Profiling Ultra High Risk for Psychosis

Lisa Harvey

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Thesis declaration form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

Name: LISA HARVEY

Date: 17/07/15

Overview

This thesis evaluates the Ultra High Risk (UHR) for Psychosis evidence, and seeks to clarify how research exploring differences demonstrated by cannabis and ketamine users on measures and tasks related to the psychosis prodrome can contribute to understanding the factors involved in this stage. The thesis also examines the literature on cognitive biases and insight in the UHR state, summarising the evidence for measures and tasks which sensitively differentiate the UHR state from other stages of Psychosis development.

Part 1:

A systematic review exploring evidence for cognitive biases and insight in individuals assessed as being at Ultra High Risk for Psychosis was carried out. Results showed that specific questionnaires and tasks were sensitive to identifying differences in UHR individuals when compared to both Healthy Controls, and to First Episode Psychosis comparator groups. Specific symptoms of psychosis were also correlated to other mechanisms, such as attribution biases, coping strategies and level of insight.

Part 2:

Drug models have been used to gain insight into the symptomatology of prodromal psychosis. This research made further investigation into psychological constructs related to prodromal psychosis using computer tasks and questionnaire measures, in groups of chronic ketamine and cannabis users. Participants were tested using the Ambiguity of Attribution task and the White Noise task. Self-report questionnaires measuring depression, anhedonia, and positive / negative indicators for psychosis were administered.

Results showed that the drug using groups had higher self-reported depression (BDI), schizotypy (O-LIFE) and psychosis (PQ-B) than controls. In the Ambiguity of Attribution task, Controls had significantly higher distinction between self and other, and higher mutual information used than the two drug-use groups. The ketamine group demonstrated higher predictability in tapping style on this task than the other two groups. There were no differences between groups on the White Noise task. Participants in the ketamine group reported higher distress related to drug-use than the cannabis group. Questionnaire scores of depression, schizotypy and positive and negative symptoms related to early psychosis are higher in chronic users of ketamine and cannabis. Performance on the Ambiguity of Attribution task was impaired in the drug-using groups, when compared to controls. These findings suggest that these groups of individuals are a useful population for research into prodromal psychosis.

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Cognitive bias and insight in Ultra High Risk for psychosis populations:

A systematic review

Introduction

Background to defining Ultra High Risk for psychosis

In the last twenty years, there has been a considerable amount of research carried out into the prodromal phase of, At Risk Mental State (ARMS) or Ultra High Risk (UHR) for psychosis (O'Connor, 2013, Olsen & Rosenbaum, 2006; Correll et al 2010; Fusar-Poli et al 2013). Predominantly, studies have retrospectively identified early emergent patterns in the prodromal phase of psychosis which could possibly predict the early onset of psychosis, identifying opportunities for intervention and prevention prior to First Episode Psychosis (FEP) (Klosterkotter et al , 2001; Mason et al, 2004; Thompson et al, 2011).

Several studies have been carried out looking specifically at the symptoms present in early psychosis, and particularly at specific symptoms such as hallucinations and delusions, and how these relate to underlying cognitive processes (Langdon et al, 2008; Freeman et al, 2014). Evidence emerging to date has shown that there appears to be a trajectory into early psychosis, with several researchers suggesting that there are early and late stages to a prodrome (Bechdolf et al, 2012). These studies suggest that further investigation into the specific cognitive processes underlying prodromal psychosis may help chart the possible symptom changes and factors which may constitute a later transition to a psychotic disorder.

Trajectory of the Prodrome – Clinically Assessing Ultra High Risk

A psychometric instrument for rating symptom severity in individuals at Ultra High Risk for psychosis was developed in the late 1990s in the USA (McGlashan et al, 2010). This was then followed up by development of the Basic Symptoms criteria for assessing risk, as first evidenced by a European group of clinicians and researchers (Kloesterkotter et al, 1996; Schultze-Lutter et al 2012). Out of these early approaches, the first clinical assessment for prodromal psychosis was developed in Australia in the Personal Assessment and Crisis Evaluation clinic, where Clinicians (Yung et al, 2006)

used the Comprehensive Assessment of At-Risk Mental State (CAARMS) to assess a combination of: a) attenuated psychotic symptoms, b) brief limited intermittent psychotic episode and c) trait vulnerability plus a marked decline in psychosocial functioning (genetic risk and deterioration syndrome [GRD]). This was later followed by an assessment developed in the USA (Miller et al, 2003) the Structured Interview for Prodromal Symptoms and associated Scale of Prodromal Symptoms (SIPS/SOPS). These instruments also defined UHR as meeting one of the three critera contained in the CAARMS. The Schizophrenia-Proneness Inventory (Schultze-Lutter et al,2007) took a different approach to defining UHR, instead using Basic Symptom clusters combined with self-perceived perceptual and cognitive changes: COGDIS (the 9 cognitive changes that are most associated with later transition to psychosis) and COPER (10 cognitive-perceptive BS) thus basing UHR definition on an earlier less prominent group of symptomatic changes (summarised in Fusar-Poli et al, 2013).

What is the evidence? Predictors of Psychosis

There have been several reviews carried out in the last ten years investigating and summarising the best predictors for transition to later psychosis, and suggesting factors which may contribute to our understanding of UHR for psychosis. In the North American Prodromal Longitudinal Study (Cannon et al, 2008) 5 clinical predictors for psychosis were: 1.GRD; 2. High Unusual Thought Content; 3. High Suspicion / Paranoia; 4. Low Social Functioning and 5. Substance Misuse. A later European Study (Ruhrmann et al, 2010) found 6 predictors for transition to psychosis; 1. Positive Symptoms; 2. Bizarre Thinking; 3. Sleep Disturbances; 4. Schizotypal Disorder; 5. Level of functioning in the last year and 6. Years of Education. As can be seen from these findings, there are a number of factors in different areas which need to be given consideration, meaning that correctly defining or diagnosing UHR is a complicated process.

Another review of the evidence for UHR for psychosis (Correll et al, 2010) paper ended the with a table of open questions to future researchers of UHR. Two of the specific open questions to address

were: "how to increase the sensitivity, specificity and predictive power of true prodromal symptoms and symdrome,' and "what are the predictors and mechanisms of true prodromal symptom emergence". Several studies have highlighted the fact that transition rates to psychosis do not necessarily show a homogenous type of presentation when early symptoms are examined retrospectively (Fusar-Poli et al, 2013). Interestingly, the psychotic disorders working group also suggested that Attenuated Psychosis Syndrome be included in the DSM-5 as an area for further study in an appendix 'Attenuated Psychosis Syndrome' They recognised that what was discovered through research and what was observed clinically in UHR individuals was inconsistent, and felt there was a need to further clarify UHR parameters. (Tsuang et al, 2013).

Cognitive Biases in Attribution

For the purposes of identifying specific cognitive processes which may be present in early stages of psychosis, researchers and clinicians have examined cognitive distortions in thinking, which cover a range of domains: for example jumping to conclusions, intentionalising, catastrophising, emotional reasoning and dichotomous or black and white thinking, are all included in the Cognitive Biases Questionnaire for psychosis (Peters et al, 2013) Some of these distortions relate specifically to the concept of attribution, the idea that events or experiences are caused by either self, and therefore are internally regulated, versus being caused by other, and are therefore externally controlled.

Historically, work exploring attribution biases has examined whether those in early psychosis or with a diagnosis of schizophrenia tend to misattribute the source of sounds or events to others, or conversely perceive themselves to have greater control than over situations or events has shown that these biases are present in these populations (Fine et al, 2007; Garety et al, 2011). In several studies, experimental tasks investigating the 'Jumping to Conclusions' bias, using the Beads Task (Merrin et al, 2007) and perceptual misattribution, relating to sense of agency or locus of control using the Verbal Self-Monitoring task (Johns et al, 2001) have established differences in individuals experiencing positive symptoms of psychosis or Schizophrenia (Freeman et al, 2014; Allen et al,

2004).This research has typically focused on populations of individuals who are already identified as experiencing positive symptoms. Would the same biases be found in populations of individuals who had been identified as being at UHR for psychosis? If so, would measures that explore how individuals make sense of events, and attribute control over them either to themselves or others, provide a more detailed understanding of early cognitive distortions which may contribute to later onset of psychosis? Examining studies employing questionnaires which assess locus of control, and how much an individual feels that they have the ability to influence a situation, alongside questionnaires or tasks which more explicitly ask participants to identify the source of a perceptual experience (ie. self/other) may further clarify these processes.

Cognitive Insight

Separate to cognitive biases or problems with cognitive reasoning is cognitive insight. Previous studies into both Schizophrenia (Engh et al, 2010) and Psychosis (Martin et al, 2010; Warman et al, 2007; Buchy et al, 2010) have shown that reduced cognitive insight (using the Beck Cognitive Insight Scale) has negatively impacted on prevalence of psychotic symptomatology. These studies also found that there was a difference in level of insight in two overarching factors between individuals with a diagnosis of psychosis or schizophrenia, and non-psychiatric help-seeking individuals: self-reflectiveness and self-certainty. The level of self-certainty in patients already diagnosed with a psychotic disorder, suggested that at this stage, individuals were less capable of challenging their own thoughts or possible cognitive distortions. On the other hand, non-psychiatric populations demonstrated a capacity for greater self-reflectiveness, meaning that they were more able to challenge their own possible biases. Understanding these two factors in cognitive insight, may be another important way of making sense of how and why Cognitive Biases become more powerful over the trajectory of a psychotic illness developing. For this reason, this study will also examine research including measures of cognitive insight.

Rationale and Questions for this review

In 2006, a systematic review of different measures available to characterise the UHR for psychosis state was published (Olsen & Rosenbaum, 2006). The review concluded by suggesting that instruments which further elucidated the phenomenological aspects, or underlying mechanisms of anomalies in self-experience, may help to further develop the field, in terms of adding to the evidence for the aetiology and development of psychotic symptoms. There have been several previous studies which have summarised the effect of impairments to neurocognition (Kelleher et al, 2012; Addington & Barbato, 2012), and social cognition (Lee et al, 2015; Barbato et al, 2013; Healy et al, 2013) in UHR populations. In populations already identified as either Schizophrenic (Brunelin et al, 2006; Hoffman et al, 2007), experiencing First Episode Psychosis, or as being diagnosed with a psychotic disorder, there is also evidence for cognitive biases, and level of cognitive insight relating to symptoms outcomes and the trajectory of the illness. These studies have helped to inform psychological treatments and interventions.

However, seemingly little is known about the cognitive biases and level of cognitive insight which is present in the early prodromal phase, when UHR individuals may experience some alteration to their usual cognitive processes and level of awareness, but perhaps not to the extent of those in later stages of psychosis. This study aims to systematically review the literature for studies which investigated cognitive bias or level of cognitive insight specifically in UHR help-seeking clinical populations, with a view to answering the following questions:

1. Which cognitive biases/insight processes are found in UHR populations?
2. How are these biases, or levels of insight identified in UHR populations?
3. How does cognitive insight or bias change over the trajectory of psychosis, from UHR stages through to onset?
4. Do biases or level of insight correlate with specific symptoms, or symptom clusters?

To what extent are symptoms in UHR populations confounded by other factors (e.g. depression?)**Method**

Search Strategy

A systematic search of the literature was conducted by searching PsychINFO, Medline, Embase and Web of Science. The Cochrane Systematic Review Library was also searched to check for recent relevant reviews to the topic. Search terms focused on three areas, with several terms used for each: a) At Risk Mental State for b) Psychosis c) cognitive biases (see Table 1).

Table 1

Literature Review Search Terms

At Risk Mental State (Including exploded terms)	Psychosis (Including exploded terms)	Cognitive Biases
Prodromal	Psychosis-Proneness	Cognitive processes
Ultra High Risk (UHR)	First Episode Psychosis	Cognitive styles
Clinical High Risk (CHR)	Schizophrenia Prodrome	Cognitive insight
High Risk (HR)	Schizophrenia-Proneness	Attribution biases
Onset disorders	Positive Symptoms (for psychosis)	Attribution style
	Negative Symptoms (for psychosis)	Cognitive appraisal
		Jumping to conclusions (JTC)
		Schema
		Theory of Mind
		Metacognition
		Social cognition
		Cognitive ability

Limits were set on the databases to include journal articles only published since January 2006, to follow up on the last systematic review to specifically summarise studies including measures of cognitive bias in ARMS for psychosis populations (Olsen & Rosenbaum, 2006). The search included papers submitted up until May 2015. Several searches were carried out within the chosen databases, to combine different terms from the separate areas. There were several hundred search results after combining different terms. The search strategy was refined to combine 'At Risk Mental State' and exploded terms, with 'Psychosis' and at least one of the terms from the 'Cognitive Biases' list. To ensure other relevant papers had not been missed, reference lists from retrieved journal articles, and review articles relevant to the topic were also checked. The retrieved articles were searched using the inclusion and exclusion criteria set out below.

Inclusion and Exclusion Criteria

Inclusion Criteria

Sample Populations: For the purposes of looking specifically at the prodromal / at risk stage of psychosis, samples of clinical help-seeking individuals identified either by clinical researchers or clinicians as meeting criteria for UHR for psychosis were sought.

Age: Studies with participants as young as 11 years of age were included in the review, as these represented cohorts of participants who were using services for ARMS in adolescents. The age range inclusion was defined as 11-40 years of age, as this represented the younger population generally most at risk for developing later psychosis.

Design of study: Both cross-sectional and longitudinal studies were included in the review.

Measuring UHR: Participants in the included studies had to have been defined as UHR for psychosis by one of the following formally validated measures: CAARMS, SPI-A, SIPS/SOPS, ERIaos or a combination of measures which together gave good indication of the domains covered in the formal semi-structured interviews.

Questionnaire or task measuring cognitive bias / insight: As well as being assessed for prodromal symptoms and being defined as UHR, participants had to be assessed on at least one other measure (either a questionnaire, semi-structured interview or a task) which related to a cognitive process associated with cognitive biases or insight.

Exclusion Criteria

Sample Populations: Studies which did not include a prospective UHR clinical group (ie. studies which compared individuals already defined as being in FEP with healthy controls only), or studies which examined 'schizotypy' or 'delusion-proneness' in healthy populations and defined this as 'At Risk' for psychosis were excluded. They did not represent the help-seeking population we wished to examine. Studies were also excluded if individuals were defined as 'At Risk' ONLY by virtue of being a relative of someone with Schizophrenia or a psychotic disorder, without a formal assessment of UHR through completion of a semi-structured interview. Case reports were also excluded, due to the poor quality of evidence available from single cases.

Neurocognition: Studies were excluded if they only examined impairments to cognitive functioning as measured by test batteries assessing memory, verbal performance, and executive functioning and so on, with no investigation into cognitive biases or insight. This also included studies which may incorporate an electro-physiological component measuring implicit changes to usual cognitive functioning using for example Electroencephalographic (EEG) data.

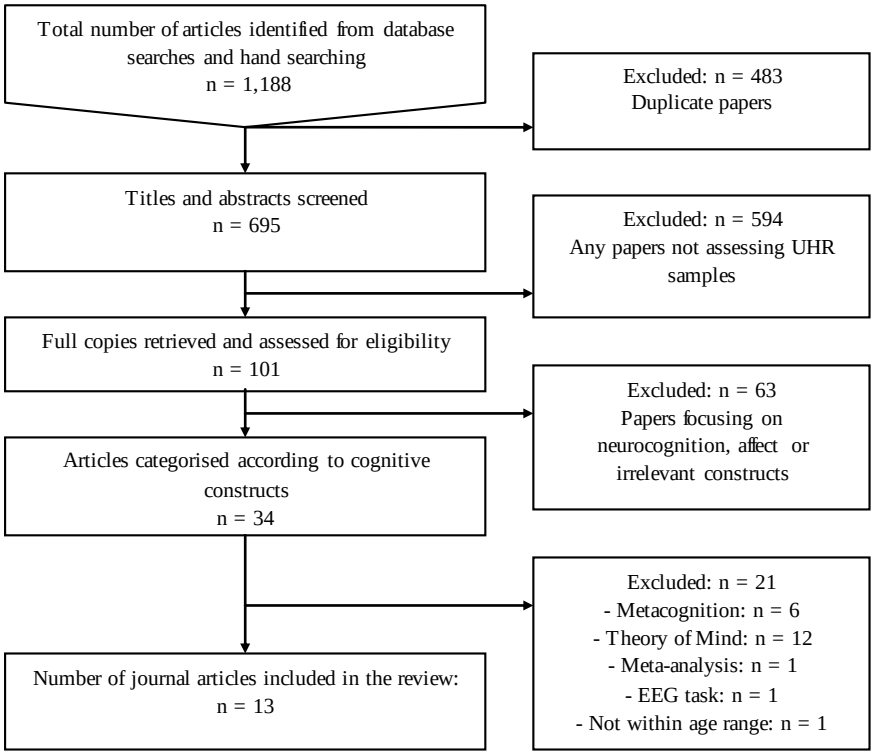
Affect Dysregulation / Emotional Recognition: Also excluded were studies which incorporated only a measure assessing impairments to affect or emotional processing, without looking directly at cognitive processes.

Quality Assessment

As there were a range of studies included in this search, including both cohort and cross-sectional designs, a quality appraisal tool suitable for assessing both types of design was used to screen the studies (Health Evidence Bulletin, 2004) (Appendix 1). A total score was given for each study based on these three areas: a) suitability of design to the question b) methodological limitations including chosen population and control group, selection bias and follow-up considerations and c) whether the findings were adequately analysed and interpreted. The last item on the checklist relating to whether or not results were relevant locally was removed, as this did not apply to the scope of this study.

Results

Figure 1. Flowchart of study selection



The database searches combining the three criteria identified a total of 695 publications. These were searched for relevance to the research question. After the papers had been reduced by identifying the articles which looked specifically at UHR populations and removing articles which examined affect, neurocognition or other unrelated non-cognitive constructs, a total of 34 articles remained. To further focus the scope the studies, we expanded the exclusion criteria. The papers which focused primarily on Metacognitive processes and Theory of Mind were removed. One paper which included an EEG measure as its primary outcome was also excluded. Finally, one meta-analysis examining social cognitive deficits in Ultra High Risk Populations was also excluded. This meta-analysis was checked for references however, as although it summarised studies predominantly interested in Social Cognition, some of the studies included had incorporated attribution measures. Studies which appeared relevant to this review were screened. A flowchart of study selection is presented in Figure 1.

The results from the studies are presented in Table 2. The papers were examined for their quality and grouped according to their area of investigation under these headings: Attribution biases, Schema, Cognitive Insight (in bold) in Table 3.

Table 2.

