2.1- Design

The study design is longitudinal and includes two independent groups consisting of CHR-P individuals and healthy controls. CHR-P participants will be followed up after two years to assess illness outcome and be further subcategorised. Assuming that approximately 22% of the CHR-P group will develop psychosis over two years (Fusar-Poli et al., 2020), this will yield subgroups who do or do not develop psychosis.

The participating sites are: London, Amsterdam, Maastricht, Melbourne, Seoul, and Toronto (Figure 1). All participants will undergo EEG data acquisition in addition to PSYSCAN-related measures such as neuroimaging, biological, cognitive and clinical assessments of symptomatology (see (Tognin et al., 2020) for PSYSCAN-related procedures). Differences will be sought between CHR-P individuals and healthy controls and between CHR-P individuals who transition and those who do not transition to psychosis using data driven computational analyses.

2.2- EEG Data

2.2.1- EEG Data Acquisition

The different sites have a range of EEG amplifiers and recording facilities. At the London site, a Compumedics Neuroscan SYNAMPS2 amplifier is used and a Brain Products EEG cap. EEG recording take place in an electrically shielded EEG laboratory at the NIHR and Wellcome Trust funded King's Clinical Research Facility, King's College Hospital. The minimum sampling rate required for all sites in the study is 500Hz (0.05Hz-100Hz filter settings). However, at sites with a suitable EEG amplifier, a fast sampling rate of 5kHz (with 0.05Hz – 1 kHz filter settings) is used to allow for advanced artefact correction for gamma band analyses (See: (Nottage and Horder, 2015). The left mastoid (M1) serves as the online reference channel, a right mastoid (M2) and the nose electrode is included for offline re-referencing, and the ground is at AFz. Electrodes are also placed outer to the eyes to capture vertical and horizontal electrooculograms (VEOU, VEOL, HEOL and HEOR). All sites record a minimum of 32 EEG channels according to the 10-20 system. However, sites with the technological capability utilise extra electrodes from the 10-10 system and include additional inferior temporal (FT9 & FT10 and Left and Right Cheek), nasion, and cerebellar electrodes (PO09 & PO010) as well as an externally placed electrode to record the powerline noise.

2.2.2- Computerised Tasks Included in the PSYSCAN EEG Study

- **Auditory Steady State Response (ASSR)**: The ASSR 40Hz condition has previously reported a diminished gamma band amplitude and is reported to predict individual risk assessment in CHR-P subjects (Tada et al., 2016). Subjects listen passively to a series of 20Hz, 36Hz, 40Hz and 44Hz click trains through a pair of earphones. The computer screen is switched off to avoid unnecessary screen refresh artefacts and participants are instructed to close their eyes for the duration of the task. The click trains are 750ms long, with 600ms inter-stimulus intervals and there are 72 click trains of each frequency.
- **Pitch Deviant Auditory Oddball with eyes closed:** The P300, recorded in the Auditory Oddball paradigm, is a robust event-related potential (ERP) marker often used in EEG research and known to be reduced in CHR-P (Bramon et al., 2008) as well as in first episode psychosis (Lho et al., 2019). However, the current study aims to assess the gamma and theta spectral components in this paradigm. A common methodological issue may lead to inaccurate detection of gamma activity. It is reported that gamma activity may be generated by extra ocular muscles at the back of the eyes associated with saccades (Yuval-Greenberg et al., 2008) rather than with cognitive processes. To avoid this confound, participants are instructed to keep their eyes closed. In addition, the computer screen is turned off for this task to reduce unnecessary screen refresh artefacts. In the current paradigm, participants are required to press a button in response to a target tone (1000Hz, 50ms duration) in a series of standard tones (500Hz, 50ms duration). There are 55 target tones, with a 20% probability of a target tone occurring. The time between tones is randomly jittered between 1066ms and 1288ms.
- **Resting State:** Participants are instructed to 'relax but try not to fall asleep'. Instructions through the in-ear earphones indicate 30 second periods of eyes open and eyes closed. An additional 5 minutes of eyes closed is recorded at the end of this period to best ensure a minimum of 2 minutes clean eyes closed data. The computer monitor is switched off.
- **Visual Working Memory (VWM):** This paradigm is intended to probe memory related theta and gamma oscillations. Theta is impaired in a visual delayed matching to sample memory task in people with schizophrenia (Griesmayr et

