PROTOCOL TITLE: Reward learning as a potential mechanism for improvement following cognitive remediation: a pilot study

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AMENDMENTS:

1.	2.	3.	4.

Table of Contents

1. Introduction

Cognitive impairment is common in people diagnosed with schizophrenia (Harvey et al., 2022). The deficits are global and impact on both neurocognition (attention, memory, planning) and social cognition (difficulties perceiving and processing emotions) (Pinkham et al., 2014; Vaskinn & Horan, 2020). Approaches to remediation of these deficits have included integrated programs with a combined approach to neuro cognition and social cognition and stand-alone programs focussing either on neuro cognition or social cognition (Fernandez-Sotos et al., 2019; Iozzino et al., 2021; Trapp, Heid, Roder, Wimmer, & Hajak, 2022). There is evidence from randomized controlled trials and meta-analysis for the benefit of Cognitive Remediation therapy (CR) on global cognition (Effect Size ES =0.45) with greater benefit if CR is combined with some form of rehabilitation (ES=0.59) (Dark, Harris, Gore-Jones, Newman, & Whiteford, 2018). The core components of CR appear to be intensity of practice (2-4 times a week); the combination of drill and practice of tasks with strategy training and a context that facilitates use of new skills learnt. However, response to therapy is variable and research still needs to clarify conclusively the relevance of participants' characteristics and therapy implementation methods in influencing potential benefits.

The evidence for the mechanisms by which CR is effective are yet to be clarified (Jha, Lin, & Savoia, 2016). A core component of CR is strategic learning principles ensuring tasks are scaffolded based on previous successful achievement and chances of successful task completion are optimized. There is therefore close reinforcement of learning. One proposed potential mechanism for effect of CR is reward learning which potentially is the pathway to improved cognition and the motivational negative symptoms (Jha et al., 2016). In schizophrenia there is impairment in reward anticipation (Grimm et al., 2014; Subramaniam et al., 2015) and representation (Gold, Waltz, Prentice, Morris, & Heerey, 2008) leading to poorer decision-making, motivational deficits and negative symptoms (Billeke & Aboitiz, 2013; Gold et al., 2008; Juckel et al., 2006; Park et al., 2015).

Reward Learning (RL) is a term used to identify the cognitive processes responsible to adapt behaviour following positive or negative feedback. RL is a basic adaptive function of every living organism and provides the possibility to adapt and change in response to internal and environmental demands. This process has been studied extensively in neuroscience and linked to the brain dopamine system. The dopamine hypothesis of schizophrenia is the single most influential theory in our understanding of the neurochemical basis of the illness. This theory suggests that fundamental dysregulation in this system is responsible for the illness symptoms. Dysregulation in the dopamine system is also linked to RL abnormalities which in turn are thought to influence cognitive and

negative symptoms. A growing body of basic neuroscience literature has identified two complementary and interactive neural systems in the dopamine system responsible for predicting outcome and learning from feedback (Schultz, Dayan, & Montague, 1997). The first of these systems, responsible of rapid learning, is mediated by the basal ganglia. This system, referred to as the "fast system", is believed to represent the predicted value of actions and rewards. These predictions bias actions and underlie learning based upon positive and negative feedback. The second slower system is based primarily in the prefrontal cortex, and allows more detailed, conscious and abstract representations of values and rewards. These representations of value are instrumental in allowing individuals to flexibly respond to reward value and adapt to novelty in the environment. There is consistent evidence that people with schizophrenia are impaired at making rapid behavioural adjustments in response to feedback and that these impairments are associated with negative and cognitive symptoms (Hanssen et al., 2020; Waltz & Gold, 2007; Waltz et al., 2010). Problems using this system are evident in situations requiring rapid change in responses to environmental changes when a situation previously rewarding begins to be associated with disadvantageous outcomes. In contrast, a number of studies suggested that gradual/procedural learning system seems intact in people with schizophrenia (Schmand, Kop, Kuipers, & Bosveld, 1992),(Exner, Boucsein, Degner, & Irle, 2006) but antipsychotic medication dosage, particularly those with high levels of dopamine 2 (D2) receptors blockades, may exert a negative effect on this system.

Social environments are dynamic with constant rapid changes, hence social situations require a rapid behavioural adjustment in response to ever-changing social feedback. People with schizophrenia have impaired social functioning and recent studies have shown that they also have impaired social reward processing (Catalano, Heerey, & Gold, 2018; Robberegt & Fett, 2017). Social approval induces rewarding feelings and is associated with increased activation in regions and networks associated with reward (Izuma, Saito, & Sadato, 2008; L. Rademacher et al., 2010; Spreckelmeyer et al., 2009). In those with schizophrenia there is reduced activity in common reward brain regions during the experience of social reward (Lee & Reavis, 2017), suggesting that they may have a reduced experience of the rewarding feeling of positive social attention. Positive social interactions have benefits for mental well-being and give life a sense of meaning (Uchino, Cacioppo, & KiecoltGlaser, 1996). In particular receiving praise and attention from others improves self-esteem (Hill, 1987) and increases motivation (Leary, 2007). Although social reward has major impacts on functional outcome, only recent efforts have explored social reward processing in schizophrenia.

Further behavioural evidence suggests that the RL difficulties to be more pronounced in learning from positive rather than negative feedback (Gold et al., 2008). This provides a further link between the effects of impaired RL and negative symptoms as learning preferentially from negative outcomes is likely to lead to behavioural avoidance, social withdrawal and have a negative impact on motivation. This hypothesis is supported by recent research suggesting that the magnitude of RL impairment, particularly for positive feedback, is associated with negative symptoms severity (Gold et al., 2012).