Studies investigating cognitive bias or insight in UHR for psychosis. (All participants in UHR met criteria for ARMS according to formal assessment tool)

Author(s) country and date	Country	UHR Sample	Design and Methodology	Other measures used outside of clinical instruments for psychosis	Cognitive bias / process	Key findings
1. Addington and Tran (2009)	Canada	- N = 38 - M =28; F = 10 - Mean age = 19.7 yrs	- Cross-sectional - UHR assessed using COPS for SIPS - Controls – N/A - Clinical assessment, schema scales, other questionnaire.	1. Brief Core schema scale (SR) 2.Young schema Questionnaire-short (SR) 3.Calgary Depression Scale (SR)	- Evaluation of **self and other schema.** - Subscales in positive self/other; negative self/other	1. Unusual thought content / suspiciousness / total positive symptoms associated with negative-self schema and negative-other schema. 2. Depression, negative self and negative other were accounted for 10% of variance in thought disorder. 3. Depression, negative self and negative other accounted for 35% of variance of suspiciousness. 4. Depression, negative self and negative other accounted for 41% of variance of total positive symptoms.
2.An et al. (2010)	Korea	- N = 24 - M = 14; F = 10 - Mean age = 20 yrs	- Cross-sectional - UHR assessed using COPS for SIPS - Controls – 39 HC; 20 FEP - Clinical assessment by psychiatrists, other questionnaires.	1. Ambiguous Intentions Hostility Questionnaire (some items are rater driven) 2. Rosenberg's Self-Esteem Scale (SR) 3. Beck Depression Inventory (SR) 4. Paranoia scale (SR) 5. PANSS (persecution and suspiciousness items)	- **Attribution bias**: Perceived hostility, Composite Blame and Aggression biases. - Does this relate to persecutory ideation?	1. The UHR patients showed lower self-esteem, more depressive symptoms and more self-rated persecutory ideation than HC and FEP. 2. UHR and FE participants exhibited a significantly higher Hostility bias than the HC. 3. For the Composite Blame bias, UHR patients showed significantly more Blame bias than the HC and the FEP participants. 4. Perceived Hostility and Blame correlated with paranoia and suspiciousness/persecution. 5. Blame bias was still significantly correlated with suspiciousness/persecution when controlling for depression and self-esteem.
3. Broome et al. (2007)	UK	- N= 23	- Cross sectional	1. Freeston Intolerance of	- **Attribution bias**: Jumping	. 1. No significant difference in

Author(s) country and date	Country	UHR Sample	Design and Methodology	Other measures used outside of clinical instruments for psychosis	Cognitive bias / process	Key findings
		- Mean age = 24.9 - No information on gender	- UHR assessed using CAARMS, PANSS and SAPS - Controls – 23 HC - Clinical assessment, other self-report questionnaires, beads task, bead span working memory test, cognitive functioning test.	Uncertainty scale (SR) 2. Peters Delusion Inventory (PDI) (SR) 3. SAPS (delusion subscale) (CR) 4. Beads task measuring JTC	to conclusions - Intolerance of uncertainty	UHR and HC on the easy version of the beads task. 2. On both of the harder versions of the task (60:40 and 44:28:28) the UHR group drew fewer beads than HC before responding. 3. Highly significant differences between the UHR and HC groups on the total PDI score, and on each of the distress, preoccupation and conviction PDI sub-scales. 4. UHR group had a significantly shorter span for correct responses than controls on the beads span task. 5. The UHR group had significantly higher ratings on the Freeston Intolerance of Uncertainty scale than HC.
4. De Vylder et al. (2013)	USA	- N= 33 - Mean Age = 18.7 years - M = 27, F = 6	- Cohort (followed up for transition rates) - UHR assessed using COPS for SIPS - Controls – HC gender matched - Clinical assessment, other questionnaires at baseline, and then followed up.	1. The Internal, Personal, and Situational Attributions Questionnaire (SR) 2. Hamilton Rating Scale for Depression (SR) 3.Hamilton Rating Scale for Anxiety (SR)	**Attribution Bias**: externalising bias; personalising bias	1. UHR patients and HC had nearly identical attributional styles, with both externalizing and personalizing biases. 2. The exaggerated self-serving bias associated with paranoia was not evident in this UHR group. 3. Among UHR participants, there was no association of attribution with suspiciousness or subthreshold paranoia (or any clinical measures), or eventual transition to psychosis. 4. Attribution was comparable among those UHR patients who did and did not make a later transition to psychosis.
5. Johns et al (2010)	UK	- N= 31 - Mean age = 24.7 yrs - M = 19, F = 12	- Cross-sectional - UHR assessed using PACE criteria in CAARMS, PANSS - Controls: 31 HC matched for age and IQ	1. Hamilton Rating Scale for Anxiety (SR) 2.PANSS (CR) 3. VSM Task 4. National Adult Reading Test	-**Attribution bias**: defective self-monitoring, external attribution of internal speech	1. In the reading aloud condition, participants in UHR group made more total errors than controls when their speech was distorted. 2. UHR made more misidentification responses, (excluding unsure) than controls, but only under

Author(s) country and date	Country	UHR Sample	Design and Methodology	Other measures used outside of clinical instruments for psychosis	Cognitive bias / process	Key findings
			- Clinical assessment, questionnaire, IQ test, task.			severe distortion. 3. Across all levels of distortion, UHR participants made more misidentification errors than controls when the words presented were positive or neutral, but not when they were negative. 4. In the reading aloud with alien feedback condition, no significant differences between group in total errors or misidentification responses. 5. The UHR participants responded more slowly than HC overall when making misidentifications. 6. Misidentifications in UHR were correlated with a lower severity of unusual thought content and a lower severity and frequency of perceptual abnormalities on the CAARMS. 7. Severe symptomatology on the CAARMS in UHR was significantly associated with longer reaction times. 8. Misidentifications did not correlate positively with the level of prodromal symptoms reported by UHR participants. Instead, negative correlations between misattributions and the severity and frequency of attenuated positive symptoms were found: individuals with more marked symptoms made fewer misattributions.
6. Lappin et al (2007)	UK	- N= 33 - Mean age = 24.6 yrs (19 – 29) - M = 17, F = 16	- Cohort (followed up for transition) - UHR assessed using PACE criteria on CAARMS, IGC and PSE - Controls = FEP both compulsory treatment (104) and voluntary (45) matched for age and gender. - Clinical assessment using 3 measures, then Insight	1. Item Group Checklist (IGC) summing the SCAN's (Schedules for Clinical Assessment in Neuropsychiatry) based on Present State Examination (PSE). 2. Schedule for Assessment of Insight (SAI-E).	- **Cognitive Insight**: including subscales on Illness Awareness, Symptom Relabeling and Perceived Need for Treatment.	1. Total symptom score was significantly higher in All FEP and in Voluntary FEP than in the UHR group. 2. Insight in UHR group was significantly less impaired than in All FEP group. There were significantly lower scores in FEP subjects in both 'Perceived Need for Treatment' and 'Symptom Relabeling', but not 'Illness Awareness'. 3. Comparison of insight measures between UHR and the subgroup of Voluntary FEP revealed a

Author(s) country and date	Country	UHR Sample	Design and Methodology	Other measures used outside of clinical instruments for psychosis	Cognitive bias / process	Key findings
			scale, followed up later.			significantly greater impairment in overall insight in the FEP group. They had significantly lower scores for 'Symptom Relabeling', but not for 'Illness Awareness' nor for 'Perceived Need for Treatment'. 4. Following assessment, 6 participants made a subsequent transition to psychosis (mean time to transition = 14.3 months). The mean length of follow up in the study without transition to psychosis was 22.7 months.
7. Olvet et al. (2015)	USA	- N= 73 - Age range: 12 - 20 - M = 47, F = 23	- Cross-sectional - UHR assessed using one of 3 criteria for SOPS, then categorised into positive symptoms group. Only UHR + included. - Controls: 50 HC matched for age. - Clinical assessment, other questionnaires, correlations.	1. Global Assessment of Functioning (GAF), Global Functioning Social (GF:Social) and Global Functioning Role (GF:Role) (CR) 2. Children's Depression Inventory or Beck Depression Inventory (BDI / CDI) (SR) 3. Sheehan Disability Scale (SDS) (SR) 4. Beck Anxiety Inventory (BAI) (SR)	**-Cognitive Insight**: Using awareness of functional impairment and perceived disability, checked against clinician judgement.	1. At baseline the UHR+ group reported significantly higher scores on the SIPS positive total Score, SIPS negative total Score, BDI/CDI percentage score and the BAI total score compared to the HC group. The UHR+ group also reported impairment on baseline GAF, GF: Social, GF: Role, SDS Social and SDS Work/School compared to the HC group. 2. Poor SR social functioning was related to poor CR social and role functioning, poor GF, and more severe depression and anxiety symptoms. 3. There were significant correlations between the SDS Social and all clinical measures, except the SOPS total positive and negative symptoms. There were also significant correlations between the SDS Work/School and the GF: Role, GAF, BDI/CDI and BAI. Poor self-reported work/school functioning was related to poor CR role (but not social) functioning, poor GF and more severe depression and anxiety symptoms.
8. Ruhrmann et al (2008)	Germany	- N= 58 (EIPS), 157 (LIPS) - Mean age EIPS = 26.2; LIPS = 25.7 - EIPS: M = 40, F =	- Cross-sectional - The EIPS and LIPS criteria were assessed by the Early Recognition Inventory, ERIraos and PANSS - Controls = 87 HC - Clinical assessment, other questionnaires.	1. Modular System for Quality of Life (MSQoL) (Subscales: Physical Health, Vitality, Psychosocial, Material, Spare Time, Affective, General) (SR) 2. The Symptom-Checklist, SCL-90-R (SR) (subscales: Somatization, Uncertainty in social	- **Cognitive Insight**: LOC, coping strategies and subjective quality of life - Also looking specifically at the differences in gender.	1. In LIPS group, males showed significantly lower scores in three domains: Psychosocial QoL, Spare time QoL and General QoL. 2. In the HC group, males exhibited higher Physical Health scores. 3. In the EIPS group, no significant gender-related differences emerged.

Author(s) country and date	Country	UHR Sample	Design and Methodology	Other measures used outside of clinical instruments for psychosis	Cognitive bias / process	Key findings
		18; LIPS: M = 94, F = 63		interactions, Depression and Fearfulness) 3. Stress Coping Questionnaire, SVF-120 (SR) 4. The Questionnaire of Competence and Control Beliefs (FKK) (SR)		4. Both EIPS and LIPS showed a significantly lower sQoL than HC on every scale. 5. A significant main effect of gender was revealed on Vitality. Significant interactions between group and gender emerged on every dimension except Material QoL . 6. Compared to the EIPS group, the LIPS group reported significantly higher Uncertainty in social interactions and Fearfulness scores as well as more marked basic symptom s, positive psychosis spectrum symptom s and PANSS-positive and PANSS-negative symptom scores.
9. Schmidt et al (2014)	Switzerland	- N= 21 - Age range 11-34 - M = 7; F = 14	- Cross-sectional - UHR assessed using COPS for SIPS, BS assessed using SPI-A - Controls = 22 FEP - Clinical assessment, questionnaires.	1. Mini International Neuropsychiatric Interview (MINI/KID) (CR) 2. Stress Coping Questionnaire (SR) 3. Competence and Control Beliefs questionnaire (SR)	- **Attribution Bias:** Locus of control-Externalising bias / internalising bias / control beliefs - Negative or positive coping strategies	1. Significant differences between the groups in coping strategies: a) More UHR (62%) than FEP (37%) patients showed positive strategies outside the normal range; b) Negative coping strategies: used excessively by the majority of both UHR and FEP patients. c) In UHR deficits in self-efficacy linked to low self- concept. In FEP most deficits accounted for by tendency to act overly-self-confident. d) UHR demonstrated a fatalistic externalising bias but not social externalising bias, attributing things to chance excessively, and thinking situations were beyond their control. e) FEP revealed no evidence for an externalising bias, and reported greater self-efficacy.
10.Taylor et al (2014)	UK	- N = 113 - Mean age = 20.4 - M = 46, F = 67	- Cross sectional - UHR assessed using first 4 subscales of the CAARMS, positive symptoms only Unusual Thought Content, Non-Bizarre Ideas , Perceptual	1.Brief Core Schema Scale	- Evaluation of **self and other.** - Subscales in positive self/other; negative self/other	1. The NH group scored significantly lower on negative-self than the FEP, ARMS, and HSC groups. There were no significant differences between the other groups. 2. The NH scored significantly higher on positive-self than the UHR and HSC groups.

Author(s) country and date	Country	UHR Sample	Design and Methodology	Other measures used outside of clinical instruments for psychosis	Cognitive bias / process	Key findings
			Abnormalities, and Disorganized Speech - Controls = 20 FEP, 28 HS and 30 NH (PLEs - assessed with CAPE) - Clinical assessment by trained research assistants, then BCSS.			There were no significant differences between the other groups. 3. For negative-other, the NH group scored significantly lower than the FEP, UHR, and HSC groups. 4. Two correlations were significant across all groups: a) 'Non Bizarre Ideas – distress' with Negative-Self and b) 'Perceptual Abnormalities – distress' with Negative-Other. 5. There were no relationships between Unusual Thought Content - distress or Disorganised Speech - distress and core schemas. 6. There was no relationship between psychotic symptoms and Positive Self or Positive Other.
11. Thompson et al (2012)	Australia	- N= 30 - Mean age: 19.1 - M = 14, F = 16	- Cross-sectional - UHR assessed using PACE criteria for UHR - Controls – 30 HC matched for gender and age. - Clinical assessment, neuropsychological testing, questionnaires.	1. Adult Nowicki Strickland Internal External (ANSIE) locus of control scale (SR) 2. Social and Occupational Functioning Assessment Scale (SR) 3. Two individual scales assessing role functioning and social functioning independently (SR) (Cornblatt et al. 2007) 3. Brief Psychiatric Rating Scale 4. Scale for the assessment of negative symptoms. 5. Wechsler Abbreviated Scale of Intelligence (Vocabulary and Matrix Reasoning) 6. Wechsler Memory Scale III (Spatial Span) 7. Trail Making tests A and B 8. Depression Anxiety and Stress Scale (SR)	- **Attribution bias** – Locus of Control - Subjective view of functioning	1. The mean ANSIE LOC score for the UHR group was higher than for the controls indicating a more externalized LOC style. This remained statistically significant when adjusting for age, gender and IQ. 2. For UHR individuals, LOC score was correlated with total SANS score but not with total BPRS score, DASS total or DASS depression, anxiety or stress sub-scores. 3. LOC score was correlated with the BPRS item of suspiciousness as a broad measure of paranoid symptoms.
12. Uchida et al (2013)	Japan	- N= 60 - Mean age = 19.5 yrs - M = 22, F = 38	- Cross-sectional (followed up for transition) - UHR assessed using Japanese version of CAARMS	1. Beck Cognitive Insight Scale (SR) (Two component scores: self reflectiveness and self-certainty. A composite index representing	- **Cognitive Insight**, looking at self-certainty, self-reflectiveness and composite scores.	1. The BCIS-J self-certainty mean score was significantly higher for the UHR group than for healthy participants. 2. There were no significant differences in self-

Author(s) country and date	Country	UHR Sample	Design and Methodology	Other measures used outside of clinical instruments for psychosis	Cognitive bias / process	Key findings
			- Controls – 200 HC recruited from university. - Clinical assessment, assessment of cognitive insight, followed up for transition.	cognitive insight is calculated by subtracting self-certainty from self-reflectiveness.)		reflectiveness or composite index scores between the UHR and control groups. 3. In the UHR group, self-certainty scores were significantly correlated with attenuated delusional symptoms in the CAARMS. Self-reflectiveness and composite index scores were not correlated with attenuated delusional symptoms. 4. In antipsychotic- free individuals with UHR, the self-certainty score was positively correlated with delusional symptoms. The composite index score was negatively correlated with delusional symptoms. The self-reflectiveness scores showed no significant correlation to delusional symptoms. 5. Five participants in the UHR group transitioned to psychosis during the follow-up period. The mean duration of follow-up was 21.92 months. The mean self-certainty score of participants in the UHR group who transitioned to psychosis was higher than that of participants who did not transition, but only at a marginally significant level.
13.Winton-Browne et al (2015)	UK	- N = 23 - Mean age = 24.8 yrs - M = 11, F = 12	- Cohort longitudinal prospective (followed for transition rates) - UHR assessed using CAARMS and PANSS - Controls – 'matched' control groups for the tasks only - Clinical assessment, questionnaires, tasks, then followed up on average 31 months later to complete same measures.	1. Hamilton Rating Scale for Depression (SR) 2. Hamilton Rating Scale for Anxiety (SR) 3. Peters Delusion Inventory (SR) 4. Global Assessment of Functioning (GAF) 5. Beads task (JTC) 6. VSM (Misattribution)	-**Attribution bias**: - Jumping to Conclusions - Verbal Self-Monitoring	1. Participants in the UHR group drew fewer beads before reaching a decision on the moderate difficulty (60:40) beads task and made more externalizing misattribution errors during distorted feedback in the VSM task than controls. 2. At follow-up there was a significant improvement in mean VSM task performance. The UHR group participants made fewer externalising misattribution errors during distorted feedback at follow-up than at baseline 3. Mean performance on the beads task remained the same at baseline and follow-up on the moderate (60:40) and hard (44:28:28) versions of the task 4. There were no significant mean baseline

Author(s) country and date	Country	UHR Sample	Design and Methodology	Other measures used outside of clinical instruments for psychosis	Cognitive bias / process	Key findings
						differences between the UHR group who later made a transition and those who did not, in terms of VSM (% misattribution errors with distorted feedback) or JTC (60:40 Draws to Decisions), demographic or clinical measures (age, gender, GAF, PANSS-positive, Ham-A, Ham-D). 5. There were no differences in longitudinal change in JTC or VSM measures between the group to transition and those who didn't, and no differences in GAF at follow-up.

UHR = Ultra High Risk; FEP = First Episode Psychosis; HC =Healthy Controls; HSC = Help-seeking Controls; NH= Non-help-seeking; FR = Familial Risk; EIPS = Early Initial Prodromal State; LIPS = Late Initial Prodromal State; SR = Self Report; CR = Clinician Rated; JTC = Jumping to Conclusions; VSM = Verbal Self Monitoring; LOC = Locus of Control; BS = Basic Symptoms; COPS = Criteria of Prodromal States; SIPS = Structured Interview for Prodromal Syndromes; SOPS = Scale of Prodromal Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SANS = Scale for the Assessment of Negative Symptoms; PANSS = Positive and Negative Syndrome Scale; PACE = Personal Assessment and Crisis Evaluation; CAARMS = Clinical Assessment for At Risk Mental State; SPI-A = Schizophrenia-Proneness Instrument – Adult.