al., 2014), "Configural-relational" memory depends on hippocampal function and theta oscillations (Cashdollar et al., 2009; Hannula et al., 2015). Theta synchronises between the hippocampus and the neocortex in humans (Kaplan et al., 2014) and gamma-theta synchronisation occurs during visual memory (Holz et al., 2010), so neocortical theta and gamma should be detectable in the scalp EEG. In the current visual working memory task, participants are presented with two natural scenes with a 2.3 second delay between them (see Figure 2). Both scenes are made up of identical items but in some pairs of images, one or more of the objects are in a different location in the second scene. The participant must indicate if the two pictures match by a button press for 'yes' or 'no'. Where necessary, the "Yes"/"No" in the response prompt has been translated into the language suitable for that site. There are 50 image pairs used in each session (25 matched and 25 mismatched) randomly selected from 78 possible images.

- **Visual Annular Grating:** A black and white circular grating appears on the screen with a central, small red dot (see Figure 2). Participants are instructed to fixate on the dot and to press a button as soon as possible when the grating disappears. This task is known to produce an occipital gamma signal (Muthukumaraswamy & Singh, 2013). There are 50 stimuli, presented every 5 seconds. The time that the gratings are visible is randomly varied between 1.5 seconds and 2.5 seconds.

2.2.3- EEG Analysis

High frequency Analyses (>20Hz) - Matlab

EEG pre-processing and analysis will be completed using Matlab for gamma band investigations. Powerline, eye and muscle artefacts will be removed using a gamma artefact removal algorithm developed by our researchers to remove artefacts without excluding EEG high frequency oscillatory activity (See (Nottage and Horder, 2015)). Fast Fourier Transform (FFT) will then be performed to convert the EEG signal to time-frequency domain for extraction of the amplitude of gamma band activity. The time-locked, gamma response, as in the ASSR, can be determined by first averaging across trials, before performing the FFT. This averaging reduces the effect of artefacts, allowing data collected at a lower sampling rate to be used. After decimating to the same sampling rate, data from all sites will be subject to identical processing pipelines

for this time-locked gamma response, prior to group averaging. However, the technical requirements for artefact correction of the exploratory, resting and non-time-locked (induced) high frequency analyses, may mean that data from some sites might need to be excluded from such additional high frequency analyses. Whilst the gamma response in the ASSR is the primary outcome measure for this study, the EEG recorded in the Annular Grating, VWM, Auditory Oddball and Resting paradigms will also undergo analyses of the frequencies above 20Hz.

Low Frequency Analysis and ERPs– Brain Vision Analyzer2

The P300, Resting State and VWM task will be subject to confirmatory analyses of ERPs (Fusar-Poli et al., 2011), peak alpha, frontal theta and delta (van Tricht et al., 2014) and theta band activity (Jhung et al., 2013) respectively using Brain Vision Analyzer2 (BrainVision Analyzer, 2019) in the large, global sample we will have available to us. The inclusion of these analyses is crucial as they may have contributary predictive properties as previously reported. Further spectral analyses will additionally be conducted on the data acquired on the VWM paradigm and the resting state to assess synchrony across brain regions and frequency bands.

2.3- Informed consent, Data Acquisition and Visits

During the screening visit, the study is explained to potential participants both verbally and in written form by a Participant Information Sheet (PIS) where the aims, methods, anticipated benefits, and potential hazards are described. Participants are given ample time to consider whether they wish to take part and to have any questions they may have answered. It is made clear that participation is voluntary, that all clinical and EEG data collected will be anonymized, and that it is the participants' right to withdrawal from the study at any time without giving a reason. Informed written consent is obtained for those individuals that meet inclusion criteria and wish to participate in the study. Both CHR-P individuals and controls are evaluated at baseline, completing a clinical assessment, a cognitive assessment, and an EEG assessment and resting state magnetic resonance imaging (rsMRI) assessment are carried out (see Table 1). All the data are acquired in accordance with the PSYCAN protocol (See: (Tognin et al., 2020)). Participants receive a small amount of financial compensation for their time and to cover any travel costs they may incur.