Despite the significance of RL problems in people with schizophrenia there is no therapy targeting this problem. The impact that a course of CR has on RL problems in people with schizophrenia has recently been explored (Cella et al., 2014) . The results of the study show that this therapy can improve the sensitivity to positive and negative feedback and that improvement in these parameters were moderated by negative symptoms severity. However, this study used a standard CR protocol and may not have achieved the maximum effect on RL problems. Further the pilot nature of this study did not allow investigating the retention of RL improvements and more crucially how these may impact cognitive and negative symptoms and more broadly recovery. Reward learning difficulties in people with schizophrenia are associated with negative symptoms (NS) and it is plausible that by reducing RL difficulties a reduction in NS could be observed.

It is proposed that the structure of CR enhances rewards and motivation to engage in increasingly challenging tasks and this is a potential mechanism by which CR can achieve functional outcomes in this group. The specific CR interventions used in this study will be a computer-based program, CIRCuiTS (Computerized Interactive Remediation of Cognitive and Thinking Skills). To enhance RL, the therapy where possible, will be delivered individually with 1 participant to one therapist.

Significance

Maximising the effect of interventions such as CR requires an understanding of the mechanisms of improvement from this therapy. Currently CR is undertaken over around 3 months with 2 to 4 sessions per week. Understanding the mechanisms of effect may enable improvements in the programs that enable more efficient delivery of this effective intervention.

2. Aims/Objectives:

To investigate reward processing in individuals with Schizophrenia before and after completing a course of CR, and to compare this group with a control group of individuals with Schizophrenia and a matched non-clinical group. In addition, to explore whether working memory and negative symptoms mediate change in reward processing after CR.

Aim 1: To investigate reward learning in individuals with schizophrenia before and after engaging in a course of CR consisting of at least 20 sessions.

Hypothesis 1A: Participants with schizophrenia will demonstrate deficits in learning in both the social and non-social conditions. These differences in learning will be linked to aberrant activity in the dopamine system at a neural level in the prefrontal cortex and subcortical structures such as the basal ganglia compared with healthy controls.

Hypothesis 1B: Participants that complete CR will demonstrate improved learning in both the social and non-social conditions, again reflecting improved neural activity within the prefrontal and basal ganglia regions.

Aim 2: To investigate whether social processing working memory is a mediator of changes in reward processing following the interventions.

Hypothesis 2A: Patients with schizophrenia will show an additional deficit in social reward learning, relative to non-social reward learning.

Hypothesis 2B: CR therapy will attenuate socially specific deficits in reward learning.

Aim 3: To investigate whether working memory is a mediator of changes in reward processing following the interventions

Hypothesis 3A: Working memory will mediate improved reward processing in patients following CR therapy.

3. Study Design

The study will be a pre post pilot study to investigate whether reward processing pathways are involved in the mechanism of action of cognitive remediation (CIRCuiTS). Matched control groups will be (1) people with schizophrenia receiving treatment as usual and (2) healthy controls without a Schizophrenia Spectrum Disorder.

3. 1 Interventions

CIRCuiTs (Computerised Interactive Remediation of Cognition – Training for Schizophrenia). This is a modular computer package including tasks of a wide range of cognitive functions (particularly executive function and memory). CIRCuiTs are run for 1 hour twice a week for 12 weeks and is delivered through a computer. CIRCuiTS consist of 40 stages. Twenty sessions are considered an adequate treatment exposure and 20 minutes a "session".

In this study 20 participants with schizophrenia (intervention group) will have one face to face meeting with the therapist to orientate to the program. These participants will then complete the program (40 sessions or 12 weeks of at least 20-minute session twice a week) either online or in-

person, and independently or in a group. The therapist will have telephone (duration <1 hour) contact once a week to support online participation. Only the intervention group will complete these sessions.

3.2 Study Population

3.2.1 Intervention and treatment as usual patient groups

Participants (n=40) with a diagnosis of a schizophrenia spectrum disorder, based on current medical records will be recruited from the teams of the Metro South Addiction and Mental Health service (MSAMHS). Participants (n=20) that are not interested in completing CR will form the patient TAU control group and will complete the pre and post measures only. Thus, group intervention allocation selection will be based on individuals' preference to participate in CR. If a participant initially signs up to the intervention group but due to change in circumstances is unable to complete CR, they will be offered the opportunity to become part of the TAU group. Individuals that initially choose to complete CR therapy but then fail to complete more than 5 sessions will be re-allocated to the control (treatment as usual) group.

3.2.2 Healthy control group

In addition, matched healthy controls (n=20) will be recruited from the Metro South Addiction and Mental Health community services in the Princess Alexandra Hospital district as well as from the general population via word of mouth and the snowballing effect. This will provide a benchmark to compare the clinical groups and validate the fMRI task.

3.3 Number of participants

Forty individuals with a diagnosis of schizophrenia spectrum disorder and 20 healthy individuals without a diagnosis of schizophrenia spectrum disorder. Total N is 60 participants.

3.4 Inclusion Criteria

3.4.1 Intervention and treatment as usual patient groups

Patients of the Metro South Addiction and Mental Health Service

Primary diagnosis of schizophrenia spectrum disorder

Basic competence in written and spoken English

Capacity to consent as advised by the treating team

Aged between 18-35

No history of neurological disorders or acquired brain injury.

Estimated intelligence quotient >70

3.4.2 Healthy control group

No history of a diagnosis of schizophrenia spectrum disorder

Basic competence in written and spoken English

Capacity to consent as advised by a member of the research team

Aged between 18-35

No history of neurological disorders or acquired brain injury.

Estimated intelligence quotient >70

3.5 Exclusion Criteria for all participants

Participants known or have any suspicion that they may have a metallic object in their body. This includes things such as a cardiac pacemaker, cochlear implant, metal IUD (hormonal IUD's made of plastic are fine), neuro-stimulator, aneurysm clips, non-removable body piercing, history of shrapnel or metal fragments in the eye.

Are pregnant or possibly pregnant (unprotected sex since last menstrual period).

History of claustrophobia.

Have permanent metal braces or a molar retainer.