Table 3

Quality assessment ratings for studies investigating cognitive bias or insight in UHR for psychosis

Author(s) and date	Methodological Items								Overall Quality
	Aim of study Q1	Focus of study Q2	Method Q3	Population Q4	Bias Q5	Cohort Study Q6	Tables and graphs Q7	Analysis Q8	
Addington and Tran (2009)	+	+	?	-	?	N/A	+	+	-
An et al (2010)	+	+	+	+	+	N/A	+	+	++
Broome et al. (2007)	+	+	+	+	?	N/A	+	+	+
De Vylder et al. (2013)	+	+	+	+	?	-	+	+	+
Johns et al. (2010)	+	+	+	+	+	N/A	+	+	++
Lappin et al. (2007)	+	+	+	+	+	+	+	+	++
Olvet et al. (2015)	+	+	?	?	+	N/A	+	+	+
Ruhrmann et al. (2008)	?	+	?	+	?	N/A	+	?	+
Schmidt et a (2014)	+	+	+	+	?	N/A	?	+	+
Taylor et al (2014)	+	+	+	+	?	N/A	+	+	+
Thompson et al (2012)	+	+	+	+	+	N/A	+	+	++
Uchida et al (2013)	+	+	+	+	?	?	+	+	+
Winton-Brown et al. (2015)	+	+	+	+	+	+	+	+	++

1. Cognitive biases or insight in UHR for psychosis populations

1.1 Examining core schema.

There were two papers (1, 10) which made use of the Brief Core Schema Scale (BCSS) to examine underlying psychological processes which might be relevant to the early formation of symptoms of psychosis. The first of these studies (Addington & Tran, 2009) was the weakest study included in the review, as it did not include a comparison control group, and gave limited information on exclusion criteria. It therefore had less relevance to the part of the review question focusing on differences in UHR individuals, in that it did not directly address how they may differ or compare to individuals with different risk factors, in early psychosis or healthy controls. The second study (Taylor et al, 2013) was more relevant, and compared UHR participants with both FEP participants and help-seeking and non-help-seeking controls. There was a significant difference in results from the BCSS in the non-help-seeking group only: they scored lower in negative-self and negative-other schemas than the other three groups. They also scored significantly higher in positive-self, than the UHR and help-seeking group. The UHR group appeared to have similar core schema to both FEP and Help-seeking participants, with higher negative self / other schemas, and lower positive self schema. In summary, UHR individuals have higher levels of negative self / other schema; a tendency to negative schema is also present in help-seeking and FEP individuals.

1.2 Locus of Control – Personalising versus Externalising

There were three studies (8, 9, and 11) which included measures of Locus of Control (LOC). Two studies used the Competence and Control Beliefs Questionnaire (SKK) (8, 9) and the other study used the Adult Nowicki Strickland Internal External LOC scale (ANSIE). In the first study (8) using the SKK, the results were difficult to interpret as the measure was only completed for the EIPS group in the UHR cohort, and not the LIPS. For this reason, analyses comparing means between groups were not provided. In the second study (9) results showed that the UHR group demonstrated a fatalistic

externalising bias but not a social externalising bias, meaning that situations or events were attributed to chance excessively; this indicated that these participants held a belief that situations were beyond their control. Conversely, the FEP group in this study showed no externalising bias. In the third study (11) there was a higher mean score on the ANSIE in the UHR group than in the controls, indicating a more externalized LOC style. This remained statistically significant when adjusting for age, gender and IQ. UHR individuals have a tendency to demonstrate an externalising bias whereas those in FEP are more likely to have an internal LOC and higher self-certainty.

1.3 Attribution style or biases

1.3.1 The Internal, Personal, and Situational Attributions Questionnaire (IPSAQ)

The IPSAQ was used in one study (4) to investigate the attribution style of individuals at UHR for psychosis. The study was medium quality. In the study, the researchers did not match the groups for gender. The study found no difference in attributional style between UHR and HC individuals. The UHR group exhibited similar patterns of personalising and externalising bias to the control group. This study also found that when the UHR and HC groups were combined, females showed a higher externalising bias. As the groups were not matched for gender, this may have had an impact on the results. In summary the IPSAQ did not identify differences in attributional style in the UHR group.

1.3.2 Measuring Attribution biases using tasks

There were three studies which made use of tasks measuring attribution biases, namely the Jumping to Conclusions beads task, and the Verbal Self Monitoring task (3, 5, and 13). The last study (13) combined results from the previous two studies' baseline data, and followed this up at a later date, in order to establish whether there had been individual changes in performance on these tasks after a period of time (average 31 months). The first study (3) was given a medium quality rating as it did not provide any information on the gender balance in the UHR group and the HC group. The other two studies (5 and 13) were two of the highest quality studies included in the review.

The UHR group displayed differences in their performance in the JTC beads task from the HC group, on both of the harder versions of the task (60:40 and 44:28:28) drawing fewer beads before responding, demonstrating a tendency to jump to conclusions (3). In this study the UHR group also showed a significantly higher score on the Freeston Intolerance of Uncertainty Questionnaire. The UHR group had a significantly lower score than the HC group on the bead span working memory task, exhibiting a shorter bead span remembered. Data from the longitudinal study (14) showed that when baseline data from the JTC bead task was followed up with the same UHR participants, they performed in a similar fashion at follow up, with no change to results. This was the case even when functioning had improved and specific symptom profiles had reduced.

The UHR group also exhibited differences from the HC group in the VSM task. There were two conditions with three levels of feedback distortion in the task. In the reading aloud condition, participants in the UHR group made more total errors than the HC group when their speech was distorted. They also made more misidentification responses, (excluding 'unsure' responses) than the HC group, but only under severe distortion. Across all levels of distortion, UHR participants made more misidentifications than HC participants when the words presented were positive or neutral, but not when they were negative. However, in the reading aloud with alien feedback condition, there were no significant differences between the groups in total errors or misidentification responses. This shows that the UHR group demonstrated a misattribution bias to being able to correctly identify the source of a voice, when compared to a HC group, under certain conditions. The UHR group also responded more slowly than the HC group, when making misidentifications, demonstrating a difference in processing speed under conditions which they performed worse in.

When the UHR group was followed up and asked to complete the task (13), they showed a significant reduction of externalising misattributions made under all levels of voice distortion, indicating that there had been an improvement in their ability to distinguish what was coming from self or other. At follow-up, those who had transitioned to psychosis were compared with those who had not, and there was no difference in these groups in performance on the VSM task. In summary, performance on both the JTC and VSM tasks may be good predictors or indicators of the UHR populations. However,

whilst the JTC task is sensitive to attribution bias regardless of change in function, VSM appears to be representative of state not trait bias, perhaps linked to changes in other factors.

1.3.3 *Ambiguous Intentions Hostility Questionnaire (AIHQ)*

There was one study (2) which investigated attribution bias using the AIHQ. This was one of the high quality studies included in the review. The questionnaire was specifically developed to detect paranoia, where different scenarios are described and respondents have to indicate whether they perceive them to be accidental, ambiguous or intentional. Three biases emerge from the questionnaire: Hostility bias, Aggression bias and a composite Blame bias. The composite Blame comprises perceived intent, anger and blame for each situation. The questionnaire is rater-driven after an individual has responded to the situations. The UHR group and FEP participants exhibited a significantly higher Hostility bias than the HC. However, for the Composite Blame bias, the UHR group showed significantly higher Blame bias than the HC and the FEP groups. The AIHQ could therefore be a very useful tool in distinguishing individuals at UHR for psychosis from those who are not, by paying attention to elevated Blame bias scores.

1.4 Cognitive Insight to functioning, quality of life and illness

There were four studies which were included in the review as they had investigated level of cognitive insight present in UHR individuals (6, 7, 8 and 12). Apart from one study which was high quality (6), the studies examining cognitive insight were medium in quality, due to biases in selection or matching of groups (see table 3). In the high quality study, the Schedule for the Assessment of Insight (extended) (SAE-I) was administered to well-matched groups of UHR and FEP participants. Lower scores in the three domains: Perceived Need for Treatment, Symptom Relabeling and Illness Awareness indicate higher level of impairment. The UHR demonstrated significantly less impaired insight to their illness than in the FEP group. There were significantly lower scores in FEP subjects in both 'Perceived Need for Treatment' and 'Symptom Relabeling' but not 'Illness Awareness'. The

UHR group were also compared to the 'Voluntary' FEP subgroup (participants who had not been treated under section or admission) and there was a significantly greater impairment in overall insight in this FEP group as they had significantly lower scores for Symptom Relabeling, showing a propensity to not use accepted terms for their experiences of psychosis.

The other studies included different methods of measuring insight. In one study (7) the researchers tested UHR participants' (recruited by positive symptom scales only) insight to their level of functioning and perceived disability due to early symptoms of psychosis, using the Sheehan Disability Scale and Functioning scales, and comparing the scores from these with scores from clinical assessments, thus comparing subjective and objective assessments of impairment. The UHR+ group reported impairment on baseline GAF, GF: Social, GF: Role, SDS Social and SDS Work/School compared to the HC group. Poor subjectively rated social functioning was related to poor objectively rated social and role functioning and poor Global Functioning in the UHR+ group. In another study (8) the Modular System for Quality of Life (MSQoL) was used to examine difference in perceived level of Quality of life (QoL) between a HC group, and two UHR groups, an EIPS and LIPS group. Both of the UHR groups showed a significantly lower subjective QoL than the HC group on every subscale.

The final study examining insight (12) made use of the Beck Cognitive Insight scale – Japanese version (BCIS-J) and compared an UHR group to a HC group comprised of university students. This meant that the groups were not matched for education level. The BCIS-J contains scores on self reflectiveness and self-certainty. A composite index representing cognitive insight is calculated by subtracting self-certainty from self-reflectiveness. The UHR group had a significantly higher self-certainty mean than the HC group. However, there were no significant differences in self-reflectiveness or composite index scores between the UHR and HC groups. In summary, both the SAI-E and the BCIS were able to sensitively distinguish differences in UHR individuals who demonstrated more self-awareness than FEP individuals, and also more awareness of illness.

2. Correlations between symptoms, cognitive bias / insight and other factors

2.1 Core schema Correlations

2.1.1 Negative-self and Negative-other

In the first study (1) there was an association between negative-self schema and negative-other schema with 'Unusual Thought Content' 'Suspiciousness' and also with 'Total Positive Symptoms'. In the second study (12) two correlations were significant across all groups combined: 'Non Bizarre Ideas – distress' with Negative-Self and 'Perceptual Abnormalities – distress' with Negative-Other. There were no relationships between 'Unusual Thought Content – distress' or 'Disorganised Speech – distress' and any core schemas.

2.1.2 Other factors

In the first study (1), regression models including depression scores with negative-self and negative-other as independent variable predictors were used to examine the variance accounted for in specific symptoms. Depression, negative self and negative other accounted for 10% of variance in 'Thought Disorder', 35% of variance of 'Suspiciousness' and 41% of variance of 'Total Positive Symptoms'.

2.2 Locus of Control (LOC) Correlations

In the UHR group LOC score was correlated with the total SANS score. However there was no correlation with the total BPRS score. LOC score was correlated with the BPRS item of suspiciousness as a broad measure of paranoid symptoms across the UHR and HC groups (11). These findings suggest that LOC is associated with a greater severity of negative symptoms as well as specific positive symptoms (paranoia and suspiciousness).

Internalised LOC accounted for some of the variance in increased quality of life across all domains in the MSQoL in EIPS individuals (8). Negative coping strategies (including 'Passive avoidance', 'rumination', 'resignation', and 'aggression') were moderately correlated with self-concept and fatalistic externality across the groups. They were also correlated with social externality in the FEP

group (9) Positive coping strategies (including 'distraction', 'situation control', 'positive self-instructions', and 'social support') were moderately correlated with self-concept and internality across the groups. In the UHR group they were correlated with fatalistic control beliefs (9). There was no correlation between LOC and DASS total or DASS depression, anxiety or stress sub-scores in the UHR group (11).

2.3 Attribution style or bias and symptoms

2.3.1 Attribution questionnaires and symptoms

In UHR group the perceived Hostility bias and Blame bias from the AIHQ were significantly correlated with the paranoia score of the PS and the suspiciousness/persecution item score of the PANSS (2). In the UHR group there was no association of externalising attribution bias on the IPSAQ with suspiciousness or sub-threshold paranoia (or any clinical measures), or eventual transition to psychosis (4).

2.3.2 Tasks and symptoms

In the UHR group there were no significant or trend correlations between task performance in the JTC bead task (on any version) and either the PANSS (both total score and positive sub-scale), or the delusion subscale of the SAPS (3). When the groups were combined there were statistically significant correlations between the total PDI score and all three PDI sub-scales, with the intermediate (60:40) version of the task. There was a very significant correlation between scores on the 'conviction' sub-scale of the PDI and performance on the intermediate and hard versions of the JTC task (3).

Misidentifications in the VSM task were correlated with a lower severity of 'Unusual Thought Content' and a lower severity and frequency of 'Perceptual Abnormalities' on the CAARMS. There was a significant relationship between reaction times for misidentification errors and the severity of perceptual abnormalities on the CAARMS: severe symptomatology was associated with longer reaction times. The overall level of misidentifications in the UHR group did not correlate positively

with the level of prodromal symptoms they reported. Instead there was a negative correlation between misattributions and severity and frequency of attenuated positive symptoms in the UHR group, with individuals with higher APS symptoms making fewer misattributions in the VSM task (5).
In the longitudinal study following up on baseline performance in the JTC beads task, performance on the JTC task (DTD 60:40) at follow up was significantly correlated with the PANSS delusion and PANSS hallucination items but not with overall PANSS-positive scores. It was also reported that those developing a more conservative style in the JTC task also had lower delusion scores at follow up time (13).

2.3.3 Other factors

Correlations with Rosenberg's Self-Esteem score and BDI score entered as covariates showed that there were only two correlations between AIHQ and symptom profiles (Blame bias and Suspiciousness / Persecution score of PANSS) in the UHR group when controlling for these scores. This indicates that level of depression and self- esteem contributed significantly to other correlations present before entering these scores as covariates (2). In the study measuring JTC using the bead task, there was an inverse correlation between number of beads drawn before a decision and score on the Freeston Intolerance of Uncertainty scale. There was a significant negative correlation between beads drawn on the intermediate version of the task and level of uncertainty (3).

2.4 Cognitive Insight and symptoms

2.4.1. Cognitive Insight questionnaires and symptoms

Total symptom score (as measured by the Item Group Checklist and relating to CAARMS data) correlated significantly with total illness insight on the SAI-E when the All FEP and UHR groups were considered together: a higher symptom score was associated with poorer insight. However this

correlation was not significant within the UHR group, or within the FEP group when considered individually (6).

The BCIS-J self-certainty score significantly correlated with attenuated delusional symptoms (CAARMS-J). The BCIS-J self-reflectiveness and composite index scores were not correlated with attenuated delusional symptoms. Correlations carried out with UHR individuals not using antipsychotic medication, revealed that the self-certainty score was significantly positively correlated with delusional symptoms. In the same medication-free group, the composite index score was negatively correlated with delusional symptoms. There was no correlation between the self-reflectiveness score and delusional symptoms in this group (12).

2.4.2. Other factors

Poor self-reported social functioning was related to poor clinician-rated social and role functioning, poor global functioning, and more severe depression and anxiety symptoms. There were significant correlations between the SDS Work/School and the GF:Role, GAF, BDI/CDI and BAI (7). In EIPS-UHR group (9), 'Depression'(SCL-90-R) as the sole predictor accounted for reductions in subjective QoL dimensions in 'Vitality', 'Psychosocial QoL', 'Material QoL', 'Spare time QoL', and 'General QoL'. 'Somatization' (SCL-90-R) predicted reduction in'Physical Health', and 'Fearfulness' predicted reduction in 'Affective QoL'. In the LIPS-UHR group Depression (SCL-90-R) was a significant predictor in reduction of QoL in all areas apart from 'Physical Health', indicating that 'Depression' overall was a very important predictor in subjective appraisal of Quality of Life (8).

Discussion

1. Identifying cognitive biases and processes unique to UHR individuals

Schema

The results showed that using the Brief Core Schema Scale (BCSS) to identify differences in self and other appraisal was not specifically relevant to the UHR group, as they had similar appraisals to FEP and HS controls. Therefore identifying negative-self and negative-other schemas could be used as a more general indicator of bias in help-seeking populations as well as early psychosis populations.

Locus of Control – Externalising and Internalising Biases

The IPSAQ, the FKK and the ANSIE were all used to measure the extent to which UHR individuals exhibited biases in their perceived locus of control between internal and personal reasons, and external factors. The results showed that the IPSAQ was not sensitive to identifying differences between those in UHR stage when compared to a healthy control group.

On the other hand, the interpretable results from the study using the FKK LOC measure showed that UHR individuals had a tendency to a fatalistic externalising bias, but not a social externalising bias. This was also related to a low self-concept. This measure seemed to provide a good distinguishing indicator of cognitive bias specific to individuals who are UHR. The FEP group in the same study exhibited a different profile, showing a more internalised locus of control, related to a greater self-concept. This finding may provide an important insight into processes underlying transition to psychosis. As individuals become more convinced that they have control over situations, even when they do not, this might underlie a shift in perception or trigger delusion formation. The study (11) using the ANSIE also showed that individuals in the UHR group had an externalised LOC compared to a HC group who demonstrated a more internalised LOC. The results suggest that these measures might be suitable for identifying UHR individuals, alongside other clinical measures.

Attribution Bias measured by tasks – JTC and VSM

The use of the bead task to ascertain whether a JTC bias was present was sensitive to distinguishing differences between the UHR and HC groups. Participants in the UHR group were more likely to respond to the harder versions of the task based on drawing fewer beads, than the HC, demonstrating a tendency towards jumping to conclusions. Furthermore, this tendency remained stable in individuals over a period of time (average 31 months), suggesting that the UHR group in this study exhibited this bias as more of a trait, than a state relating to other symptoms. This suggests that an elevated JTC bias may be a good indicator for indentifying people at UHR for psychosis.

Similarly, the UHR group demonstrated a bias towards misattribution of speech to other rather than self, under specific conditions and levels of distortion on the VSM task, when compared to a HC group. The finding that they also demonstrated a slower response time than the HC group to the task was also relevant, as this seemed to implicate problems with information processing, or perhaps a desire to perform better. Interestingly, a slower response time was correlated with better overall performance in the task, and less misattribution. This task appears to be sensitive to distinguishing those at UHR from healthy individuals by identifying misattributions towards other.

Unlike the JTC task, when the participants were asked to perform the VSM task at follow-up, they performed significantly better than at baseline. One interpretation of this finding is that there may have been a reduction of symptoms such as perceptual abnormalities or thought intrusions which may have impaired earlier performance. If so, this suggests that the misattribution bias towards other measured by this task might be related to state-like factors, rather than being a fixed trait in those at UHR. Alternatively, variation in scores at follow up might be due to poor test-retest reliability.