2.4- Data Analysis

2.4.1- Sample Size

The study is powered on the primary hypothesis that there are gamma band differences between CHR-P and HC groups. Given that there are no large-scale studies addressing gamma band alterations in CHR-P samples we have used the effect size from a meta-analysis conducted in patients with a first episode of psychosis (Thuné et al., 2016). Power calculations using G*Power reveal that, using the meta-analytical pooled effect size of 0.6, the sample size required (two-tailed alpha value of 0.05, power of 80%, HC:CHR-P allocation ratio of 0.4) to detect this effect is 79 CHR-P participants and 31 HC. Our sample size will exceed these numbers to ensure that we detect group differences in EEG measures if present in participants.

2.4.2- Statistical Analysis

Differences between HC and CHR-P subgroups will be calculated using t-test. To investigate associations of gamma band oscillations with structural and functional alterations, correlation analyses will be applied to test relationships between gamma amplitude, blood oxygen level dependent (BOLD) response acquired during the neuroimaging protocol and clinical presentation as assessed using the Comprehensive Assessment of At-Risk Mental States (CAARMS). Finally, all measures will be subject to data driven computational analyses to develop and validate predictors of outcome in conjunction with other data modalities from the PSYSCAN project (For PSYSCAN measures, standardisation methods and computational analysis aims see (Tognin et al., 2020)).

2.5- Participants

CHR-P participants will be recruited from CHR-P services at each site (see 2.2 for details). All participants taking part in this EEG study will have already been recruited and enrolled for the PSYSCAN study (see (Tognin et al., 2020)). Healthy controls are recruited from the local population through advertisements in the local areas local to each site.

2.5.1- Inclusion Criteria

- CHR-P individuals fulfilling one or more of the following criteria (i-iii according to CAARMS 12/2006) (Yung and and, 2005) and iv according to the Schizophrenia Proneness Instrument – Adult version (SPI-A) (Schultze-Lutter et al., 2007):
    - i) Attenuated Psychotic Symptoms (APS): characterized by attenuated positive symptoms (ideas of reference, odd beliefs/magical thinking, perceptual disturbance, digressive speech, odd behaviour/appearance)
    - ii) Brief intermittent psychotic symptoms BLIPS): characterized by full-blown psychotic symptoms which last less than one week and resolve spontaneously)
    - iii) Genetic Risk and Deterioration (GRD): characterized by a first degree relative of an individual with a psychotic disorder and/or a schizotypal personality disorder, plus a marked reduction in Global Assessment of Function score.
    - iv) Basic Symptoms (BS): subtle, subclinical self-experienced disturbances in drive, stress tolerance, affect, thinking, speech, perception and motor action.
- Aged 16-40 years old.
- All participants must speak and understand English to a standard to provide informed consent and follow EEG paradigm instructions.
- Healthy controls must have no personal or family history of psychiatric disorders.

2.5.2- Exclusion criteria

- Present or past diagnosis of DSM psychotic disorder.
- Evidence of neurological conditions, major medical illness or head injury.
- Severe skin reactions to cosmetics.

2.6- Outcomes:

Primary outcome:

- Differentiate CHR-P individuals and HC based on gamma band EEG data.

Secondary outcomes:

- Develop and validate predictors of outcome including psychosis onset in conjunction with the PSYSCAN project.
- Refine predictive models using EEG data and other biomarkers evaluated in the PSYSCAN project.
- Evaluate the influence of clinical, cognitive, neuroimaging, and biological biomarker data collected for the PSYSCAN project on CHR-P outcomes.

2.7- Data Management

Methodological Considerations in Multi-Site EEG Studies

Multi-site studies provide the opportunity to collect large samples of data from a broad population. However, the involvement of multiple sites also introduces an increase in methodical challenges in controlling for site differences. At the data collection, storage, analysis and interpretation levels, important standardization measures need to be taken (for overview see: (Farzan et al., 2017)). For the current study, differing parameters that can be altered in the pre-processing stages have been employed for future directions. For example, while some sites have the resources for collecting data at a sampling rate of 5000Hz, for the main inter-group analyses, sampling rates will be decimated to the limits of the lowest sampling rates available at any site. The same procedure must be applied to the limitations of all parameters, e.g., channel selection. However, the higher sampling rate and extra channels will allow further analyses to be carried out on data from a sub-set of the sites.