Weigh more than 120kg

3.6 Participant Information and Informed Consent

A member of the research team will conduct the consent process. As part of the consent process the potential participant will be given the Patient Information and consent sheet. The information will also be read to the person and any questions answered by the research team member. The potential participant will be allowed as much time as they require to consent. During the consenting process, all participants will be informed that they have the right to withdraw consent from the study at any time without prejudice and withdrawal from the study will not affect their current or future care. Revocation of consent forms will be completed for those participants who choose to withdraw from the study.

3.6.1 Intervention and treatment as usual patient groups

Consent will only be obtained from patients who are deemed to have capacity to provide informed consent by their treating team. Capacity will be determined by collaboration between the treating clinician and delegated research assistant and will comply with the guidelines within the NHMRC National Statement on Ethical Conduct in Human Research 2007. Participants under 18 years of age require parent or legal guardian consent to participate. Under 4.5.8 of the National Statement, people with a mental illness, "consent should be witnessed by a person who has the capacity to understand the merits, risks and procedures of the research, is independent of the research team and, where possible, knows the participant and is familiar with his or her condition" (e.g., Treating Clinician). We will ensure that a witness also signs the consent form. In the event where the

research assistant is unable to find a witness who is familiar with the patient, an independent witness will be used for this process. The research team will encourage the witness to be a person chosen by the potential participant and is not part of the research team.

3.6.2 Healthy control group

A member of the research team will also obtain consent for the healthy control group. Consent will only be obtained from participants that meet all inclusion and exclusion criteria including a TOPF score of >70. The researcher will use clinical judgement to decide if the participant has the capacity to consent.

3.7 Screening assessment

Participants who meet all inclusion criteria and none of the exclusion criteria will be invited to participate in the study. Metro South Addiction and Mental Health community medical records will provide confirmation of diagnosis for clinical participants.

4. Procedures

4.1 Recruitment

4.1.1 Intervention and treatment as usual patient groups

Potential clinical participants will be recruited from the Metro South Addiction and Mental Health community services in the Princess Alexandra Hospital district. Flyers advising about the study will be distributed to clinicians and placed in the community clinics to make potential participants aware of the study.

4.1.2 Healthy control group

Matched healthy controls will also be recruited from the general population via word of mouth and the snowballing effect. Flyers advising about the study will also be distributed in the community clinics to make potential participants aware of the study.

4.2 Measures and Assessments

Please see Fig 1. for an outline of the study assessments and procedure.