Measuring Cognitive Insight with questionnaires

Both the SAI-E and the BCIS-J were used to measure cognitive insight in UHR groups. Whilst they measure different constructs – the SAI-E measures insight specifically into illness looking at

'Perceived Need for Treatment', 'Symptom Relabeling' and 'Illness Awareness' and the BCIS measures 'self-reflectiveness' versus 'self-certainty' – the questionnaires have been previously shown to tap into similar concepts of have convergent validity tapping into similar constructs of self-awareness (Uchida et al, 2013). Both questionnaires identified differences in UHR groups when compared to comparison groups.

The SAI-E showed that UHR individuals had better overall insight into their illness than FEP individuals, but both groups had similar scores on the 'Illness Awareness' subscale, indicating that even in a UHR state, individuals are still aware of a change in their wellbeing, and a move from 'wellness' to 'illness'. Even in FEP individuals who were voluntarily being treated as opposed to having been admitted to hospital or given compulsory treatment under order, there was a distinctly lower level of insight when compared to UHR individuals, specifically in 'Symptom Relabeling'. This finding indicates that once in FEP, individuals are more likely to present with alternative explanations for their illness, rather than accepting standardised labels, than individuals at UHR.

The BCIS-J identified a higher level of self-certainty present in individuals in the UHR group when compared to HC. Although this did not directly affect the overall level of self-awareness or 'cognitive insight' measured by the composite score, it is interesting that this finding was present. This may implicate early beginnings of delusion formation (Beck, 2002), whereby individuals at UHR for psychosis develop greater self-certainty (perhaps as a coping strategy, or due to data gathering biases) which may preclude changes in beliefs about the cause and nature of events. Both of these measures would therefore be suitable to be used specifically to help identify individuals at UHR for psychosis.

Previous studies with individuals at UHR (Kimhy et al, 2013) have shown that they seem to retain a certain capacity to remain objective about explanations for delusional experiences, be aware of cognitive distortions, and are more open to feedback from others. This seems to be reflected in the results of these studies using Cognitive Insight scales, so that whilst there is a change in insight, changes are protective in nature, allowing reflection on illness progression, which may prevent the development of full-blown psychosis (Warman and Martin, 2006).

2. Correlating cognitive bias and insight with specific symptoms in early psychosis – insight for treatment or intervention?

Externalising / Internalising Bias and symptoms

In one study (11), Externalised LOC scores were positively correlated with negative symptoms and paranoid symptoms (CAARMS) in the UHR group. Also, having a high self-concept and fatalistic externality bias correlated with a tendency towards using negative coping strategies including 'rumination' and 'aggression'. These strategies were also correlated with social externality in the FEP group (9). Positive coping strategies like 'distraction', or 'positive self-instructions' were associated with a tendency towards higher self-concept and internality across the groups. In the UHR group they were correlated with fatalistic control beliefs (9). This suggests that exhibiting an externalising bias, can lead to the formation of paranoid ideas, and also may link to coping strategies employed at different stages of the prodromal state. For example, in the early prodromal UHR group, individuals may still be attempting to control perceived external threats through distraction or social support, whereas later, in FEP, individuals may be more likely to respond to perceived social externalised control with aggression, or by spending longer focusing on it. The different coping strategies employed along the continuum of psychosis is worthy of further investigation in future studies.

JTC / VSM tasks and symptoms

In the groups were combined in the study using the JTC bead task, there were statistically significant correlations between the PDI total score and sub-scale scores, with the intermediate (60:40) version of the task. The significant correlation between scores on the 'conviction' sub-scale of the PDI and performance on the intermediate and hard versions of the JTC task (3) was in keeping with previous studies with individuals who are delusion-prone as measured by the PDI (Balzan et al, 2012, Garety et al, 2005), suggesting that this measure is good at identifying those who may be prone to confirmation biases as demonstrated by performance on the JTC bead task. Also, as this performance remained stable over time, this may be a trait factor which is more easily attributed to individual differences,

rather than as a response or way of coping to other factors. However, those who did develop a more conservative style in the JTC task, had lower delusion scores at follow up time, suggesting that developing some insight into jumping to conclusions (whether consciously or otherwise) may lead to a reduction in delusional symptomatology.

Number of misidentifications in the VSM task were positively correlated with a lower severity of 'Unusual Thought Content' and a lower severity and frequency of 'Perceptual Abnormalities' on the CAARMS and lower severity and frequency of attenuated positive symptoms in the UHR group. In other words, individuals with higher APS symptoms made fewer misattributions in the VSM task (5). This is another very interesting finding. One interpretation is that the effort or type of response made by individuals experiencing high levels of symptoms was greater than those with lower symptoms, meaning that although they may respond more slowly (response time was positively correlated with high symptoms) to the VSM task, their overall performance was better. It may also suggest that individuals with higher had slower but paid more attention to monitoring of source, than those with lower symptoms.

Cognitive Insight and symptoms

Elevated self-certainty on the BCIS was significantly associated with an increase in attenuated delusional symptoms. Furthermore, correlations carried out with UHR individuals not using antipsychotic medication, revealed that the self-certainty score was significantly positively correlated with delusional symptoms. This seems to suggest that having a high degree of certainty in one's own beliefs leads to an increase in the formation of delusions. This is in keeping with Beck's (2002) cognitive formulation of delusion formation in which individuals continue to maintain the validity or truth of a certain belief in spite of the majority of others challenging this belief. A self-certainty bias therefore may serve as a very important predictor of those who are more at risk of developing delusional psychotic symptoms.

Total symptom score (IGC) was significantly correlated with total illness insight on the SAI-E across FEP and UHR groups: a higher symptom score was associated with poorer insight (5), suggesting that as symptoms relating to psychosis increase, and the illness develops, individuals experiencing these symptoms lose sight of the fact that they are unwell. One interpretation of this is that as individuals progress through various symptom domains, their associated decline in functioning becomes subjectively minimised. For example, there was little difference between EIPS-UHR and LIPS-UHR groups in their subjective appraisal of quality of life. Further studies could seek to investigate how objective decline in functioning through clinician appraisal is matched to subjective appraisal, through the course of prodromal psychosis.

Having said this, those who subjectively rated themselves poorly in social functioning in an UHR group (7) WAS related to objectively rated poor social functioning, as well as more severe depression and anxiety symptoms. Furthermore, when depression was controlled for in this study, it accounted for much of the variance in quality of life scores. It may be that UHR individuals retain some insight to a decline in functioning, but are unable to make the link to other co-morbidities which might be present, such as depression or anxiety. Again, this may serve as a useful clue to early intervention to prevent later development of psychotic symptoms, by providing treatment for anxiety or depression to those help-seeking individuals who report subjective changes in functioning.

Appraisal of self / other and symptoms

Analysis of the BCSS (1) showed that negative self and negative other schemas were associated with some psychotic symptoms: 'Unusual Thought Content' 'Suspiciousness' and also with 'Total Positive Symptoms' in the SIPS. Negative-Self also correlated (10) with 'Non Bizarre Ideas – distress' and Negative-Other with 'Perceptual Abnormalities' in the CAARMS. This suggests that at the level of core schema and beliefs, individuals are more likely to experience symptoms relating to UHR for psychosis if they have negative self or negative other appraisal. When depression was entered as a factor in the correlation model, it accounted for much of the variance

in the first study. This has important implications for clinical work, as it could be that help-seeking populations, who are experiencing sub-threshold psychotic symptoms in the above domains, may also be experiencing depression, and this may provide a useful starting point for treatment, to prevent development of psychosis.

Also, the study administering the AIHQ to participants found a significant association between perceived Hostility and Blame biases and the paranoia score of the PS and the suspiciousness/persecution item score of the PANSS (2). This suggests that external hostility appraisals, and perceived lack of control of a situation by self could contribute to the formation of paranoid and suspicious appraisals of others. Again, this could indicate strategies to use in psychological interventions with those presenting with early signs of paranoia or suspiciousness, in order to make re-appraisals of intentions from others.

3. Strengths and Limitations

Clinical Assessment

One of the strengths of this review was that all of the papers apart from one (9) made use of the SIPS/SOPS or the CAARMS to initially assess suitability for inclusion to the UHR group in their studies. Both of these assessments have been investigated and validated in previous studies, and they have similar inclusion criteria for defining UHR. Another strength, was that every study also employed an exclusion criteria relating to assessment of having a current or previous psychotic disorder, according to accepted formal psychiatric criteria (DSM-IV / SCID / ICD-10) for inclusion into the UHR group, and many for inclusion to comparator groups. This meant that individuals involved in the studies in this review were 'truly' prodromal, in that they had never experienced psychosis before.

Measures for Cognitive Biases and Insight – Reliability and Validity

Whilst it was beyond the scope of this study to thoroughly investigate the reliability and validity of every measure used, to assess whether or not measures were suitable for UHR populations, the studies were checked to establish whether the researchers had considered these factors in the selection of the measures. All studies mentioned reasons for employing measures, and where appropriate made comparisons to other alternative measures, with extended reasoning as to their final choice. Furthermore, questionnaires measuring other factors of interest (eg. PDI for delusions, BDI for depression) were overall well-established measures with acceptable reliability and validity. Less is known about the reliability and validity of both the tasks evaluated, as different researchers have established that performance does not correlate to changes in symptoms (Peters et al, 2006). A possible weakness in the review is that there were a multitude of different measures combined in very different methodologies, which made direct comparison between studies more difficult.

Clinical Implications – Main findings

Whilst some interesting findings emerged from individual studies, with a limited amount of replication of results in UHR to specific measures and correlations between specific biases and symptoms, it is important to note that the UHR for psychosis population is complicated and complex in presentation. This is partly related to the different stages (EIPS / LIPS) which theoretically relate to different symptom clusters, but is also due to the influence of other clinical factors such as anxiety, self-esteem or depression. Several authors of studies included in this review commented on the heterogeneity of the UHR group, establishing that even when individuals made transition to later psychosis, there were a wide range of factors which seemed to be implicated in the trajectory of the illness. This also related to the types of presentation seen in both UHR and FEP clinical populations. Whilst some are very keen to receive treatment or help, others seem unaware of their difficulties, and reluctant to engage with services (Lappin, 2007). It was also noted that even in initial stage of the

psychosis prodrome, functioning and perceived Quality of Life could be sufficiently adversely affected as to warrant clinical intervention at this stage (Ruhrmann et al, 2008).

Summary

Cognitive biases and Cognitive insight levels are related to being at UHR for psychosis. Instruments which measure these biases or level of insight should be used as screening tools for UHR for psychosis, and also in future research, to better understand or replicate findings from studies included in this review. The impact of factors such as depression, self-esteem and coping strategies should be taken into consideration when developing interventions for those at UHR for psychosis.

UHR individuals have higher levels of negative self / other schema; a tendency to negative schema is also present in help-seeking and FEP individuals. UHR individuals have a tendency to demonstrate an externalising bias whereas those in FEP are more likely to have an internal LOC and higher self-certainty.The IPSAQ did not identify differences in attributional style in the UHR groups, but did in the FEP groups. This is in keeping with evidence showing that FEP but not UHR individuals have a tendency towards internal control. Performance on both the JTC and VSM tasks may be good predictors or indicators of the UHR populations. The AIHQ could therefore be a very useful tool in distinguishing individuals at UHR for psychosis from those who are not, by paying attention to elevated Blame bias scores. Both the SAI-E and the BCIS were able to sensitively distinguish differences in UHR individuals who demonstrated more self-awareness than FEP individuals, and also more awareness of illness.

Further research is needed. The DSM-5 included Attenuated Psychosis Syndrome as an area for future research, and this review suggests that this research makes further investigation into the relationship between cognitive biases / cognitive insight, and the trajectory of prodromal psychosis.

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Appendix 1

Health Evidence Bulletins - Wales: Questions to assist with the critical appraisal of an observational study eg cohort, case-control, cross-sectional. (Type IV evidence)

Sources used: Critical Appraisal Skills Programme (CASP, Anglia and Oxford RHA) questions and Polgar A, Thomas SA. Chapter 22. Critical evaluation of published research in Introduction to research in the health sciences. 3rd edition. Melbourne: Churchill Livingstone, 1995; Undertaking systematic reviews of research on effectiveness. University of York: NHS Centre for Reviews & Dissemination, 2001; Weightman AL, Barker, JM, Lancaster J. Health Evidence Bulletins Wales Project Methodology 3. Cardiff: UWCM, 2000.

Paper details Authors:

Title:

Source

A/ What is this paper about?

	Yes	Can't tell	No
1. Is the study relevant to the needs of the Project?			
2. Does the paper address a clearly focused issue? in terms of • the population studied? • (case-control study only) Is the case definition explicit and confirmed? • the outcomes considered? • are the aims of the investigation clearly stated?			

B/ Do I trust it?

	Yes	Can't tell	No
3. Is the choice of study method appropriate?			
4. Is the population studied appropriate? • (cohort study) Was an appropriate control group used – ie were groups comparable on important confounding factors? • (case-control study) Were the controls randomly selected from the same population as the cases?			
5. Is confounding and bias considered? • Have all possible explanations of the effects been considered? • (cohort study) Were the assessors blind to the different groups? • (cohort study) Could selective drop out explain the effect? • (case-control study) How comparable are the cases and controls with respect to potential confounding factors? • (case-control study) Were interventions and other exposures assessed in the same way for cases and controls? • (case-control study) Is it possible that overmatching has occurred in that cases and controls were matched on factors related to exposure?			

Part Two: Empirical Paper

Profiling ultra high risk for psychosis? Chronic cannabis and ketamine users' performance on tasks of attribution assignment and hallucination-proneness.

Abstract

Introduction: Recent research has investigated biological, genetic, social, cognitive and emotional factors which contribute to high risk for transition to psychosis. Various drug models (acute and chronic) have been used to gain insight into the symptomatology of prodromal psychosis. This study aimed to further investigate psychological constructs related to delusion-formation and sense of agency using computer tasks and questionnaire measures, in groups of chronic ketamine and cannabis users.

Method:

Three groups were compared a) chronic ketamine users b) 20 chronic cannabis users and c) a control group (N=20) who had used some non-legal drugs recreationally in their past. Participants were tested using the Ambiguity of Attribution task and the White Noise task. Self-report questionnaires measuring depression, anhedonia, positive and negative indicators for psychosis were administered.

Results:

The two drug using groups had higher self-reported depression (BDI), schizotypy (O-LIFE) and psychosis (PQ-B) than controls. On the Ambiguity of Attribution task, the control group had significantly higher distinction between self and other, and higher mutual information used than the two drug-use groups. The ketamine group also had less entropy, and higher predictability in tapping style on this task than the other two groups. There were no differences between groups on the White Noise task. Participants in the ketamine group reported higher distress related to drug-use than the cannabis group.

Conclusions:

This study provides further evidence that questionnaire measures of depression, schizotypy and positive and negative symptoms related to early psychosis are higher in chronic users of ketamine and cannabis. Performance on a task measuring ambiguous attribution was also worse than controls in these groups. Findings suggest that these groups of individuals are a useful population for research into prodromal psychosis.

Introduction

Early Intervention in Psychosis

The early or prodromal phase of psychosis is understood to be a critical time for intervention with young adults in order to prevent the illness developing into a full-blown first episode of psychosis (FEP) (Marshall et al, 2013; Altamura et al, 2001). Research into the duration of untreated psychosis (DUP) has also shown that untreated prodromal psychosis symptoms, which are notoriously hard to profile accurately, are associated with development into more enduring and severe psychotic illness and diagnosis of schizophrenia (Birchwood et al, 2013). Early Intervention Services have been commissioned to treat clients in the prodromal stage of illness, and research has shown that there are better clinical outcomes following interventions from these teams, with reduced likelihood of more severe and enduring mental health problems (McFarlane et al, 2014; Amminger et al, 2011).

At Risk Mental State (ARMS) and predicting psychosis

What are the best predictors for identifying those at high risk for psychosis? There have been a variety of methods to examine the psychosis prodrome. One of the ways the prodrome is theoretically constructed, is by retrospectively examining the factors present in the prodromal phase of psychosis, in populations who later make the transition to first-episode psychosis. These retrospectively constructed models lead to two clusters of symptom patterns: 1) Basic Symptoms where the individual may experience cognitive, perceptual and affective changes, but to a very subtle degree (Schultze-Lutter, 2009; Nelson et al, 2011), and 2) Attenuated Symptoms, which are more associated with an Ultra High Risk group (UHR) who were more readily identified due to a combination of positive and negative symptoms combined with other risk factors such as young age and family vulnerability (Schultze-Lutter et al, 2013; Thompson et al, 2011). In both basic and attenuated symptom groups, the individual may not take notice of subtle changes in their subjective experience of life. Which group of symptoms are more useful to examine in Ultra High Risk for Psychosis? It

could be argued that the Basic Symptoms cluster needs further research, as being able to map specific symptomatic patterns in groups with less external observable risk factors, may help early detection of the early initial prodromal state (EIPS) (Bechdolf, 2012) with a high probability of transition into psychosis.

Assessing prodromal symptom clusters

Semi-structured interviews

One way of screening individuals to assess whether or not they meet criteria for ARMS, or are in the prodrome to psychosis is to carry out semi-structured interviews which systematically go through an inventory of positive and negative symptoms and ask about related functioning and distress levels. Interviews such as the Positive and Negative Symptoms Scale (PANSS) and the Scale for the Assessment of Negative Symptoms (SANS) have been shown to measure corresponding factors across symptoms, giving a reliable indication of risk for psychosis (Rabany et al, 2010).

The Structured Interview for Prodromal Syndromes (SIPS) and the Scale of Prodromal Symptoms (SOPS) have also shown reliability and validity with other constructs of High Risk for psychosis (Simon et al, 2005; Miller et al, 2003). The Schizophrenia-Proneness Interview – Adult version (SPI-A) was designed to be administered alongside both the SIPS/SOPS and the PANSS in order to build up a fuller picture of the experiences contributing to UHR (Schultze-Lutter et al, 2007). The Comprehensive Assessment for At Risk Mental State (CAARMS) is another semi-structured interview, designed in Melbourne at the Personal Assessment and Crisis Evaluation clinic (Yung et al, 2005).

All of these semi-structured interviews are designed to assess and monitor severity, frequency, pattern and distress level of symptoms of psychosis, on a range of subscales covering positive symptoms, cognitive change attention/concentration; emotional disturbance; negative symptoms; behavioural change; motor/physical changes; general psychopathology.

Self-report questionnaires – psychosis specific and other mental health constructs

As prodromal symptoms tend to be non-specific, prospective detection of prodromal psychosis is complicated by a likely high false-positive rate. A large percentage of those categorised by semi-structured interviews as being in 'at risk mental state' (ARMS) will not make the transition to threshold psychotic disorder. It has been argued however, that those seeking help who fall into an ARMS category are still in need of more specific interventions which focus on their difficulties (Ruhrmann et al, 2010).