Travelling Heads

While every effort has been made to reduce between-site effects through the methodology and standard operating procedures (SOP) protocol, variability may still arise from differing make or model of acquisition or presentation equipment and software. To measure these differences, six healthy subjects – or 'Travelling Heads' - underwent two EEG sessions on consecutive days at each of the six participating sites. This approach, adopted in previous multi-site studies, will allow for assessment of heterogeneity within- and between-laboratory settings such as acquisition and presentation equipment, and room condition (e.g., temperature, lighting, and electromagnetic noise). Determinants and degrees of variance can then be assessed for their effects on data and applied to post-hoc calibration methods for attenuation.

Data Security

Data Security Privacy laws and regulations are adhered to for all procedures undertaken during this study. The collection and processing of participants' personal information is limited to the details as defined and approved in the ethics application. All data and personal information collected from participants during the investigation is treated with the strictest confidentiality. Once recruited and consented to the project, all participants are allocated a participant ID number which is attached to all research documentation. All documentation collected, which would allow the identification of personal data, is stored in a secure location at King's College London's Institute of Psychiatry, Psychology and Neuroscience in a locked cabinet and only accessible by the researcher and the CI. All clinical and EEG data is anonymised and stored under password protection on the King's College London's Institute of Psychiatry, Psychology and Neuroscience on our secure, encrypted server. Research data will be stored for a minimum of 5 years following the completion of the study and for follow-up purposes. Anonymised clinical and EEG data from the Amsterdam, Maastricht, Melbourne, Seoul and Toronto are transferred to the London site also via our secure, password-protected, encrypted server.

2.8- Ethics and regulatory approval

This study was reviewed and given a favorable opinion by the National Research Ethics Service (NRES) London - Fulham Research Ethics Committee (Ref: 16/LO/1829), in accordance with the Helsinki Declaration of 1975 and 2008 amendment and with the UNESCO Universal Declaration on human rights. The study is being conducted according to the principles of the Declaration of Helsinki (Amendment 2008), and all applicable regulatory requirements.

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3- DISCUSSION

The current manuscript presents the protocol for an international, multi-modal and longitudinal study that seeks to identify predictors of outcome in CHR-P individuals;

running in conjunction with the PSYSCAN study. The primary investigative technique used is EEG and the primary variable of interest is the spectral response in the gamma band. Further, investigatory spectral analyses will also be applied to assess amplitude and synchrony across brain regions and frequency bands during rest and cognitive tasks. Participants will be followed up over 2 years and potential transition to psychosis will be evaluated. The successful identification of predictors of outcome may have the potential to aid development of an EEG assessment that would refine individual risk prediction in the CHR-P state along with other biomarkers. To our knowledge, this is the first international, multi-modal, multi-site, longitudinal study of this scale investigating the gamma band response as a predictor of outcome in the CHR-P state.

We believe that the protocol described here address some of the challenges faced by previous studies of this kind, including the limitation of precision psychiatry to clinical or socio-demographic predictors only to predict poor outcomes (Salazar de Pablo et al., 2020). It will therefore enable us to identify predictive biomarkers which will inform clinical practice. An achievable goal would be generating a stepwise, multi-level assessment analogous to the reliable, sequential, diagnostic testing employed for other medical vulnerabilities (e.g. myocardial infarction) as this method may provide the greatest refinement of prognosis accuracy (Schmidt et al., 2017). Therefore, the multi-modal nature of our study has been designed to allow for the stepwise consideration of variables with a goal of generating a valid risk assessment model for implementation in the clinical environment. A potential limitation of the current study protocol is that CHR-P subjects are not compared to subjects with non-psychotic psychiatric disorders or subclinical symptoms.