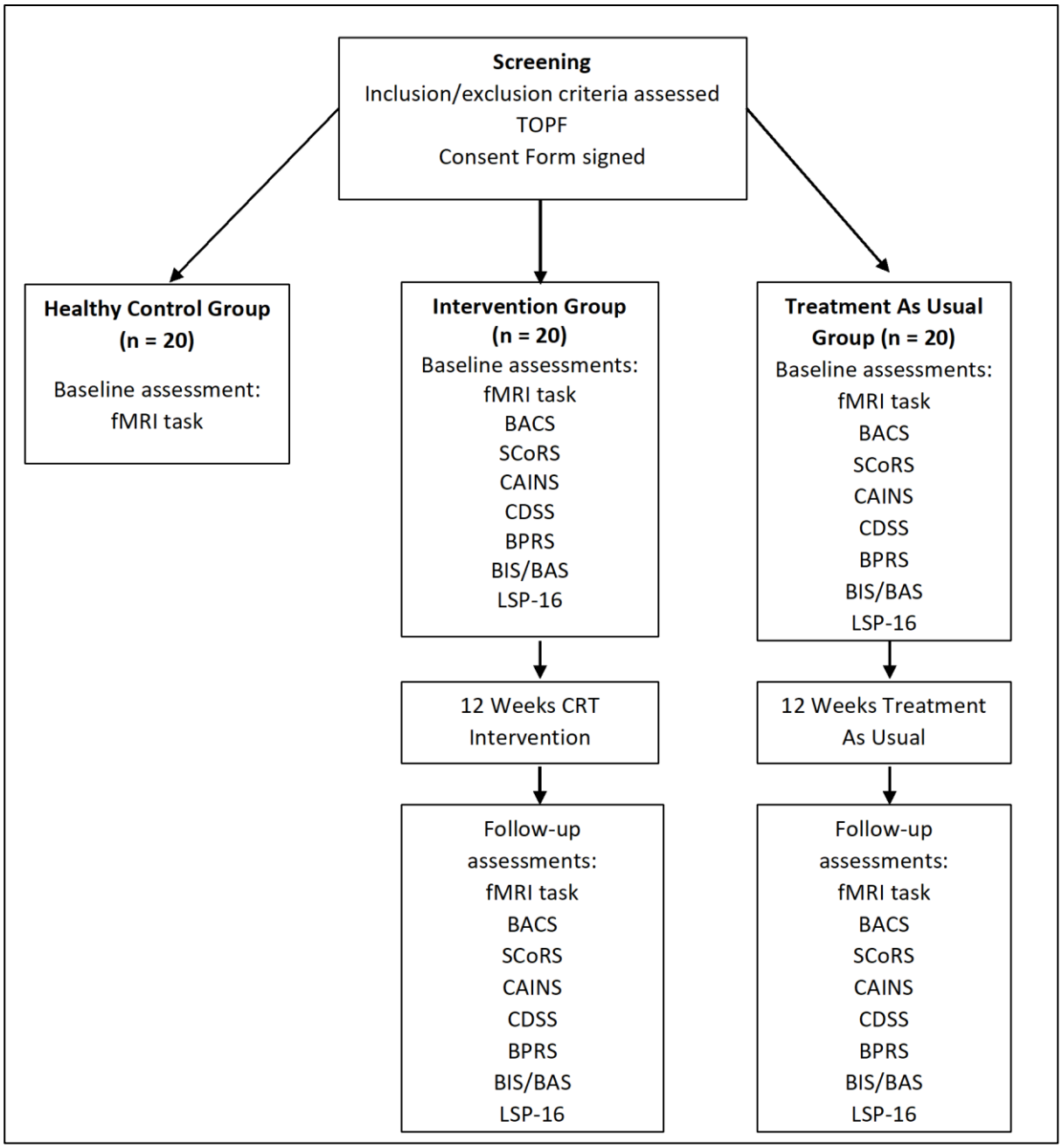

Fig 1. Schematic of study design

Life Skill Profile (LSP – 16) The Life Skills Profile - 16 (LSP - 16) was developed by an Australian clinical research group to assess a consumer's abilities with respect to basic life skills. Its focus is on the consumer's general functioning and disability rather than their clinical symptoms. There are 16 items, with a anchored four-point scale. Higher scores indicating a greater degree of disability (i.e. a score of 3 represents greater dysfunction and a score of 0 represents good functioning). A total LSP scale score is calculated by adding individual scores for the whole scale together. Therefore, for the LSP-16, the total score can range from 0 to 48. Items with missing data

are excluded from the calculation. Test of Premorbid Function (TOPFF) (Wechsler, 2009) is based on a revision of the Wechsler Test of Adult Reading (WTAR) and provides an extended intelligence quotient (IQ) range of prediction of premorbid IQ.

Brief Assessment of Cognition in Schizophrenia (BACS)(Atkins et al., 2016).The Brief Assessment of Cognition in Schizophrenia (BACS) was developed to assesses the aspects of cognition found to be most impaired and most strongly correlated with outcome in patients with schizophrenia. The BACS require less than 35 min to complete in patients with schizophrenia. The BACS was found to be as sensitive to cognitive impairment in patients with schizophrenia as a standard battery of tests that required over 2 h to administer.

Schizophrenia Cognition Rating Scale (**SCoRS**) is a 20-item interview-based clinical assessment that evaluates cognitive deficits and the degree to which these deficits impair patients' day-to-day functioning ref. The SCoRS assessment collects information generated from three different sources: (1) An interview with the patient, (2) an interview with an informant for the patient (ideally a person who has regular contact with the patient in everyday situations, such as a family member, friend, or social worker), and (3) a rating based on the clinical judgement of the clinician who administered the scale to the patient and informant. In addition to the 20 individual items, there is also a global rating assigned by the clinician.

Clinical Assessment Interview for Schizophrenia (Schizophrenia (CAINS)(Forbes et al., 2010) The Clinical Assessment Interview of Negative Symptoms (CAINS) is a measure of negative symptoms of schizophrenia comprising two scales with nine items rating the category of motivation and pleasure and four items rating the category of expression. The time frame for ratings is the past one week. The anchor points go from 0 no impairment to 4 severe impairments. The ratings are based on a semi structured interview.

Calgary Depression Scale for Schizophrenia (CDSS) (Addington, Addington, & Maticka-Tyndale, 1993). The CDSS was developed specifically to assess depression in people with schizophrenia. It is a nine-item semi structured clinician rated scale.

Brief Psychiatric Rating scale (Overall & Gorham 1962)

Is a widely used scale for the assessment of symptoms of schizophrenia and schizophrenia spectrum disorders. The scale has 18 items rated on a 7-point scale from not present to7 extremely severe. It has good psychometric properties in terms of reliability and validity and sensitivity (Hedlund & Viewag, 1980). BPRS score of 31 corresponds to “mild illness”; 41 “moderately ill” and 53 “ markedly“markedly ill” (Leucht et al 2005).

Behavioural Inhibition System/ Behavioural Activation System (BIS/BAS). The BIS/BAS is a self-report scale measuring behavioural inhibition and activation (Demianczyk, Jenkins, Henson, & Conner, 2014). The questionnaire uses a 5-point Likert type response scale with 1 strongly disagree, 2 Disagree, 3 Neutral, 4 Agree, and 5 Strongly agree.

fMRI Measures:

Structural and functional MRI images are acquired by a 3T Siemens Magnetom TrioTim system using a 12-channel head coil. The sequences acquired and their parameters are as follows:

T1-weighted imaging: MP2-RAGE sequence. Time to acquire image: 5:02, Inversion 1: 700ms, Inversion 2: 2220ms, repetition time (TR): 4000 ms, echo time (TE): 2.96 ms, Voxel size: 1 mm isotropic, FoV= 230 mm, 192 slices with full brain coverage,;

T2-weighted imaging. Fluid Attenuated Inversion Recovery (FLAIR) sequence, time to acquire image: 2:44, Repetition Time: 9000ms, Echo Time: 81ms, Inversion Time: 2500ms, Flip Angle: 150 degrees, voxel size: 0.72 x 0.72 x 5.2mm. 30 Slices with full brain coverage.

fMRI imaging. Functional T2*-weighted BOLD images are acquired using a multiband, echo-planar sequence, across the whole brain (TR: 0.628 ms, TE: 30 ms, resolution: 2.4 mm isotropic, FoV: 192 mm, flip angle: 52 degrees). 54 slices with full brain coverage. During fMRI imaging, participants will complete a computerised experimental task (see below). For each task condition, approximately 720 full brain images will be acquired, providing 1440 volumes acquitted in approximately 12 minutes.

Diffusion weighted Imaging. A NODDI (Neurite Orientation Dispersion and Density Imaging) sequence with two shells and 90 gradient directions (B1=1000 with 30 directions, B2=2500 with 60 directions) with 6 B0 measurements will be acquired in the AP phase encoding direction, and an additional 6 B0 measurements will be acquired in the PA phase encoding direction. Total acquisition time: 7:24. Time of Repetition: 4100ms, Echo time: 75ms, voxel size: 2mm isotropic, 68 slices with full brain coverage.

Susceptibility Weighted Imaging (SWI): Time to acquire image: 2:56, RepetitionTime: 27ms, EchoTime: 20ms, flip angle: 15 degrees, voxel size: 0.89 x 0.89 x 2.5mm. 64 slices with full brain coverage.