For this reason, self-report questionnaires which are non-psychosis specific, such as the Beck Depression Inventory (Beck, 1996), and Global Assessment of Functioning (Jones et al, 1995) have been widely used as an efficient screening tool to pinpoint areas for intervention. They also appear to be sensitive to detecting improvement or reduction of distress or difficulty related to psychotic-like experiences or symptoms, over time (Amminger et al, 2011). Other self-report measures directly measuring early psychosis symptoms include the Self-Screen Prodrome (SPro, Muller et al, 2010), the Prodromal Questionnaire–Brief (PQ-B; (Loewy et al, 2011), the Youth Psychosis at Risk Questionnaire-Brief (YPARQ-B; Ord et al, 2004), and the Prevention through Risk Management and Education: PRIME-Screen revised (Miller et al, 2003). These measures show differing levels of reliability and validity for identifying at-risk mental state for psychosis when compared with other measures known to predict this. Overall, each screener demonstrates satisfactory and comparable test–retest reliability to identify ARMS by self-report (Kline et al, 2012).

Identifying populations at risk – methodological approaches

In carrying out research into prodromal psychosis, what are the best ways to identify populations which may properly represent 'at risk for psychosis' individuals? Previous research has shown that for the majority of individuals who end up in Early Intervention care pathways, there has usually been some type of mental health help-seeking before this (Ruhrmann et al, 2008; Rietdijk, 2012). As an extension of this help-seeking behaviour, other studies have sought to identify which types of other

mental disorders (such as depression and social anxiety) act as possible predictors for development of a later psychotic disorder (Rietdijk et al, 2013). Other studies have veered away from help-seeking populations, and have attempted to identify the stable personality traits or individual differences which may make people more prone to experiencing psychosis or psychotic-like phenomena (Kelleher & Canon, 2010; Debanne 2014).

Drug Models for Psychosis – A research paradigm

There is a wealth of literature showing associations between chronic cannabis use and development of psychosis (Di Forti et al, 2009; Van Os et al, 2002; Moore et al, 2007). Several studies suggest that cannabis use increases the risk of the incidence of psychosis in previously healthy individuals (Fergusson et al, 2003; Michaels & Novakovic, 2015) and is also associated with poorer prognosis for those already diagnosed (Van Winkel & Kuepper, 2014; Buckley et al, 2009). The association between the two is not fully understood: it could be that cannabis is initially used to self-medicate psychotic symptoms or mask early signs of psychosis, an antidote to negative symptoms of psychotic onset, for example (Di Forti et al, 2007). It has also been proposed that chronic use of cannabis, particularly 'skunk', affects regions of the brain which are used in belief formation about the surrounding environment or the self, which precipitate psychotic experiences (D'Souza, 2007; Bhattacharyya et al, 2009). This is a popular and complicated area of research, and more is being understood about individual differences in neurology, the endocannibinoid system and how different compounds found in cannabis (such as Tetrahydrocannabinol and Cannabidiol) affect the brain (Atakan, 2012).

Acute versus chronic drug models

It has been proposed that chronic ketamine use may provide a useful model in mapping processes theoretically involved in delusion formation (Freeman et al, 2012). Data from human and animal studies have shown that chronic exposure to NMDA receptor antagonists such as ketamine may be more accurate in modelling aspects of psychosis than acute exposure (Jentsch & Roth, 1999; Morgan & Curran, 2006). In the literature exploring acute psychotomimetic effects of cannabis, highly psychosis-prone individuals experienced increased effects after acute cannabis administration compared to controls (Mason et al, 2009; Favrat et al, 2005). Despite advantages in carrying out cross-sectional chronic drug-user studies, temporary pharmacological manipulations with generally healthy participants (studies of acute effect) may not represent the population of interest accurately. Repeated exposure to psychotomimetic drugs may provide a better model for exploring psychosis, as the characteristics of these groups tend to be more enduring, and mimic the slow onset of behavioural-psychological change present in prodromal psychosis (Tang et al, 2015; Morgan et al, 2009; Freeman et al, 2009).

Chronic cannabis and ketamine use mimics prodromal psychosis

More recently, studies have used the association between dependence on cannabis or ketamine and schizotypy, to construct a drug model for understanding psychotic-like experience and to map prodromal psychosis in particular (Morgan et al, 2012). In the Morgan et al study (2012), dependent ketamine and cannabis users were compared with dependent cocaine, poly-drug recreational users, and healthy controls on outcomes of the SPI-A (Schizophrenia-Proneness Instrument – Adult). Across the subscales of the SPI-A the ketamine-dependent group displayed a strikingly similar profile to a prodromal group from a previous study (Schultze-Lutter et al, 2007) who made the transition to a psychotic disorder or episode. The cannabis-dependent group also shared a similar profile to prodromal individuals, on all subscales apart from 'affective / dynamic'. This study is interesting, as it

identifies a useful non-clinical sample population, with whom research can be conducted into mapping prodromal psychosis, namely chronic cannabis and ketamine using populations.

Examining underlying mechanisms in early psychosis symptoms

1. *Sense of Agency*

In psychosis and schizophrenia, one of the defining characteristics in positive symptomatology is that individuals find it difficult to distinguish between actions or events which they can confidently attribute to themselves, and those which they feel compelled to attribute to others, or to sources external to themselves. An example of this would be where an individual with a diagnosis of schizophrenia may experience movements of their body which they did not cognitively and explicitly feel responsible for causing. Thus they would have a 'feeling of agency' in that they would feel and experience the movement in physical and sensory terms, but not a 'sense of ownership', in that the movement would not be experienced as being generated by themselves. An example of this might be where an individual experienced a jerking arm movement, which they could physically feel and observe (affective experience) but would attribute the cause of the movement to a source external to themselves (meaning-making experience) .

This concept is expanded on by proposing two levels of consciousness in which the 'sense of agency' may originate, which include both an implicit, sensori-motor 'feeling of agency' level and an explicit, belief-like 'judgement of agency' level. For an individual to experience a complete and integrated 'sense of agency', it is argued that they must experience both of these levels of consciousness – the affective and the correct cognitive appraisal – to fully believe and understand themselves to be an agent of their own actions (David et al, 2008).

Tasks previously used to assess the 'sense of agency' in schizophrenic patients include: recognition of own or other's hand performing movement (Deprati et al, 1997); distinguishing one's own limb's position from an 'alien' hand (Farrer et al, 2004); judging onset of key-press action (Haggard et al,

2003); random and cued joystick movements with and without visual feedback (Spence et al, 1997; Farrer et al, 2004). These tasks examine either implicit sub-conscious processes using brain-mapping techniques, or explicit conscious processes using subjective judgements.

The feeling of agency must be conceptually processed for a judgment - an attribution of agency - to occur. This suggests that it is at this level that individuals with a diagnosis of schizophrenia would formulate beliefs about perceptual experiences. Is this process relevant to prodromal psychosis? Could the transition from implicit to explicit processing provide a framework for better understanding how an individual experiencing basic sub-clinical symptoms may go on to transition to FEP under specific conditions?

Ambiguity of Attribution Task

Schizophrenic patients have a tendency to make more attribution errors than healthy controls and to experience actions of self as belonging to others. This has been used to identify brain regions associated with attribution to self and other (Farrer et al., 2003; 2004). In healthy controls, brain regions sensitive to self and other modulate continuously with the degree of control that a participant actually had. However in schizophrenic participants they did not modulate with degree of control, suggesting that the feeling of 'being the cause of an event' is a variable state in the healthy brain, but not in schizophrenic brains. Based on this evidence, the Ambiguity of Attribution task was developed (de Bezenac, 2015) to explore a continuum of self/other subjective experience. This uses a novel button-press task with particular interest in ambiguous conditions in the middle of this continuum. The task asks respondents to rate whether an auditory tone coming from a computer was generated by their button-press, the computer, or combination of both (the ambiguous conditions). Understanding the conditions or factors which contribute to more pronounced interruptions to this continuum could help to clarify an underlying process of prodromal psychosis.

2. *Affective Salience*

A second theory underpinning prodromal psychosis is that individuals may attach emotional significance and affective meaning to certain experiences, stemming from an impairment or interruption to 'normal' emotional or affective processing. Affective dysregulation is thought to be a factor which contributes to experiences resembling hallucinations and delusions, in the general population (Van Rossum et al, 2009). Internal representations (thoughts) or external objects (environments) acquire new meaning or emotional value or prominence, possibly due to alterations in top-down processing (Hoffman et al, 2007; Vercammen and Aleman, 2010).

White Noise Task

In these affective salience studies, it has been found that speech illusions can predict transition to schizophrenia spectrum disorders. Galdos et al (2010) designed a task measuring affective meaning identified in speech played in neutral random signals and found that the rate of speech illusion present increased with increasing level of familial risk for psychotic disorder, suggesting that it may sensitive to detecting early signs of prodromal psychosis. The task measures both the incidence of speech illusions (hearing a voice when none is present) and also asks participants to assign a quality to the 'voice' heard (negative, positive, neutral) when in fact all the voices present are neutral in quality. The task has two aims: 1) to measure auditory hallucination-proneness, independent of affective meaning, by recording the number of speech illusions detected and 2) to understand bias towards negative or positive affect attribution, when the voices heard are neutral in quality.

Current research rationale: combining tasks with other measures of early psychosis

There were three aims of the study carried out here. Firstly, it aimed to assess the validity of investigating early psychosis using chronic ketamine and cannabis users as a model. It attempted to develop on from the findings of Morgan et al (2012), by comparing quantitative scores on specific

questionnaires instead of the more complex data gathered from the SPI-A interview. This study aimed to identify whether data gathered from the questionnaires in this study aligned with constructs known to be relevant to early psychosis. On the basis of Morgan et al's findings, we hypothesised that the ketamine group would have the highest level of symptoms associated with prodromal psychosis (affective, cognitive, perceptual) with the cannabis group having a similar profile in all sub-scales apart from those related directly to affective disturbances. We expected that the control group would show much lower levels of symptoms associated with early psychosis.

Secondly, we hypothesised that there would be significant differences in performance on two tasks, between drug groups and controls. In the Ambiguity of Action Task (sense of agency), the hypothesis was that in the two drug use groups, there would be more of a marked distinction between attribution to self and other, with more misattribution in the ambiguous trials, and across the task overall. It is hypothesised that the control group would be more capable of subtle differentiating, with lower misattribution across the task.

In the White Noise Task (affective salience) we hypothesised that the two drug groups would be more likely to identify a speech illusion in the white noise conditions, and the control group would be less likely to. Secondary to this, we were also interested in investigating whether there was more bias towards identifying actual speech present as having a positive or negative quality, across the conditions (clear speech present, soft speech present, no speech present) to understand if this implicated a bias in affective processing. We did not have a prediction about which groups would exhibit biases towards positive or negative affect.

Lastly, the study endeavoured to establish if there is any correlation between scores on specific subscales in the questionnaires (e.g. perceptual disturbance) and on the White Noise and Ambiguity of Attribution tasks. This would hopefully provide some clues as to how tasks could be used alongside self-report measures in order to form a fuller picture of which individuals may have increased risk for psychosis. The study also aimed to investigate the relationship (if any) between level of distress

reported in relation to both substance use and psychotic symptoms, and level, severity and frequency of symptoms reported.

Method

Power Calculation

Power analysis for this study was carried out based on scores obtained on the SPI-A by controls, chronic ketamine users and chronic cannabis users (Morgan et al, 2012). In the study, there was a significant difference in SPI-A scores with a large effect size across several domains. Assuming equal group sizes, a power calculation was carried out using the "G*Power 3" computer program (Faul, Erdfelder, Lang and Buchner, 2007), specifying alpha = 5% and desired power = 80%, the required sample size is estimated at 27 (9 individuals per group). Given that the current study employed a number of questionnaires rather than the SPI-A, as well as two newly designed or modified tasks, the number of participants per group were increased to 20.

Participants

Participants were recruited through online advertisements, and snowballing (Atkinson and Flint, 2001) via an associate of the researcher. Specific selection criteria were adhered to for each group, in order to minimise possible group differences in age, gender, premorbid IQ and use of 'other' drugs apart from the main drug (ketamine; cannabis). Participants in the drug groups were asked to complete a screening tool (the Severity of Dependency Scale) and were required to score 3 or above in order to take part. In order to be considered a 'chronic' user of cannabis or ketamine, participants had to have used the relevant substance for a period of at least one year, for at least five days a week. Preference was given to daily users.

Initially, the researchers planned to select participants based on number of days of current use. However, due to a ketamine shortage at the time of recruitment, it was difficult to find participants who fit the criteria. The recruitment for the ketamine group was therefore based on previous use in stead. In order to meet criteria for inclusion to the ketamine group, participants had to have been using ketamine five times a week for a period of one year or more, prior to the onset of the ketamine drought in the end of 2013.

Participants were also excluded from the study if they scored above 3 (apart from for cannabis use in ketamine users) for any drug other than ketamine or cannabis, as this would have reflected dependence on other substances besides cannabis or ketamine which could have confounded results. All participants in the control group were required to have used an illegal substance at least once in their lives. Participants were aged between 18 -40. All participants were paid £20 for their time.

Procedure

Testing took place either in a UCL laboratory, in participants' homes, or in a community centre in Bristol. Participants initially filled out consent and demographic forms, after which they were interviewed about their drug use history, and complete a verbal IQ test (see below). They were asked specifically about whether they had ever tried a drug, whether they used it now, how frequently and the average dose per session. For both the cannabis and ketamine group, all participants completed an updated version of the Cannabis Experiences Questionnaire which included questions on different types of aversive effects of using either cannabis or ketamine (such as loss of concentration etc) and also level of distress associated with that effect (Adapted Cannabis-Ketamine Questionnaire ACKQ, see below).

Questionnaire Measures

Participants were asked to complete several questionnaires. These questionnaires were specifically chosen to measure a range of constructs relevant to psychosis. They were also chosen to mimic some of the domains which might be contained in a semi-structured interview (SPI-A; Morgan et al 2012). The questionnaires below were arranged around specific facets of positive and negative symptoms of psychosis, either in their entirety, or in their subscales.

Depression - The Beck Depression Inventory

The Beck Depression Inventory (Beck, 1996) is a 21- item multiple choice self-report inventory, with items being categorised into four subscales: Anhedonia, Non-Anhedonia, Somatic and Cognitive. Respondents rate each item by circling all the numbers which apply to them (1-4 for each item). The BDI is widely used by health professionals to diagnose depression, and was chosen as it has been regularly used to identify depression levels in Ultra High Risk for psychosis populations (Grano et al, 2013; Rietdijk et al, 2013) and has demonstrated superior internal consistency and construct validity in this at-risk sample (De Vylder et al, 2013) than other instruments measuring depression.

Capacity to take pleasure / Anhedonia - The Temporal Experience of Pleasure Scale

The Temporal Experience of Pleasure Scale was chosen for properties in measuring level of pleasure associated with everyday experiences. It consists of two factors, a 10-item anticipatory pleasure scale measuring pleasure associated with anticipation of future or past events, and an 8-item consummatory pleasure scale measuring pleasure associated with openness to direct experience (Gard et al, 2006). The questionnaire was chosen for its capacity to distinguish between the types of pleasure taking, as previous studies have shown that individuals prone to schizophrenia and psychosis are able to feel consummatory pleasure, but report lower anticipatory scores, which may relate to levels of anhedonia experienced in onset psychosis (Mote et al, 2013; Strauss, 2013).

Early Positive Psychotic Symptomatology - Prodromal-Questionnaire- Brief (PQ-B)

To directly assess psychotic-like experience, and early or baseline psychosis, including positive symptomatology, the Prodromal-Questionnaire- Brief (PQ-B) was chosen. The original version contains 92 items. The PQ-B is a shortened 16-item version of the full questionnaire which was validated specifically for identifying people who might be at risk of psychosis (Ising et al, 2012; Loewy et al, 2011). In particular its factors correlated with the CAARMS (a much longer and more complex interview-based measure) meaning that a score of 6 or more would indicate an At Risk Mental State Outcome from the CAARMS, with high sensitivity (87%) and specificity (87%) (Ising et al, 2012). Endorsement of three or more positive symptoms on the PQ-B differentiated between those with prodromal syndrome and psychotic syndrome diagnoses on the SIPS versus those with no SIPS diagnoses with 89% sensitivity, 58% specificity (Kline et al, 2012).

Schizotypy, or psychosis-proneness including positive and negative symptom indicators – The Oxford-Liverpool Inventory of Feelings (O-LIFE)

The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE; Mason & Claridge, 2006) was used to measure some of the positive or negative symptoms of psychosis which may be experienced in the general population, tapping psychosis-proneness in subclinical groups. It was originally introduced in 1995 as a four-scale questionnaire for measuring psychosis-proneness, principally schizotypy. The O-LIFE has been used in a variety of experimental and clinical studies, establishing its reliability and validity in measuring factors relevant to psychosis (Mason and Claridge, 2006).

Spot the Word – Pre-morbid Verbal IQ

In Spot the Word (participants are presented with pairs of items comprising one word and one non-word, and are asked to identify the word. Data show that performance correlates highly with verbal intelligence as estimated by Mill Hill Vocabulary score and by performance on the National Adult

Reading Test (NART) (Baddeley et al, 1993). It was used in this study as a pre-morbid indicator of IQ across participants.

Adapted Cannabis Ketamine Questionnaire – ACKQ

The Cannabis Experiences Questionnaire (Barkus, 2006) was adapted for this study so that it could also be administered to Ketamine users, which has been done in previous research (Stirling & McCoy, 2010). The adapted version contained12 items relating to subjective experiences individuals may have had as a consequence of their chronic ketamine or cannabis use, including items related to memory, concentration and physical effects. Participants were first asked to say whether or not they had EVER had the experience and then to rate the level of distress caused by it from 0-4, with higher scores indicating more distress.

Severity of Dependence Scale – SDS

The Severity of Dependence Scale (Gossop et al, 1995) was developed as a tool to be administered to individuals using substances in order to determine how dependent upon that substance they had become. It includes five questions with a four-point likert response scale.

Cognitive Assessments

The two tasks were presented to participants via laptops (please see Appendix II). Before each task was initiated, participants were played short snippets of the sound and offered earphones if they found it difficult to hear. The volume was also turned to the maximum level.

1. White Noise Task

The White Noise task was run using the psychology software tool E-RUN (1.1.4.6). Sound clips were kindly provided by Jim van Os (Galdos et al., 2011) from a UK version of the White Noise Task. Since the baseline rate of speech illusion in Galdos et al. (2011) was low (9% in controls and 30% in people with schizophrenia), sound clips were shortened in an attempt to increase the sensitivity of the task. This was achieved by cutting each clip from four seconds to one second in duration, ensuring that all speech clips began at the time of speech onset. A description of the task is outlined below and Figure 1 shows the sequence of stimuli presented to participants via laptop.