4- STUDY STATUS

The study status is ongoing. Recruitment commenced in January 2017 and ethical approval to collect data ended in September 2021. Data collection was being conducted according to the principles of the Declaration of Helsinki (Amendment 2008), and all applicable regulatory requirements. This study was reviewed and given a favourable opinion by the National Research Ethics Service (NRES) London - Fulham Research Ethics Committee (Ref: 16/LO/1829).

Author Contributions

Prof. Philip McGuire gained funding. PM, PF-P and JN designed the study. SK is acquiring the data. SK and JN will analyse the data. SK and GSP drafted this manuscript which was edited by PF-P and JN. All authors read and approved the final manuscript.

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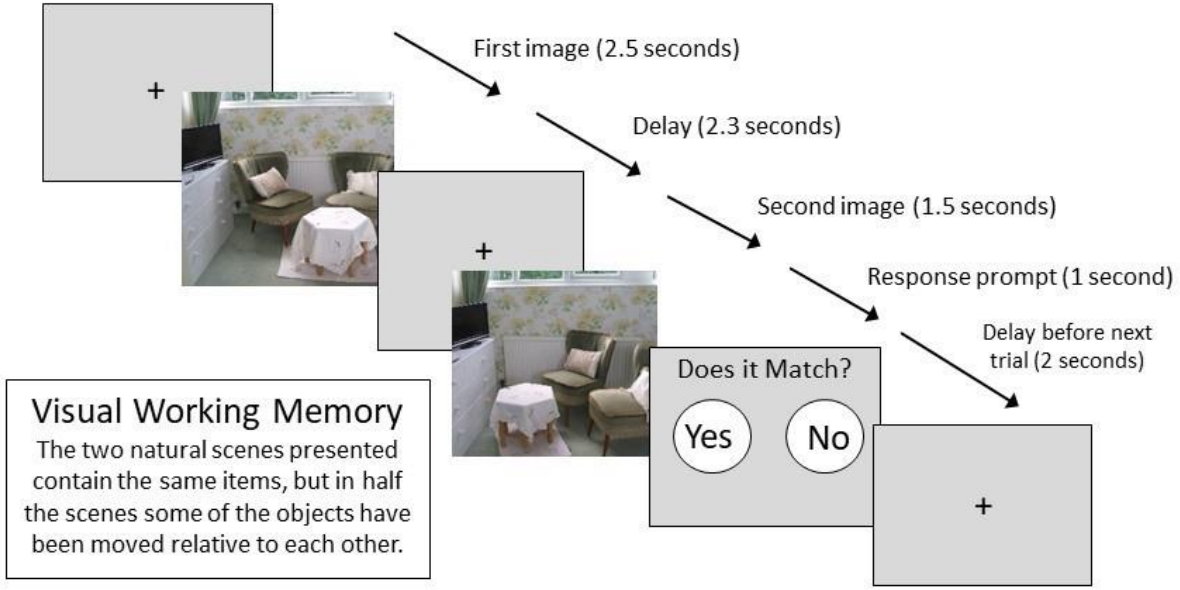
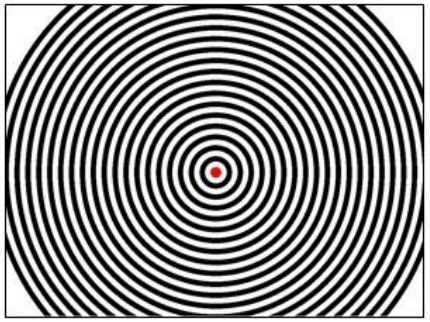
Figure 1: Participating sites

Figure 2: Visual Paradigms



Visual Working Memory

The two natural scenes presented contain the same items, but in half the scenes some of the objects have been moved relative to each other.



Annular Grating

Participants fixate on the red dot, and press a button when the grating disappears. This occurs randomly after between 1.5 and 2.5 seconds

Table 1: Visits and study procedures in CHR-P individuals and HC

	Screening Visit	**Baseline Visit**	**24 months Visit[a]**
Participant information and informed consent	X		
Clinical assessment		X	X
Cognitive assessment (*Hopkins Verbal Learning Test Revised*)		X	X
EEG assessment		X	X

[a]Timing is relative to the baseline visit ±1 month.

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