Experimental Task:

During functional MRI imaging, participants will complete a computerised experimental task. This is a simple reinforcement learning task with two conditions, a social reward condition and a non-

social reward condition (see figure 1 below). Participants view an image on a computer screen, a leaking bucket on the non-social condition, and a face in the social condition. The goal is to fill the bucket with water (non-social condition) or to make the person smile (social condition). Three button responses are available to achieve these goals, represented on the screen by a square (left button), diamond (middle button) and pentagon (right button). Participants are told that one of these will; probably be a good choice (fills bucket or increases smile), while other choices may be poor choices (opposite effect). They must try to learn which buttons are the best responses by trial and error. The reward probabilities of each choice evolve over time however, requiring participants to continually trach choice outcomes, and switch buttons over time to achieve their goal. Participants are encouraged to make button presses as quickly as possible (about 2-4 presses per second). Buttons A, B and C are randomly assigned to each reward probability for each task block. There are 10 blocks in each condition (social and non-social conditions). Blocks range from 20 to 45 seconds in length, allowing for hundreds of button choices per block, and thousands per condition. Completing both task conditions takes approximately 12 minutes. The task was developed by Dr Marcus Gray for this study, and implemented in Matlab (Mathworks) using the Cogent 2000 toolbox (Wellcome Department of Imaging Neuroscience, Queen Square, London). During the fMRI experiment the task was seen by participants through a tilted mirror attached to the head coil on the MRI scanner. Responses were made on a commercially available MR-compatible response box(Current Design, https://www.curdes.com/).

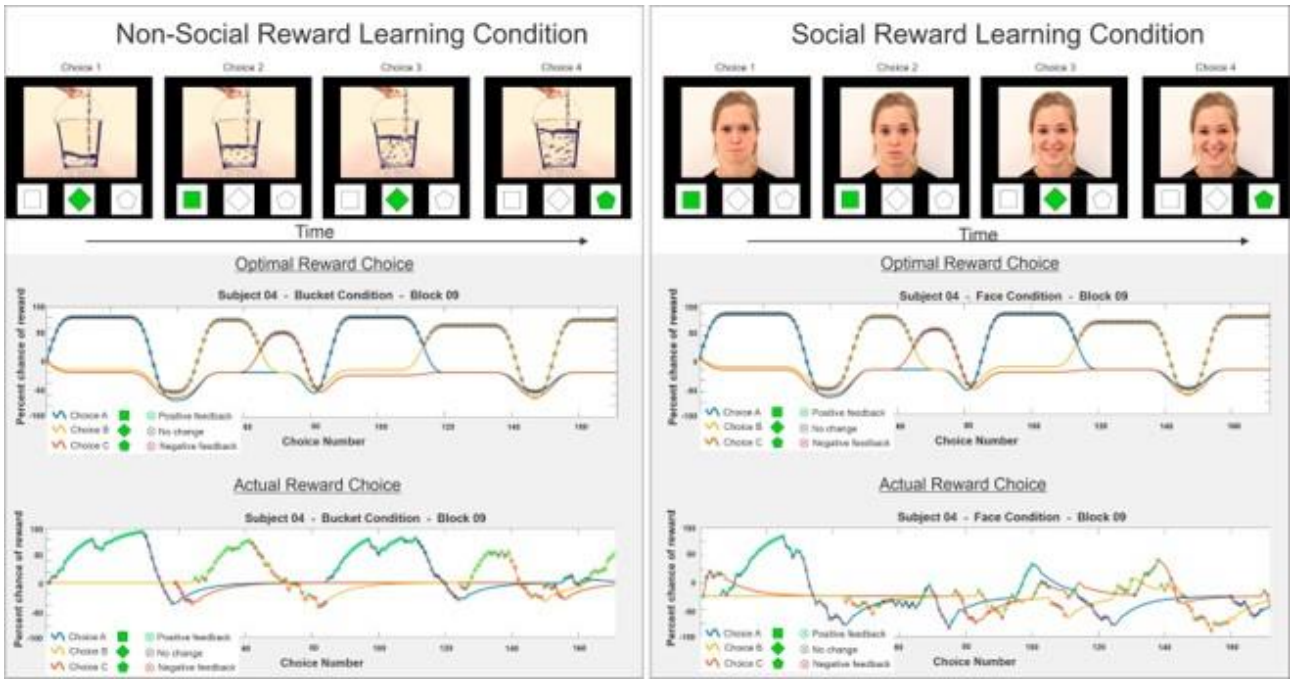

Fig. 2

Schematic diagram for the reward learning experimental task. Left Panel: Non-social reward condition, Right Panel: Social reward condition. Top: Four choices are illustrated in each condition, with progress towards the goal from left to right (filling the bucket or making the person smile). Middle: The reward probabilities are identical in the social and non-social learning conditions. At each point in time there is one optimal button choice, and reward probabilities of each choice change during each task block. Bottom: The actual choices of a test participant are illustrated, and the value of each button calculated, based on the feedback available to that participant. While the non-social choices are close to optimal, learning in the social condition is less efficient. Participants are familiarised with the task and perform two blocks of each condition prior to brain scanning.

5. Study Restrictions

Nil.

6. Safety Assessments

All clinical patients recruited in this study will be registered patients of Metro South Addiction and Mental Health service. The study team will liaise with clinical staff to ensure that there are no unforeseen contraindications to the participant being involved. The experience of the MSAMHS since 2010 with the therapy, is that CIRCuiTS is seen as safe and there is no evidence that it is associated with an increased risk of adverse events. Patients with psychosis have often had head scans. A member of the research team will support the person during the fMRI scans.

7. Adverse Events (AE) and Serious Adverse Events (SAE)

All adverse events reported between consent and final follow-up will be recorded. The investigator or designee will ask the Participant non-leading questions to detect adverse events e.g. “How have you been over the last 5 weeks”. We expect that adverse events will occur during the study related to fluctuations in the underlying mental disorder and medications. The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or a serious adverse event (SAE) as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol

7.1 Definition of a Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that, at any dose:

a) results in death

b) is life threatening

c) requires hospitalisation or prolongation of an existing hospitalisation.

d) results in disability/incapacity, or

f) Any event deemed by the investigator as being a significant medical event.