Over the course of the task, participants were presented with three separate types of stimuli: a) white noise only, b) white noise and softly-spoken low-volume neutral speech and c) white noise and clearly-spoken normal-volume neutral speech. There were 25 noise fragments in each condition, and participants were presented stimuli from the three conditions mixed together, in order to create a level of anticipation of hearing a voice in the noise. For each participant, the sequence of the mixture of different stimuli was randomly reordered (there were 15 randomised versions which the programme cycled through every time the task was presented) so that each participant's experience of the task was also varied, and the order of 'pure' white noise clips and clips with sound present were randomly assigned. The initial instructions given to the participants were:

> You are going to hear a number of short noise fragments. These will consist of noise and spoken language. Please rate each fragment separately and indicate your opinion about the spoken language by choosing one of the following options:
>
> 1 = I heard something positive; 2 = I heard something negative; 3 = I heard something neutral; 4 = I heard nothing; 5 = Not sure.

There were 75 noise clip repetitions in total, and participants were asked to rate whether they had heard something 1 -'positive', 2 - 'negative', 3 - 'neutral', 4 -'nothing' or 5 - 'not sure' by pressing 1-5 on the keyboard for each of the responses respectively, for each repetition (see Appendix 3 for a visual representation.)

Participants were also issued with a verbal instruction from the researcher at the beginning of the task that they should rate the quality of the voice heard, not the quality of the white noise, and advised that they should press 4, if they did not hear a voice. Therefore if a participant indicated numbers 1-3 as their response, this implied that they had heard a voice present in the noise. This data was then used to check whether that condition had in fact been a repetition with a voice present, or whether it had been noise only.

After the task had completed, participants were asked to rate how difficult they had found the task by indicating where on a visual analogue scale (VAS 10cm line) ranging from easy to difficult they would place a cross. They were asked to respond in a similar way on a VAS to how well they believed they had performed in the task (from 'not well' to 'very well').

2. Ambiguity of Attribution Task

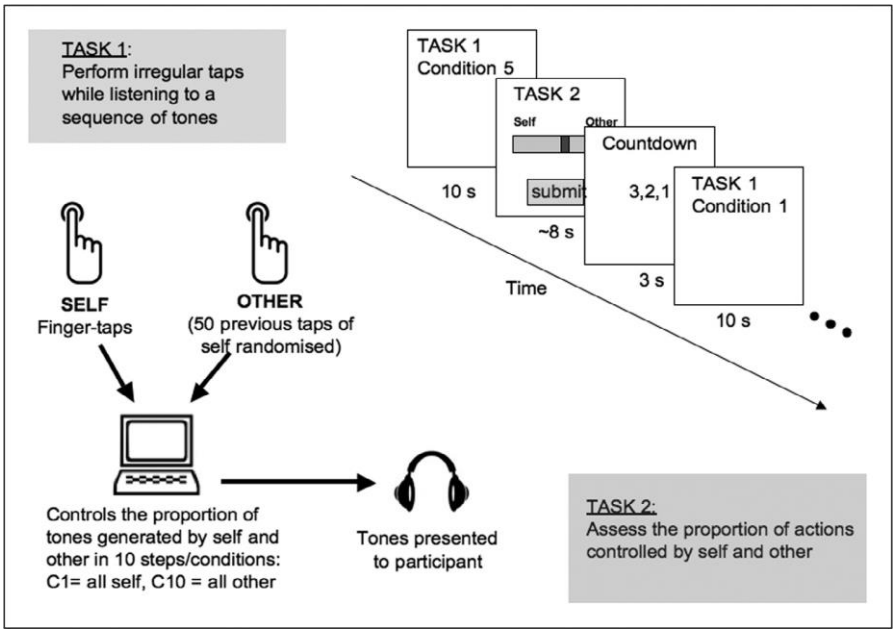
The stimuli for this sense of agency task consisted of an auditory tone which was either generated by the participant's finger taps (self), or the participant's 50 previous taps played back in random order (other). These tones were organised into ten different conditions corresponding to the proportion of control that self versus other had over tones within an individual trial (please see AAT glossary for more information on how these tones were generated.) After each trial, participants were asked to place a line on the linear scale to denote a) the level of control over tones self / other; and b) level of confidence in the previous response (i.e. were they 100% convinced it was them who created the sound). Figure 1gives a visual representation of the stimuli as presented to participants.

Before beginning the task, participants were issued with instructions detailing the type of tapping they would be asked to carry out during the task (irregular, like 'morse code' and continuous, 'without too many long gaps'). They were also played an auditory sample of this type of tapping as an example.

They were then given the opportunity to practice tapping in this manner under the 3different conditions: 1 – where the tones were entirely 'self' generated; 10 – where the tones were entirely 'other' generated; and finally 5 – where there was an ambiguous mix which was 50% generated by 'self' and 50% by 'other'. Participants were told that they would be presented with a variety of trials where their task was to decide what percentage of the tones they heard were generated by self or other. They were also told that they would be asked to rate the percentage of confidence they had in their response, ranging from 'absolute lack of confidence' to 'absolute confidence' on a linear scale.

Participants were then presented with stimuli, and their responses were collected using Pure Data (a real-time graphical programming environment: https://puredata.info/).

Figure 2. Visual representation of the Ambiguity Task (AAT)



Data Preparation

White Noise Task

The data from the White Noise task were extracted and categorised for each condition (White Noise only, Soft Audio, Clear Audio) according to response number. Researchers categorised '1, 2 or 3' as an incidence of having heard speech and making an appraisal of 'positive, negative or neutral'. All responses '4' were categorised as incidents where participants did not hear speech. The response '5' was more ambiguous, as participants were 'unsure'. Researchers decided that equating 'unsure' with *not* having heard a voice in the speech, was more conservative. Therefore, the White Noise condition responses were categorised to calculate the number of participants who heard a voice where there was none (category 1 = response of 1, 2 or 3) and the number of participants who did not hear a voice in White Noise (category 0 = 4 or 5).

Using signal detection theory, data were also manipulated to reflect the sensitivity of individual participants to correctly identify hearing a voice where there was one (hit rate) and to also ascertain how often participants correctly rejected hearing a voice where there was none (false alarm rate). From these tallies, the d-prime (d') was calculated, which equalled the hit rate – false alarm rate. The response bias (C) was also measured which combined the tendency to accurately detect a signal (hit rate / total speech incidences) with the likelihood of hearing something when no signal was present (false alarms / trials heard White Noise only in that condition). These scores are then transformed into z-scores.

Ambiguity of Attribution Task

The performance data from the three groups in the Ambiguity task were checked for normality, and three outliers (>3 sd's away the mean) from were removed (one from each group). A further three participants' data were excluded due to the data being saved incorrectly (three cannabis). Another four

participants' data were removed due to an error in the running of the task (two controls, two ketamine).Thus group numbers for this task were: cannabis (14), ketamine (19) & control (17).

The remaining data were then analysed to produce the following six outcomes:

- *Performance score*: How many standard deviations a participant is away from a perfect score. A score of 0 indicates no difference between subjective (participant's attribution rating) and objective (the particular tap-tone synchrony).
- *Sensitivity d'*: d-prime between attribution rating (subjective) and tap-tone synchrony (objective) using Fuzzy Logic (see Appendix III). A score of roughly 2 indicates good discrimination between self and other.
- *Bias towards self/other (β)*: A measure of response bias towards self or other attributions across conditions. The higher the score, the more the participant had a bias towards self, and the closer to 0 indicates bias towards other.
- *Correlation (between attribution and taptone synchrony) (r)*: A correlation between attribution (subjective control) and taptone synchrony for each repetition in one of ten conditions (objective control). Scores close to 1 indicate higher correlation between subjective and objective control.
- *Mutual Information (MI)*: An alternative score to performance and d' – a measure of sensitivity to correct attributions in task conditions, which is non-parametric. Calculated using entropy theory, but unrelated to the score below (see glossary Appendix III).
- *Entropy*: This measure applied to the tap strategy individual participants' used to inform their response to the task. The task was to perform 'irregular' taps. This score relates to the predictability of the taps, where high entropy is equal to lower predictability.

Statistical Analysis

ANOVA was used to compare the three groups on all main demographics, level of drug use, questionnaires, task performance, and subjective appraisal variables. A chi-square was performed to analyse the difference in categorical data in the White Noise Task, as well as one-way ANOVA to compare incidence of positive negative and neutral appraisal of actual speech. Pearson's correlations were carried out to investigate any associations between task performance variables with both level of drug use, and questionnaire outcomes. Correlations were also carried out between level of drug use and questionnaire scores. A correlation between distress experienced from drug-use with distress from reported positive symptoms was carried out.

Results

1. Demographics and Drug Use (Table 1)

There were no significant group differences in age, or estimated verbal IQ (Spot the Word score). Further, the groups did not differ significantly in gender, education level or employment. As expected there were significant group differences in Substance Dependence Scores reflecting cannabis dependence in the cannabis group ($F_{2,57} = 51.16$, $p<0.001$) and ketamine dependence in the ketamine group($F_{2,57} = 266.40$, $p<0.001$) (Table 1). There were also a range of levels of dependence reported by participants in both of the drug using groups. Table 2 shows the range of level of dependence of cannabis participants, and also includes data from 3 participants from the ketamine group who reported dependence on cannabis. Table 3 shows the range of level of dependence on ketamine within the ketamine group.

Table 1. Group means (sd) for age, Spot the Word score and Severity of Dependence Scale (SDS); N male/female; N in education until GCSE/A-levels, NVQ, Diploma, college/Undergraduate/Post-Graduate; N Employed/Not employed

	GROUP		
Demographic	***Control***	***Cannabis***	***Ketamine***
Age	27.2 (6.8)	27.8 (7.3)	26.9 (3.2)
Spot the Word	48.3 (3.4)	45.4 (3.8)	47.3 (5.2)
SDS Cannabis	0.10 (0.5)	**7.30 (3.4)**	1.05 (2.5)
SDS Ketamine	0.10 (0.5)	0.0 (0.0)	**9.55 (2.6)**
Gender	14/6	13/7	8/12
Education Level	1/8/9/2	3/6/10/1	4/13/3/0
Employment	12/8	16/4	17/3

Bold font indicates the group mean is significantly different from other groups at $p<0.001$

There were no significant group differences in days/month or amount per session of alcohol use ($F_{2,57} = 0.805$, $p=0.452$; $F_{2,54} = 2.976$, $p= 0.059$ respectively; Table 2). Significant group differences in tobacco use (days/month, $F_{2,57} = 14.92$, $p<0.001$; amount per session, $F_{2,56} = 6.89$, $p= 0.002$) reflected less use by controls than the other two groups in terms of i) fewer days/month use by controls than both cannabis ($p<0.001$) and ketamine ($p=0.005$) groups and fewer cigarettes per day ($p=0.027$; $p=0.002$ respectively). As expected, there were significant differences between the groups for Ketamine use (days/month, $F_{2,57} = 4.05$, $p=0.023$; amount per session, $F_{2,57} = 32.10$, $p<0.001$) and Cannabis use (days/month $F_{2,57} = 66.79$, $p<0.001$; amount per session, $F_{2,57} = 52.36$, $p<0.001$). Cannabis users used more cannabis per session than both ketamine users ($p<0.001$) and controls ($p<0.001$) and more days per month than both groups ($p=0.002$ & $p<0.001$ respectively). Similarly ketamine users used more ketamine per session than both cannabis users ($p<0.001$) and controls ($p<0.001$) and more days per month than cannabis users ($p=0.049$).

Table 2. N of participants in cannabis and ketamine group scoring within a particular range on the SDS for cannabis use

Group	SDS 3-4	SDS 5-6	SDS 7-8	SDS 9-10	SDS 11-12	SDS 13-14
Cannabis	5	4	4	3	2	2
Ketamine	1		1	1		

Table 3. N of participants in ketamine group scoring within a particular range on the SDS for ketamine use; N of participants in ketamine group reporting other dependence

Group	SDS 3-4	SDS 5-6	SDS 7-8	SDS 9-10	SDS 11-12	SDS 13-14
Ketamine	1	1	5	6	4	3

Table 4. Drug use percentage of participants ever used; mean (sd) for amount used on average day; mean (sd) N days used per month in the last year; 'ketamine past' mean (sd) N amount and N of days used in year previous to the last year

	GROUP								
	Control			***Cannabis***			***Ketamine***		
Drug	***%***	***amount***	***days***	***%***	***amount***	***days***	***%***	***amount***	***days***
Alcohol (units)	100	7.8 (4.5)	14.1 (7.5)	100	8.7 (3.2)	11.0 (8.6)	100	13.0 (10.9)	11.6 (8.6)
Tobacco (cigarettes)	90	**1.4** (2.6)	8.3 (12.6)	100	7.2* (5.3)	**27.8** (7.3)	100	9.0** (9.8)	20.0** (13.3)
Cannabis (mg)	100	63.8 (147.5)	1.6 (2.2)	100	**1175.0** (553.3)	**28.1** (4.7)	100	223.8 (292.6)	10.1 (11.7)
Ketamine now (mg)	40	275.0 (35.4)	0.01 (0.05)	50	-	-	100	**1594.1** (958.0)	**3.0** (6.6)

Ketamine past (mg)	-	-	-	-	-	-	100	6275.0 (3884.8)	29.2 (2.2)
MDMA(mg)	90	229.1 (254.5)	0.6 (0.8)	80	341.7 (180.0)	0.4 (0.7)	100	265.7 (203.5)	0.6 (1.0)
Speed (mg)	45	-	-	45	100.0 -	1 -	100	1465.8 (1424.9)	4.2 (2.7)
Mephedrone (mg)	35	116.7 (129.1)	-	30	100.0 (223.6)	-	90	-	-
Benzos (mg)	45	8.3 (7.5)	0.3 (0.6)	100	6.3 (9.5)	1.2 (1.6)	100	14.5 (29.2)	3.0 (5.3)
Cocaine (mg)	80	693.7 (632.7)	1.1 (1.1)	70	516.7 (426.2)	1.5 (1.9)	95	808.9 (941.7)	1.8 (1.9)
Hallucinogens	65	-	0.5 (0.7)	60	-	1 -	95	-	-
Opiates (mg)	10	-	-	15	-	-	30	-	-

*< 0.05, ** < 0.01**, bold print<0.001**

As the ketamine group were not able to give data based on their use in the last year, data was collected to examine last time of use, amount used daily in the past, and number of years of heavy use (Table 5).

Table 5. N of ketamine participants in each range for last year used ketamine; Amount used daily (g) in past; N of years using daily

	Year last used			**Amount per day (g)**			**N of years use**		
	2012	2013	2014	1-5	6-10	11-15	3-4	5-6	7-9
N of participants in Ketamine group	2	9	9	11	6	3	8	3	9

The results taken from the urine samples were also collected and are outlined in Table 6. Results show that cannabis (THC) was present in 18 out of 20 participants urine samples in the cannabis group,

meaning that they had used cannabis in the previous 72 hours. There was only one ketamine participant with ketamine present (PCP) and this is in keeping with the fact that most participants had not used ketamine for a substantial period of time. Interestingly, the majority of ketamine participants also tested positive for benzodiazepine.

Table 6. N of participants in each group testing positive for substances in urine analysis, or with no detectable substance present

	GROUP		
	Control	**Cannabis**	**Ketamine**
None	14	1	3
Cannabis	4	18	7
Ketamine	1	-	1
Speed	1	-	1
Benzodiazepine	1	-	12
Cocaine	1	2	3
Buprenorphine	2	-	3
Opiates	1	2	2

2. Questionnaire Measures (Table 7)

Table 5. Group mean (sd) scores on the BDI, O-LIFE, TEPS, PQ-B

	GROUP		
Questionnaire	**Control**	**Cannabis**	**Ketamine**
BDI Total	**5.3** (5.6)	12.2 (9.0)	12.5 (7.5)
BDI Anhedonia	**1.2** (1.4)	2.7 (2.0)	2.4 (1.6)
BD1 Non-Anhedonia	**3.9** (4.6)	9.6 (7.4)	10.1 (6.2)
BDI Cognitive	**1.7** (1.7)	4.0 (3.6)	5.2 (3.7)
BDI Somatic	**3.7** (4.3)	8.3 (6.1)	7.3 (4.7)
O-LIFE Total	**11.9** (6.7)	19.5 (7.3)	20.3 (6.6)
Unusual Experiences	**2.1** (1.6)	6.1 (3.7)	5.2 (2.7)
Cognitive Disorganisation	5.5 (4.0)	6.4 (2.6)	7.5 (2.9)

Introvertive Anhedonia	1.4 (1.2)	2.4 (2.0)	2.0 (1.4)
Impulsive Nonconformity	**3.0** (1.7)	4.6 (2.0)	5.7 (1.8)
TEPS Total	86.1 (11.7)	81.9 (12.6)	82.0 (13.6)
Anticipatory	46.5 (6.7)	46.1 (7.5)	43.6 (7.6)
Consummatory	39.3 (6.2)	35.8 (6.7)	40.1 (4.9)
PQ-B Total	**3.0** (3.2)	8.5 (4.2)	8.3 (3.9)
Distress	**8.8** (11.3)	26.8 (20.3)	25.3(12.3)

There was a significant group difference in BDI Total scores ($F_{2,56} = 5.62$, $p = 0.006$), as well as the individual sub scores: 'Anhedonia' ($F_{2,56} = 3.99$, $p = 0.024$), 'Non-Anhedonia' ($F_{2,56} = 6.14$, $p = 0.004$), 'Cognitive' ($F_{2,56} = 5.81$, $p = 0.005$) and 'Somatic' ($F_{2,56} = 4.54$, $p = 0.015$). Bonferroni corrected post-hoc tests showed that significance was driven by higher Total scores in the cannabis than the control group (p=0.018), and in the ketamine than the control group (p=0.013). There was no BDI Total score difference between the cannabis and ketamine groups. There were higher scores in the cannabis than the control group for 'Anhedonia', 'Non-Anhedonia' and 'Somatic' (p=0.031; p=0.016; p=0.018) subscales. There were higher scores in the ketamine than the control group for 'Non-Anhedonia' and 'Cognitive' (p=0.008; p=0.004 respectively) subscales. There were no significant differences between cannabis and ketamine groups on Total score or subscales.

There were significant differences between the groups on O-LIFE Total scores ($F_{2,57} = 9.22$, $p<0.001$), as well as two of the sub-scales: 'Unusual Experiences' (UE) ($F_{2,57} = 11.16$, $p<0.001$), and 'Impulsive Non-conformity' (IN-C) ($F_{2,57} = 11.15$, $p<0.001$). Bonferroni corrected post-hoc tests showed that significant differences were driven by higher scores in the cannabis than the control group (Total, p=0.02; UE, p<0.001; IN-C p=0.02 respectively), and higher scores in the ketamine than the control group (Total, p=0.001; UE, p=0.003; IN-C, p<0.001).