7.2 Time Period, Frequency, and Method of Detecting AEs and SAEs

All adverse events will be recorded between the time of consent and the follow-up visit. Each Participant will be monitored regularly by the investigator and study personnel for adverse events occurring throughout the study. The research team will enquire about AEs by asking the following non-leading questions:

At the first scheduled visit (baseline) participants will be asked:

"How are you feeling?" Does your current treatment cause you regular side effects? Do you have any general health conditions that cause you problems on a regular basis (e.g. that we might expect to occur over the duration of this study?"

At subsequent scheduled visits, participants will be asked:

"Since your last visit, have you had any health problems?"

7.3 Recording of AEs and SAEs

If an AE/SAE occurs, the investigator will review all documentation (e.g. hospital progress notes, laboratory, and diagnostic reports) relative to the event. We will then record all relevant information regarding an AE/SAE in to the CRF, and code the AE according to industry standard MEDDRA coding rules.

7.4 Assessment of Intensity / Evaluating AEs and SAEs

The investigator will assess intensity for each AE and SAE reported during the study. The assessment will be based on the investigator's clinical judgement. The intensity of each AE and SAE recorded in the CRF should be assigned to one of the following categories:

Mild: An event that is easily tolerated by the Participant, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event which is incapacitating and prevents normal everyday activities.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets one of the pre-defined outcomes as described in "Definition of an SAE".

7.5 Assessment of Causality

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the CIB and/or product information in the determination of his/her assessment.

The causal relationship to the study product assessed by the Investigator (or medically qualified delegate) should be assessed using the following classifications:

Not Related In the Investigator's opinion, there is not a causal relationship between the study product and the adverse event.

Unlikely The temporal association between the adverse event and study product is such that the study product is not likely to have any reasonable association with the adverse event.

Possible The adverse event could have been caused by the study Participant's clinical state or the study product.

Probable The adverse event follows a reasonable temporal sequence from the time of study product administration, abates upon discontinuation of the study product and cannot be reasonably explained by the known characteristics of the study Participant's clinical state.

Definitely The adverse event follows a reasonable temporal sequence from the time of study product administration or reappears when study product is reintroduced.

7.6 Follow-up of AEs and SAEs

All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, until the condition stabilises, until the event is otherwise explained, or until the Participant is lost to follow-up. Once resolved, the appropriate AE/SAE CRF page(s) will be updated.

7.7 Risk Management Process

Table 1 below details the Risk Identification, Evaluation and Management plan for this study.

It will ensure that risk and uncertainly are appropriately managed for the duration of the study. The risk management process is in accordance with the NHMRC National Statement on Ethical Conduct in Research Involving Humans (2007).

Table 1: Risk Analysis Matrix

Consequence

Likelihood	**Negligible**	**Minor**	**Moderate**	**Major**	**Extreme**
Almost Certain					
Likely					
Possible					
Unlikely					
Rare					

Response To Risk

	Very High	Immediate action required
	High	Urgent attention or investigation required
	Medium	Require specific attention
	Low	Manage through routine procedures

Risk Identification, Evaluation and Management Plan

	Risk	Description	Possible Effects			Risk Management strategies
			Likelihood	Consequence	Rating	
1.	Psychological discomfort during assessments	Participants in the clinical groups may experience psychological discomfort when answering questions in the clinical interview and cognitive assessments.	Possible	Minor-moderate	Medium	The PICF clearly states the potential risk of discomfort. Recruitment of experienced mental health clinicians who will be able to minimise and manage discomfort.

						Participants in the clinical groups will be clinically assessed at baseline, end of treatment and 3 months post treatment. Participants are given the opportunity to discuss any concerns/discomforts re previous appointment. Clinicians will direct and assist participants to gain support if required.
2.	Psychological discomfort with self-disclosure in a session	Participants in the clinical groups may experience discomfort in self –disclosure during sessions.	Possible	Minor-moderate	Medium	The PICF clearly states the potential risk of discomfort. Recruitment of experienced mental health clinicians who will be able to minimise and manage discomfort.

						Clinicians will direct and assist participants to gain support if required.
3.	Inconvenience of participating in the trial	Participants may be inconvenienced by time taken to participate in the trial.	Possible	Negligible	Low	The PICF for the clinical groups clearly states the battery of clinical assessments to be completed and the approximate time and frequency for clinical assessment visits. Participants will be given as many breaks as necessary throughout the clinical assessment visit. . Participants will be reminded that the trial is voluntary, and they can withdraw at any time.
4.	History of self-harm/suicidal ideation	Participant expresses suicidal ideation.	Possible	Moderate-severe	High	Recruitment of experienced mental health clinicians who are trained in conducting risk

						assessment and managing high risk situations. Research staff will have access to a clinically trained senior staff including a Project Manager and Chief Investigator who will assist research staff to conduct risk assessment and implement risk management plan if required i.e. notifying treating team and assisting in the participant accessing appropriate support (e.g. emergency services) Previously identified high risk patients and recent risk assessments will be discussed at weekly team meetings and their management reviewed by senior research staff (including Project Manager and Chief Investigator).

						Research staff will be given support and feedback on risk assessments and their management to improve skills throughout the project.
5.	Transporting participants in QLD Health work vehicles	Research staff will be transporting participants to pathology appointments and may be required to transport participants to the interview site. There may be risk associated with motor vehicle accident There may be risks associated with unpredictable behaviour of a patient whilst being transported.	Possible	Minor-Moderate	Medium -High	Research staff will have a current QLD Driver's Licence and completed the mandatory Driver Safety E-Learning Course. Recruitment of experienced mental health clinicians who will be able to and manage unpredictable behaviour. Research staff will carry a mobile phone and adhere to a sign in/out policy and advise the Project Manager of the address they will be attending.