There were significant differences between the groups in PQ-B Total ($F_{2, 57}$ =13.40, p<0.001) and PQ-B 'Distress' ($F_{2, 57}$=8.67, p<0.001) scores. Bonferroni corrected post-hoc tests showed that there were higher total scores in the cannabis than the control group, and in the ketamine than the control group (all p<0.001). There were similarly higher distress scores in the cannabis than the control group (p=0.001), and the ketamine than the control group (p=0.003).There was no significant difference between the groups on TEPS total scores ($F_{2, 57}$ = 0.722, p=0.490).

3. *White Noise Task (Table 8)*

A chi-square test was performed and no difference was found between groups in the incidence of hearing a speech illusion in White Noise, χ^2 (2) = 1.616, p = 0.446. Analysis of the signal detection parameters d' (discriminability) and C (response bias) using a one-way ANOVA showed no significant difference between the groups in either *d'* scores, ($F_{2, 57}$ = 0.176, p = 0.839) or C scores ($F_{2, 57}$ = 0.174, p = 0.841).

Table 8. White Noise Task: N in each group experiencing speech illusion Yes/No; Group means (sd) for Discriminability (d') and Response Bias (C)

		GROUP	
White Noise Task	**Control**	**Cannabis**	**Ketamine**
Speech Illusion	13/7	11/9	9/11
Discriminiability d'	2.12 (0.88)	2.34 (0.89)	2.52 (0.89)
Response Bias C	-0.19 (0.52)	-0.22 (0.44)	-0.18 (0.58)

A one-way ANOVA was also run to compare the number of times a positive, negative or neutral appraisal was made, when there was actual speech present. There were no significant differences

between the groups for incidence of positive ($F_{2, 57} = 0.433$, p=0.651) negative ($F_{2, 57} = 1.267$, p=0.290) or neutral ($F_{2, 57} = 0.425$, p=0.656) assignment of the spoken language.

4. Ambiguity of Attribution Task (Table 9)

A one-way ANOVA was carried out to determine if there was any difference between the groups on the 6 outcome measures generated from the Ambiguity task. There was no significant difference between the Bias towards self/other β scores ($F_{2, 48} = 2.223$, $p = 0.119$) or correlation r scores ($F_{2, 48} = 2.798$, p = 0.071). There were significant differences between the groups in performance scores ($F_{2, 48} = 3.716$, $p = 0.032$), and sensitivity *d'* scores ($F_{2, 48} = 5.006$, $p = 0.011$). There were also highly significant group differences in MI scores ($F_{2, 48} = 6.973$, $p = 0.002$) and Entropy scores ($F_{2, 48} = 9.672$, $p < 0.001$).

Bonferroni corrected post-hoc tests showed that d' scores were significantly higher in the control group than both the cannabis group (p = 0.050) and the ketamine group (p = 0.017) (Figure 2a). MI scores were higher in the controls than both the cannabis (p = 0.008) and ketamine groups (p = 0.006) (Figure 2b). Entropy score comparisons showed a marked reduction in ketamine users compared to both controls (p = 0.001) and cannabis users (p = 0.002) (Figure 2c).

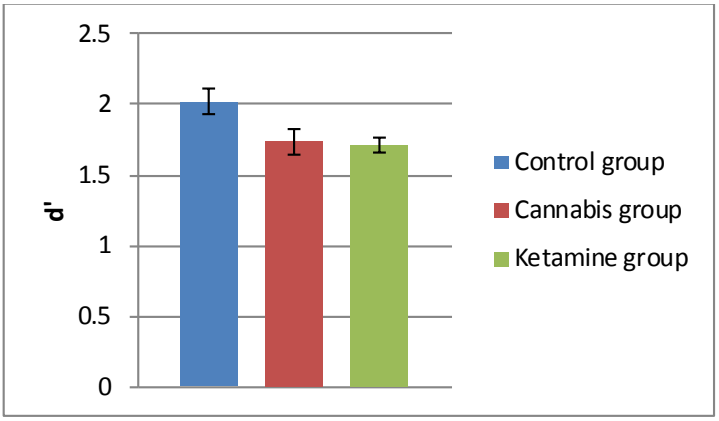
Table 9. Ambiguity of Attribution Task Group means (sd) for Performance score; Sensitivity (d'); Bias (β) towards self/other; Correlation (r) between attribution & condition; Mutual Information (MI); Entropy.

	GROUP		
Ambiguity task	**Control**	**Cannabis**	**Ketamine**
Performance Score	0.22 (0.04)	0.26 (0.06)	0.25 (0.04)
Sensitivity (d')	**2.02** (0.37)	1.74 (0.34)	1.72 (0.23)
Bias towards self/other (β)	0.54 (0.33)	0.73 (0.33)	0.82 (0.51)
Correlation (r) ***(between attribution and condition)***	0.74 (0.10)	0.66 (0.14)	0.66 (0.13)
Mutual Information (MI) ***(response strategy)***	**1.06** (0.11)	0.94 (0.12)	0.94 (0.10)
Entropy	5.99 (0.33)	5.99 (0.19)	**5.57** (0.40)

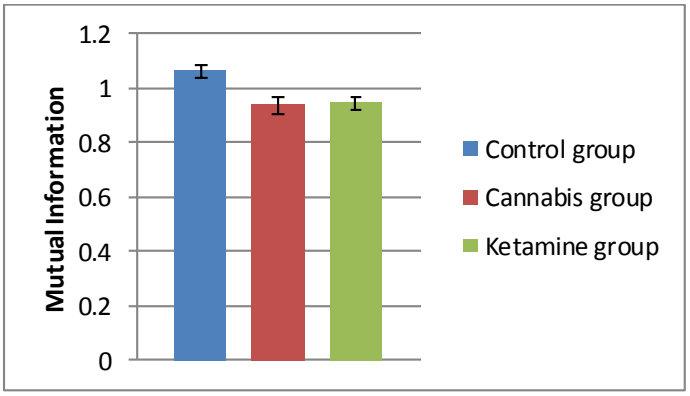
Bold type p< 0.05

Figure 3. Group means on the Ambiguity of Attribution Task for (a) Sensitivity d' (b) Mutual Information and (c) Entropy (bars represent standard error)

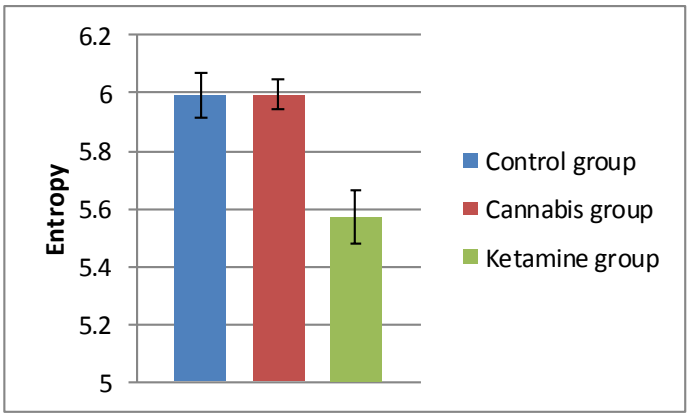
2(a)



2(b)



2 (c)



Graphs showing the pattern of misattribution over all three groups combined, misattribution by individual group, and misattribution made by each individual participant categorised into groups are included in Appendix III. These graphs show that overall, in each group there was a slight bias towards a self-appraisal rather than other.

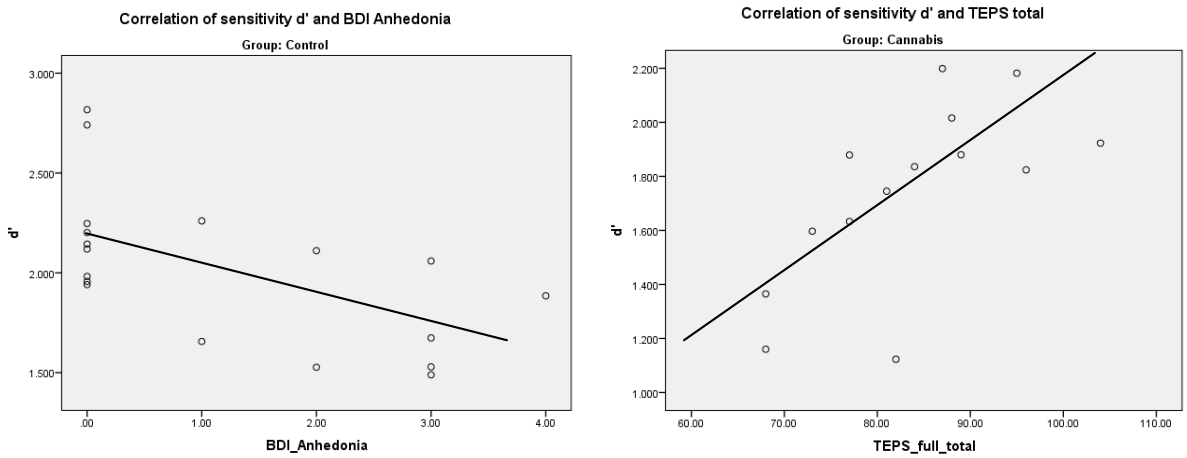
5. Correlations

In the control group, there was a significant negative correlation between d' sensitivity scores and BDI Anhedonia r = -0.594, p =0.009 (Figure 3a). In the cannabis group, there was a significant correlation between d' sensitivity scores and TEPS total score r= 0.663, p=0.009 (representing 44% shared variance) (Figure 3b).

There were no significant correlations between d' sensitivity, MI or Entropy scores and any of the questionnaires in the ketamine group. There were no significant correlations in the cannabis group between the AAT variables and cannabis use or in the ketamine group between AAT variables and ketamine use.

Figure 4. Scatter plots showing correlations (a) in the control group between Ambiguity of Attribution task d' sensitivity scores and BDI Anhedonia subscale scores and (b) in the cannabis group between Ambiguity of Attribution Sensitivity d' scores and TEPS Total scores.

(3a) (3b)



Several other correlations were statistically significant but scatterplots showed these were driven by outliers so were not meaningful (see Appendix 4).

6. Distress and metacognition (Table 10)

There were significant differences between the groups on scores from the ACKQ, Table 6.

Table 10. Group means on Adapted Cannabis Ketamine Questionnaire (ACKQ): Total score and Level of distress from the drug score.

		GROUP	
Adapted Distress Questionnaire	**Control**	**Cannabis**	**Ketamine**
Total Score	1.1 (2.02)	**8.8 (3.6)**	***12.0 (1.5)***
Distress Score	2.0 (3.9)	**19.0 (11.1)**	***32.9 (10.9)***

There were significant group differences in total scores ($F_{2,57} = 94.87$, $p<0.001$) and distress scores ($F_{2,57} = 55.99$, $p<0.001$). There were also significantly higher total and distress scores in both the cannabis and ketamine groups, than the control group (both $p<0.001$). There were also significantly higher total scores and distress scores in the ketamine group than the cannabis group (both at $p<0.001$).

There was a significant correlation between both the total scores and the distress scores on the adapted cannabis questionnaire (ACKQ), and the total and distress scores in the PQ-B in the cannabis group (Total PQ-B with total ACKQ r=0.621, p=0.003; distress PQ-B with distress ACKQ r=0.530, p=0.016). There were also significant correlations between the distress scores on the ACKQ, and the total and distress scores from the PQ-B in the ketamine group (ACKQ distress with PQ-B total

r=0.451, p=0.046; ACKQ distress with PQ-B distress r=0.521, p=0.018). The SDS total for each participant was also correlated with their Total and distress score from the ACKQ. There were no significant correlations between level of dependency (SDS) and Total number experiences or level of distress from drug use, in either the cannabis or the ketamine group.

There were no group differences in the subjective experience of how difficult participants found the White Noise task ($F_{2,56} = 0.277$, p=0.759) or how well they thought they had done ($F_{2,56} = 2.06$, p=0.137). There was also no significant group difference in the Ambiguity of Attribution task, in participants' appraisal of difficulty ($F_{2,57} = 0.034$, p=0.967) or how they thought they had performed ($F_{2,57} = 1.771$, p=0.179).

Discussion

Assessing validity of drug models for Prodromal Psychosis symptoms: questionnaire outcomes

Our first hypothesis based on the findings of Morgan et al (2012) was that the daily ketamine and cannabis users may provide models for early stages of psychosis. We set out to investigate whether chronic ketamine users would provide similar profiles to the patterns of change or impairment identified across various domains considered relevant to prodromal psychosis (Morgan et al, 2012). The SPI-A is a semi-structured interview which was used in the previous study. It assesses (amongst other constructs) four domains which overlapped with the constructs measured by the questionnaires in this study: 1) affective / dynamic; 2) perceptual disturbances (both general and bodily); 3) cognitive disturbances and 4) appraisal of self and surroundings. The results from the previous study showed that ketamine users exhibited a higher incidence of affective symptoms and perceptual disturbances (both general and bodily) than the cannabis group. The study also showed that chronic ketamine users showed very similar patterns across all SPI-A sub-scales to a prodromal group who later went on to transition to psychosis (Schulze-Lutter et al, 2007).

In the Morgan study, the cannabis group differed from both the ketamine group and the prodromal group in affective and perceptual disturbance. However, in the domains of 'cognitive impediments' and 'cognitive disturbances', the ketamine and cannabis groups showed similar patterns to the prodromal group. For this reason, we hypothesised that the chronic ketamine using participants would exhibit a) more symptoms associated with affective and perceptual disturbance (as measured by subscales on our questionnaires) than the cannabis group and b) similar incidence of 'cognitive disturbance' or 'cognitive impediment' to the chronic cannabis group. Our second hypothesis was that the control group in this study would exhibit lower scores across all these four domains, than the drug groups.

The hypothesis that controls would differ from both of the drug groups on scores from the BDI, O-LIFE and PQ-B was confirmed. There were also significant differences between the controls and the two drug groups on several subscales: BDI Anhedonia versus Non-Anhedonia, and Cognitive versus Somatic; O-LIFE Unusual Experiences and Impulsive Non-Conformity; and finally the positive prodromal symptoms indexed by the PQ-B total and distress scores.

However, we found no significant differences between the cannabis group and the ketamine group on any of these subscales, and so our first hypothesis was not confirmed. We were not aiming to directly replicate the findings from the Morgan study, as they used a semi-structured interview whereas we used questionnaire measures, and so the data are not directly comparable. However, we were hoping to see some similarities or overlap in the pattern of symptoms in the SPI-A subscales, and the patterns measured by the questionnaires in this study.

Why did we not show a difference between ketamine and cannabis users? At the time of this study there was a ketamine drought in the UK. Posts on drug forums from early 2014 reported on the rising

prices and scarcity of ketamine. A worker in Bristol Drug Project, who specialised in working with Ketamine users reported that there had been a seizure of Ketamine in India, and that the laws had also changed, meaning that those who had been smuggling or importing the drug from India had come up against more boundaries to being able to easily source the drug. Because of this, individuals in the ketamine group had substantially reduced the amount of ketamine they were using, in most cases against their will, as they were unable to obtain ketamine in its pure form. Indeed many reported being sold 'K' that was a similar white powder but actually another substance with different effects. As such, this study provided a rare opportunity to observe the symptom profiles which emerged when previously dependent ketamine users were experiencing an involuntary 'detox' from their chosen drug. This may indicate that Morgan et al's findings where the profiles on SPI-A subscales varied significantly between ketamine and cannabis users, were related to participants' continued high level of use of ketamine when the drug was readily available in the UK. In contrast we found that participants in the ketamine group, who were *previous* chronic ketamine users but not *current* users due to the drought, had similar profiles to *current* chronic cannabis users.

This finding is interesting, as the domains which were significantly different from controls, namely 'unusual experiences' and 'impulsive non-conformity' (O-LIFE), Total and Distress scores on the PQ-B and all the subscales on the BDI, suggest that these specific subscales tap into subjective phenomena which persist after much higher levels of ketamine use stop. In the previous interview-based study, the perceptual disturbance and affective dysregulation were highest in the ketamine group (Morgan et al, 2012). In our study, both ketamine and cannabis groups exhibited similar profiles to each other, and it may be that the scores would have differed if the ketamine group were still using heavily.

It is also the case that a semi-structured interview (SPI-A), due to its exploratory nature, may produce a different profile, or pattern of symptoms than a questionnaire. As such, it is difficult to know

whether the measures in this study mapped onto the same subscales. Assuming they did, the results suggest that in the domains of depression, unusual experience, impulsive non-conformity and distress caused by overall positive symptoms, there was no difference between currently being a chronic cannabis user, and having been a chronic ketamine user. One interpretation of this finding is that there had been a reduction of higher psychotic-like symptoms, related to the reduction in use of ketamine. Cognitive disturbance was no greater in ketamine or cannabis groups than the control group, which was also a difference from the Morgan et al study. These findings give further information to guide future studies which attempt to model early psychosis using varying degrees of drug-use (ie. chronic and dependent, versus ex-users).

Another possible reason our findings differed from Morgan et al is that there were differences in age between their cannabis (mean 20.8 years) and ketamine users (mean 25.1 years) whereas all our groups were closely matched for age. The ketamine users in Morgan et al also scored higher on depression than the cannabis group whereas our two groups did not differ. This may suggest that the difference in scores on the affective and perceptual domains on the SPI-A in the ketamine group relate to higher levels of overall depression. In this study, there were no differences between cannabis and ketamine groups in depression scores (BDI), and no difference in affective disturbance or perceptual changes (O-LIFE, TEPS, PQ-B).

Ambiguity of Attribution Task

We aimed to explore whether the chronic use of ketamine or cannabis would impair sensitivity to discriminating between self and other, as a model for understanding how misattribution of source may contribute to early psychosis. The task chosen to explore this, the Ambiguity of Attribution task, was designed to measure sensitivity to discerning when the individual had created sounds themselves from when sound was coming from an external source created by the computer programme. de Bezenac (2015) found that those with higher 'hallucination-proneness' and lower 'musical experience' were less able to discern whether sound had been self-created or came from another source, in situations

where it was not immediately obvious. The higher the level of ambiguity (i.e. when there was a more subtle distinction between self and other), the less sensitive those with high hallucination-proneness became to making an accurate appraisal of attribution.