6.	Psychological discomfort during MRI	Participants may become distressed (for example as a result of feeling claustrophobic) within the MRI.	Possible	Minor – Moderate	Medium-High	Screening – advised and asked if this is likely. Discussed again at the time of screening. Also advised MRI can be ended if this occurs. Advised of emergency button to press in this instance. Checked on during the MRI by radiographer using intercom system. The participant is then able to advise if they are becoming distressed.
7.	Risk of physical harm during MRI	If a participant undergoes an MRI with metal in their body this can result in physical harm to the participant (i.e. the implant may cease to	Possible	Major	High	A strict metals check procedure will be followed to mitigate the risk of scanning a participant with metal in their body. Three metal checks will occur;

		function, in the case of pacemaker, brain clip, aortic clip or neurostimulator).				Firstly, by a member of the research team at the time of recruitment and screening. The second by trained scientist, during the session and prior to the MRI scan. The third by the radiographer who will conduct the MRI scan, immediately prior to the MRI scan. The metal check will be documented using CAI developed metal checklist. If a participant responds yes to any of the screening questions, these will be investigated (e.g. by Xray, review of medical notes etc) to assess suitability for scanning. They will not be scanned unless the radiographer is confident the participant does not have metal

						within them that could result in harm during the MRI scan.
8.	An abnormality found in the MRI scan	Becoming aware of neurological abnormalities of a participant as a result of the MRI.	Rare	Minor-Moderate	Low	The Participant Information Sheet outlines the process that will be followed if abnormalities are found. The information sheet advises participants they will be notified of any abnormality identified and that knowledge of that may have consequences (e.g. ability to work in certain professions, obtain life or health insurance). With reference to this, the information sheet states, “If you do not want to know, then it is better not to participate.” Action to be taken: Pass information to Dr Frances Dark, she will determine most appropriate action to be taken,

						which may include contacting treating clinician.

8. Participant Completion

Participants are considered to have completed the study if they complete 20 sessions (equivalent to 20 hours of the program) (intervention group only) and completion of post-intervention / end assessment measures (clinical groups). The healthy control group will only be required to complete the fMRI task.

8.1 Participant Withdrawal by the Investigator

Worsening of mental state such that the patient is admitted to hospital or their ability to provide ongoing informed consent is compromised.

9. Data and analysis

9.1 Sample Size and Power

This is a pilot study to assess possible mechanism of effect of CR and the fMRI task in examining neural pathways involved in motivation not an effectiveness study.

9.2 Statistical Analysis

Participants' medication dosages will be converted to olanzapine equivalents using Leucht et al. (2016) guidelines. Outcome measures will be analysed using the SPSS Version 27 software package. A series of 3 (group: intervention, patient control; healthy control) x 2 (time: baseline, post-intervention) mixed factorial ANOVAs will be conducted to evaluate the treatment group differences for each of the outcome measures. If the normality assumption is violated, non-parametric analyses will be conducted.

Standard pre-processing of the functionally weighted images is carried out using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8, 2013; Friston, 2003). The pre-processing steps follows: slice timing on the functional images, to correct for differences in slice acquisition times within each volume using the middle slice as reference; realignment (estimate and reslice) on the functional images, to correct for inter-scan movement within each run (defined as >3 mm translation, >2 degrees rotation); co-registration of the functional and structural images; segmentation of the structural image, with heavy regularisation (0.1) recommended for MP2-RAGE sequence; normalization of the resliced images into a standardized, stereotaxic space (according to the Montreal Neurological Institute template); and smoothing of normalized images with a 8mm full-width-at-half-maximum isotropic Gaussian kernel.

We will adopt the General Linear Model approach for event-related designs will be conducted using SPM8 (http://www.fil.ion.ucl.ac.uk). For the first-level analysis task-related changes in blood-

oxygen-level dependent (BOLD) signal will be estimated at each voxel, for each participant. Head motion parameters will be included as a regressor to account for participant motion during the course of the experiment. A 1/128 Hz high-pass filter will be used to remove slow signal drifts, and a canonical hemodynamic response function with no derivatives will be selected. Computational Modelling (https://en.wikipedia.org/wiki/Computational_model) will allow the estimation of learning parameters at each point in time, during each task condition, for each participant. We will employ a Variational Bayesian framework to compute how the value of each button was estimated based on the behavioural choices made, and feedback received. This allows us to measure how learning occurred during the experimental task and the subprocesses which must underlie this learning. This provides an accurate way to calculate each participants learning rate, and learning competency, based on the computation necessary to perform the task. These learning parameters will be the primary focus of first level fMRI modelling, allowing investigation of the neural systems which carry out each learning subprocess. Second level group analyses will examine how learning in patients differed from that observed in control participants, and how Cognitive Remediation therapy altered learning efficiency and the underlying neural activity. We will correct for multiple comparisons, voxel-level threshold will be set at $p < 0.05$ family-wise error corrected.

9.2.1. Data Management

A screening log will be utilized to track potential participants and record the counts of individuals approached, consented, meeting inclusion/exclusion criteria, withdrawals, and completion. A copy of the PICF will be stored in a secure room in a locked filing cabinet separate from the CRFs.
Any potentially identifying information obtained in connection with this clinical trial will remain confidential and will only be used for the purpose of this clinical trial and it will only be disclosed with your permission, except as required by law. The information collected is classified as re-identifiable with identifying details replaced with a code). There investigators can link the code back to you if necessary, under extenuating circumstances (e.g. safety concerns). The code will be stored separately from the data. The information collected in this clinical trial will be entered into a database, using the code rather than your personal identifiable details. The clinical trial team, regulatory authorities, and Metro South Human Research Ethics Committee (HREC) and site Governance, The clinical trial team, regulatory authorities, and Metro South Human Research Ethics Committee (HREC) and site Governance will be able to inspect and have access to confidential data that identifies you by name. Any analysis, interpretation and publication of the study results will not identify individuals.

The paper files from interviews and from sessions will be stored in locked filing cabinets in a dedicated research office. Computer files will be kept on a password-protected computer at a designated site (which has high level security). Only approved clinical trial staff, Metro South Human Research Ethics Committee and site Governance may access your data. Records relating to the results of the trial will be kept for 7 years. After the 7-year period your paper records will be shredded and destroyed, and computer files deleted from the CRFs.

9.2.2. Monitoring and Quality Assurance

The investigator will submit to the Reviewing HREC, annual (or more frequent if requested) reports of the study. Senior staff of the Queensland Centre for Mental Health Research will undertake regular quality checks to ensure consent.

10. Investigator Responsibility

The Coordinating Principal Investigator will be responsible for the conduct of all aspects of the study. The study and its associated documents will be reviewed and approved by the appointed certified HREC and Research Governance (at all sites) before study start.

Prior to submission to appointed HREC and Research Governance, the investigator will sign the protocol signature page confirming her agreement to conduct the study in accordance with the protocol, GCP and other regulatory requirements locally applicable. All relevant data and records will be provided to the HREC as required.

11. Study Report

The Investigator will submit at least annual study reports to the reviewing HREC, or more frequent if required.

12. Administrative Procedures

Ethical Considerations

All documentation pertaining to the study must be prepared in accordance with the requirements outlined by the relevant ethics committee. All documentation must then be approved or given a favourable opinion in writing by an HREC as appropriate.

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements. The NHMRC National Statement on Human Research will also be utilised.

The Cognitive Remediation interventions are designed to be enjoyable and engaging with an emphasis on strategy rather than performance scores. The programs recognise that people with

schizophrenia spectrum disorders have often had repeated experiences of failure in learning situations and therefore the training of therapists and program designs emphasise doing your personal best and normalising cognitive strengths and weaknesses

Ethical Review Committee

The National Ethics Application Form (NEAF) and associated documents will be submitted for approval to the appointed multi-site HREC and written approval obtained from both the appointed HREC and Governance Office, before volunteers are recruited and participants are enrolled. The Coordinating Principal Investigator will submit the National Ethics Application Form and associated documents including Site Specific Applications from each site, to the appointed HREC and Research Governance. The Coordinating Principal Investigator has overall responsibility to ensure all reports at each site are submitted in line with the appointed HREC reporting requirements.

Informed Consent

Our criteria will ensure that recruited participants will be sufficiently competent to consent and participate in the study or to refuse consent. Current research provides evidence that while psychotic symptoms may be present, these do not robustly predict an individual's functionality in daily life and capacity to make decisions, and whilst strongly correlated with cognitive impairment, do not reflect an enduring inability to understand information related to research participation.

Participant Reimbursement

There are no additional costs associated with participating in this research project, nor will participants be paid.

Participants may be reimbursed for any reasonable travel, parking, meals and other expenses associated with the research project visit.

Notification of Primary Care Physician

It is desirable that the participants local doctor and/ or treating team be advised of their decision to participate in this research project.

Intellectual Property (IP) and Licencing

The collection of data in this study is subject to Intellectual Property (IP) and Licencing agreements which will be documented in the Research Agreement. Publication Policy

De-identified results will be disseminated in peer reviewed publications, published in international journals and conferences.

Protocol Amendments

Any amendments to the protocol will be submitted to the appointed HREC by the Coordinating Principal Investigator for approval. Any approved amendments by the appointed HREC will be

forwarded by the Coordinating Principal Investigator for submission to each Research Governance Office.

No changes (amendments) to the Protocol will be implemented without prior approval from the Reviewing Ethics Committee. If a Protocol amendment requires changes to the Informed Consent Form, the revised Informed Consent Form, prepared by the Coordinating Principal Investigator, will be approved by the Reviewing Ethics Committee and site governance officers.

Once the final Protocol has been issued and signed by the Coordinating Principal Investigator and the authorised signatories, it will not be informally altered. All protocol amendments will pass through appropriate approval steps before being implemented. Any change to the protocol constitutes an amendment.

Where the amendment affects the ongoing suitability of the study at a participating site, Research Governance approval will also be sought. The Research Governance Office will determine the ongoing suitability based on the amendment submitted.

The Coordinating Principal Investigator will submit the amendment to the appointed HREC for their approval; written approval will be obtained. Completed and signed Protocol amendments will be circulated to all appointed site Investigators.

Version Control

Version control ensures that amendments to documents are tracked and verifiable and that the correct version of a document is in use according to the relevant ethical, regulatory or local approval.

All documents will be given a version number and date e.g., Version 1.0 15-Feb-15

Each amendment to a document will require a version number and date to be updated.

If this is a **significant change** e.g., change in the content of the document, then the version number will be increased by 1.0.

If it is a **minor change** e.g., contact details, then the number after the decimal point will be increased by 0.1.

Protocol Compliance

Should there be questions or consideration of deviation from the Protocol, clarification will be sought from the Coordinating Principal Investigator. Any participant treated in a manner that deviates from the Protocol, or who is admitted into the study but is not qualified according to the Protocol, will be ineligible for analysis.

If an emergency occurs that requires a departure from the Protocol, the nature and reasons for the Protocol violation/deviation will be recorded in the CRF and the Coordinating Principal Investigator will notify the Reviewing HREC and /or Governance Office as soon as possible.

Whilst the Coordinating Principal Investigator has overall responsibility for the conduct of the study, the appointed site Investigators will have the responsibility to ensure all study personnel at their sites comply with GCP, National Statement on Ethical Conduct (2007), Australian Code for the Responsible Conduct of Research and local policies and procedures.

Archives: Retention of Study Records

All documentation will be kept by the Investigators for at least 7 years, or the maximum time frame as determined by local regulations, whichever is the longest.

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