There were several outcomes from this task which gave an estimate of an individual participant's overall sensitivity in the task which contained a range of conditions from non- ambiguous to very ambiguous. We found that on both sensitivity to discriminating accurately (d') and Mutual Information (MI) scores, the control group performed better than the ketamine and cannabis groups. This suggests that chronic use of both drugs impacted on the ability to discriminate sensitively and to respond (whether consciously or subconsciously) using higher levels of mutual information. The significant difference in MI, highlights another difference in performance on the task. Drug-using groups had less MI in their tapping styles, meaning that there was less cross-over between information generated by themselves, and information generated by the computer in their taptone asynchrony, which may indicate a slight dissonance with the task. As hypothesised, there were no significant differences between the two chronic drug use groups on the sensitivity measures,

Intriguingly, we also found differences between chronic ketamine users and chronic cannabis users. The ketamine group showed a significantly reduced amount of entropy in their tapping strategy, when compared to the other two groups. The cannabis and control groups did not differ in entropy scores. The higher the level of entropy, the less predictable a participant's tapping style over the course of the task, meaning that the task recorded and adjusted to a more random manner of tapping. The ketamine group responded with higher predictability and lower entropy in their tapping style, or in other words, they used a more stereotyped, repetitive or constrained manner of tapping across the trials.

There are different ways that this result could be interpreted. It is difficult to say whether or not having high or low entropy directly affects performance on the task. There was no correlation between entropy and d' sensitivity, meaning that participants with higher predictability in tapping style across the task, did not necessarily do any worse in the performance on the task. Anecdotally, the ketamine participants were observed to become quite complacent and bored during this task, and 13 out of the 20 participants described this as the task (out of 5) which they liked the least. It may be that their stereotyped response to this task is an indicator of reduced interest or boredom. Whether this directly relates to motivation, or anhedonia constructs is difficult to say, but may be worthy of investigation in the future. This may also in some way relate to some of the subtle unusual behaviours observed by clinicians in First Episode Psychosis, such as 'stereotypy' which forms part of the symptom checklist for 'Unusual Behaviour' (Compton et al, 2015; Matthew et al, 2013).

White Noise

Contrary to our hypothesis, no significant group differences were found on this task. This may mean that this task is not sufficiently sensitive to differences between our samples of users. It could also point to a difference between using an acute as opposed to a chronic drug model for psychosis. In a recent study administering cannabis acutely to healthy occasional users of the drug, participants experienced auditory hallucinations that the White Noise alone condition actually contained speech (Mokrysz et al, in prep). In previous ketamine studies, acute administration of the drug has resulted in cognitive distortions linked to auditory hallucinations (Pomerol-Clotet et al, 2006; Chaterjee et al, 2010; Moore et al, 2011).

As there were no significant group differences on this task, this may suggest that the chronic model of ketamine or cannabis use investigated in this study is more closely related to an 'at-risk mental state', than to a 'full-blown psychotic episode', where individuals are experiencing actual auditory hallucinations. This supports the idea that we should look to more subtle symptomatology in at-risk individuals, rather than assessing hallucinations or some of the other more overt positive symptoms.

Another interpretation of this finding is that drug-using groups are well-versed in the difference between being under the effect of a drug and being sober, and therefore may be better attuned to attending to whether or not something is real or imagined.

Linking tasks to Questionnaires – Correlations

Our final aim in the study was to explore any correlations between scores on specific questionnaire subscales (e.g. perceptual disturbance) and performance on the two tasks. Whilst the two tasks had never been used before in conjunction with the questionnaire measures used in this study, they had both been used in studies where the aim was to investigate the association between constructs believed to be contributing factors to early psychosis, namely auditory hallucinations stemming from affective meaning-making in random stimuli, and misattribution of agency. For this reason we carried out exploratory correlations between tasks and questionnaires, hypothesising that if there were significant differences on performance in a task between the groups, this may be related to differences in symptoms measured by the questionnaires.

As there were significant differences between the groups on the outcomes in the Ambiguity task, we explored whether this may correlate with some of the differences in questionnaire outcomes. Interestingly, the correlations which were significant showed a positive correlation between the capacity to take pleasure in life (measured by the TEPS), and an increased sensitivity to the ambiguity task (d') in the cannabis group. These two variables shared 44% of the variance. In a similar vein, an increase in anhedonia (BDI), was linked to a decrease in sensitivity to discerning between self and other in the control group (these two variables shared 36% of the variance). These findings highlight the association of anhedonia as a part of measuring depression which could impact on the ability to

discriminate effectively between self and other. In other words, heightened anhedonia may impact on an individual's ability to attribute source (whether something was caused by self or other) effectively.

Distress and metacognition

As the ketamine group reported significantly higher distress related to their drug use compared to the cannabis group and the control group, but had similar profiles on the other questionnaire outcomes, one interpretation may be that during the ketamine drought, participants in this group have had space to reflect on and make appraisal of their previous level of drug use, remembering associated difficulties as highly distressing experiences. It would be interesting to explore in future studies, whether cannabis users would also remember more associated distress after stopping use, or if this is specific to the effects of ketamine on perceived cognitive and day to day functioning. If so, this is in line with previous research which found that individuals were more likely to have elevated scores on the O-LIFE, if they had poor distress tolerance (Cascio et al, 2012).

It was also of note that the Ketamine group reported significantly higher levels of distress related to their drug-use, and that this was correlated to level of distress reported from Schizotypal experiences as measured by the O-LIFE. One reason that the Ketamine group may have differed from the Cannabis group, was that their pattern of use when they had had access to large quantities of ketamine was seemingly very different to cannabis users, who mostly smoked only a few times a day. Although some of the ketamine-users had contained their use to 1-2 grams a day when they had been using more heavily, several others reported having used throughout their day, so that being under the influence of the drug permeated all of their waking existence. This may have made it harder to differentiate between distress caused by 'sober' experiences, versus 'high' experiences.

There were no differences between the groups in perceived performance on the two tasks, or how difficult they were, which suggests that the groups had a similar experience of taking part in the study.

Strengths and Limitations

Demographics & Drug Use

The matching of the groups in demographic and drug usage meant that differences other than primary dug use which may have affected outcomes in measures and tasks were controlled as far as possible. This was particularly relevant in the 'other drug use' levels which did not differ in all major drugs use, including alcohol. Indeed the only difference was a higher tobacco use in the two drug using groups than controls which is a standard finding in these populations. This was a strength in this study, as research using dependent drug users is often open to the criticism that it is difficult to attribute outcomes to the use of one specific substance when many are being used together.

Relevance to psychosis model

Another strength in this study was that we were able to demonstrate significant differences between dependent / chronic drug-users, and the recreational-using control group on several questionnaire outcomes measuring symptoms related to psychosis and on the Ambiguity task. Whilst we need to be careful how we interpret these findings, there appears to be a clear overall difference in the dependent users when compared to recreational groups, which may tap into individual differences in participants across these groups. For example, the relationship between level of depression and anhedonia would be interesting to examine in more detail in a follow-up study, in order to better understand how these two factors may be the catalyst for an individual transitioning into a psychotic disorder.

Ketamine drought

In the original design of the study, we had aimed to recruit current daily users of ketamine. Due to the ketamine drought at the time of recruiting, the inclusion criteria had to be changed, so that *previous* dependent users of ketamine were recruited. Although we were initially disappointed, and concerned

that participants in the ketamine group would not provide the model we had hoped to explore, it became clear over the course of the research that carrying out this particular study with those who were still very heavy users of ketamine, would have been very difficult. Several participants from this group said that they would have been unable to attend to and concentrate on the two tasks. There was also a general consensus that if they had still been using heavily, it was unlikely they would have taken interest in the study at all. It could be argued that the data from the questionnaires collected in this study also conveyed a different type of subjective appraisal than would have been collected if ketamine group participants were still using daily.

Many participants reported 'not seeing anything negative' during their chronic use, and were only able to reflect on the harm or subjective alterations to how they experienced life, after they had stopped using ketamine. However, as ketamine-using participants had sometimes replaced ketamine use with the increased use of other drugs such as cannabis and valium, as well as alcohol, it remains questionable whether their general level of dependency on substances had changed that substantially. This may imply that there were underlying problems or processes such as depression which were still being 'self-medicated' for or perhaps avoided.

Clinical Implications

Use of brief task as screening method?

The correlation between anhedonia and sensitivity to the Ambiguity task in the control and cannabis groups, provided some insight to possible underlying mechanisms involved in the development of psychosis, specifically in delusion formation or hallucination-proneness (de Bezenac, 2015). This association suggests that the greater the capacity for pleasure, the greater the sensitivity to being able to make subtle differentiation between objective and subjective situations, with high levels of ambiguity. Could the Ambiguity task be used as a screening method for early psychosis?

It could be argued that at initial screening in Early Intervention clinics, or even earlier in a care pathway, such as when an individual presents at a GP surgery, the use of the Ambiguity task, in conjunction with the BDI may provide an additional sensitive tool for discerning those who would be categorised as At Risk for psychosis. If there was an increase in BDI scores (in particular anhedonia) and a low sensitivity to the Ambiguity task, this may indicate at risk state. Clearly longitudinal research would be needed to follow through individuals at risk so that those who do transition over time can be compared with those who do not on the Ambiguity task.

Level of Distress

Both cannabis and ketamine users reported higher distress levels on the PQ-B than the control group. Ketamine users reported higher levels of distress on the ACKQ than both the cannabis group and the control group. Taking both of these questionnaires together may provide useful information when making an assessment of presenting difficulties. Whilst one questionnaire (ACKQ) focused on symptoms, phenomena or difficulties which the participant had experienced as a direct result of having used drugs, and the other (PQ-B) asked specifically about experiences which were non-related to drug or alcohol use, the amount of distress reported in each was positively correlated. This highlights the difficulties of teasing apart some of the complicated relationship between substance-induced distress, from distress that may be more linked to an enduring change in mental functioning. It is difficult to know whether distress is experienced as a result of substance use, or is maybe worsened by it, as some studies have highlighted higher distress intolerance in those who regularly use drugs (Ozdel & Ekinci, 2014; Buckner et al, 2007). As mentioned earlier, chronic ketamine users reported that the drug took over much of their waking life.

Asking help-seeking individuals to complete questionnaires related specifically to their drug use, as well as to their subjective experiences off drugs, may provide further insight into formulating the relationship (if any) between an individual's symptoms, and their drug use. For example, would

decreasing drug use necessarily decrease distress, or would there by unwanted side effects experienced first, as a result of stopping use. How does level of distress relate specifically to psychosis symptoms, rather than to experiences directly related to drug-use, such as the pain endured from bladder problems reported, in heavy ketamine users? This would be an area which warrants further research in the future, perhaps making more use of anecdotal information shared with researchers during the substance use interviews, or by expanding the scope of the ACKQ.

A systematic review examining the evidence for reducing substance use in early psychosis has shown that a reduction tends to improve outcomes (Mullin et al, 2011). This is clinically relevant, as many outcomes for treatment in Early Intervention focus on reducing distress, and increasing functioning (Amminger et al, 2011). If individuals present to services as drug (including alcohol) users asking them to complete an SDS may further clarify their situation, as drug and alcohol dependency as opposed to recreational drug or alcohol use is associated with higher levels of psychotic symptoms (Morgan et al, 2014).This means higher scores on SDS may implicate an increase of reported subjective phenomena on the BDI, O-LIFE and PQ-B.

Future Studies

Use of novel tasks

Both the White Noise task and the Ambiguity of Attribution task were used in a novel way in this study. The aim of employing tasks was to provide an extra source of objective data to investigate the mechanisms which may underlie the formation of certain beliefs or biases which may lead to psychosis. Although there was no difference between the groups on the White Noise task, each group showed a similar pattern of response in terms of more regularly making positive rather than negative appraisals across the task. The groups also had similar incidence of speech illusion, or 'auditory hallucination', meaning that this task did not seem to be well-suited to identifying differences between dependent drug-users and the recreational drug-using control group in hallucination-proneness.

Therefore, this task may not be suitable for use in identifying differences in this factor in drug-using groups in future studies.

In contrast, the Ambiguity task showed differences between the groups on three outcome variables. This task shows real potential in being able to identify subtle individual differences between the groups. After some basic modifications in delivering instructions, as seeking to understand sense of agency in both help-seeking clinical groups of individuals, and also in drug-using groups.

Research Design

As this research was conducted as part of a joint project with two other researchers investigating other tasks and constructs, there was limited time to carry out a semi-structured interview, meaning that questionnaires were employed instead. The questionnaires provided some insight into subjective phenomena experienced across the groups, and were quick to administer which was useful under the time constraints. However, as the two tasks used in this study were quite new, it could be argued that the subjective information gathered in a semi-structured interview such as the SPI-A or the CAARMS, may provide some deeper insight into the mental processes underlying the response to the tasks.

In this research we asked some very basic questions about how difficult and how well participants felt that they had done, and also asked very brief questions about what they believed the tasks were measuring. These responses did not elucidate any differences in group which may account for the difference in performance on the task. In a future study, collecting detailed accounts of subjective experiences relating to sense of agency in a semi-structured interview may provide a better understanding of differences in performance on the Ambiguity task.

Summary

This study has provided further evidence that questionnaire measures of depression, schizotypy and positive and negative symptoms related to early psychosis are higher in chronic users of ketamine and cannabis, suggesting that these groups of individuals are a useful population for research into prodromal psychosis. The Ambiguity task also appears to have useful properties in terms of sensitivity to group differences in sense of agency. It may also help to explore the psychological mechanisms underlying a transition from subtle misattributions into delusion formation and hallucination-proneness.

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Appendix 1

Details of joint thesis

The thesis was completed as part of a joint project to investigate psychotic-like symptomatology and cognitive functioning in chronic users of cannabis and ketamine.

Two separate theses were completed as a result of the project. They were entitled:

1) Psychotic-like symptomatology and reward responsivity in chronic ketamine and cannabis users

(Alyssa Joye, Trainee Clinical Psychologist, UCL)

2) Ultra high risk for psychosis? Chronic ketamine and cannabis users' performance in tasks of attribution assignment and hallucination-proneness

(Lisa Harvey, Trainee Clinical Psychologist, UCL)

Both trainees collaborated on the study design and shared participants and data collection.

An outline of each trainee's contribution to the project is as follows:

1) Lisa Harvey: Compiled the testing protocol, including obtaining self-report measures, in collaboration with Lisa Harvey. Piloted initial testing protocol with Lisa and supervisor Val Curran. Placed advertisements for participants on classified websites and screened potential cannabis and control participants. Collected data as outlined in methodology (including two additional computer-based tasks relevant to Lisa Harvey's study – 'Ambiguity of Attribution' and 'White Noise' tasks) from 22 participants (3 controls, 11 cannabis users, and 8 ketamine users), and performed own data analyses with support from Clinical Psychopharmacology Unit colleagues. Data for 22 participants

tested by Lisa Harvey and 16 participants tested by Will Lawn (UCL PhD candidate) was used in analyses.

2) Lisa Harvey: Collaborated on designing testing protocol alongside Alyssa Joye. Piloted testing protocol with Alyssa and supervisor Val Curran. Contacted and screened potential ketamine participants. Collected data as outlined in her methodology for 22 participants (6 controls, 6 cannabis users, and 10 ketamine users). Performed own data analyses on participants she tested in addition to 22 Alyssa Joye tested and 16 Will Lawn tested.

Appendix 2

On completion of the research you must submit a brief report (a maximum of two sides of A4) of your findings/concluding comments to the Committee, which includes in particular issues relating to the ethical implications of the research.
With best wishes for your research.

Yours sincerely

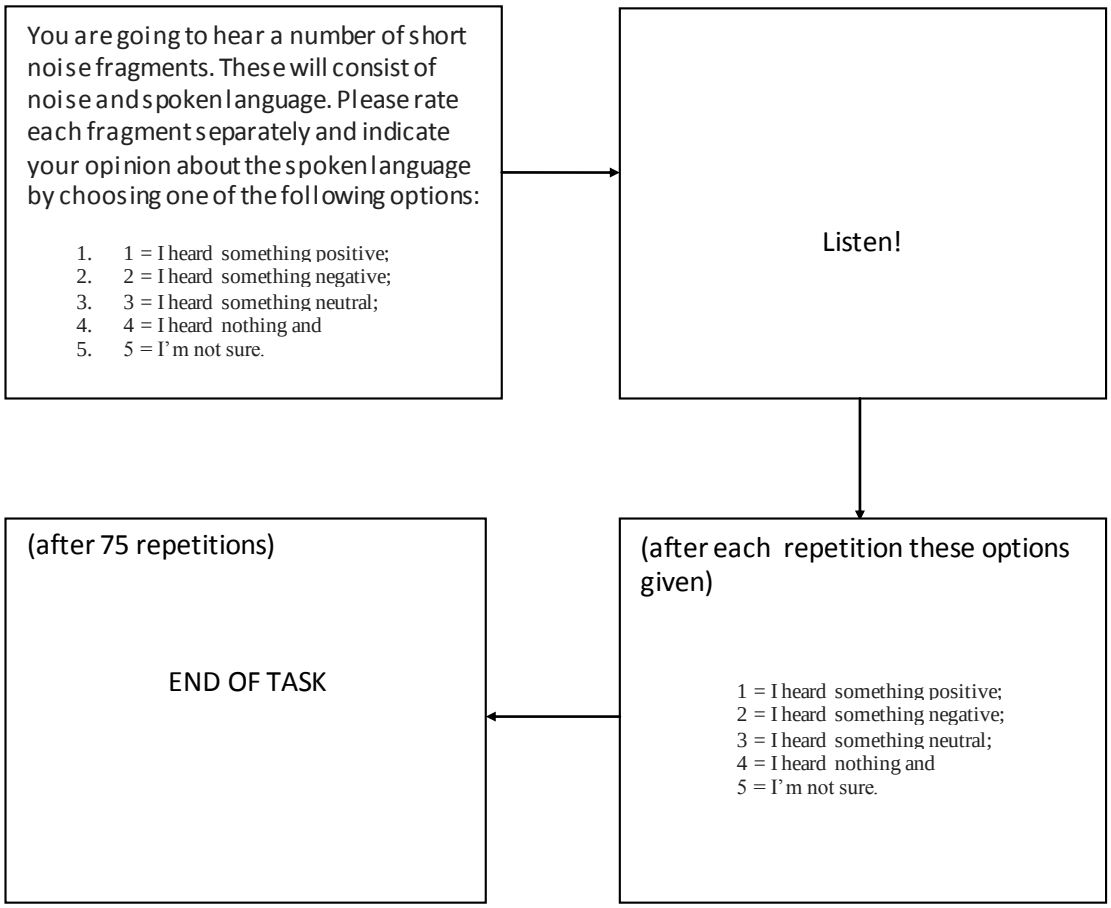
Professor John Foreman
Chair of the UCL Research Ethics Committee

Cc:
Lisa Harvey & Alyssa Joye, Applicants
Professor Peter Fonagy, Head of Department

UCL Research Ethics Committee, c/o The Graduate School, North Cloisters, Wilkins Building
University College London Gower Street London WC1E 6BT
Tel: +44 (0)20 7679 7844 Fax: +44 (0)20 7679 7043
ethics@ucl.ac.uk
www.ucl.ac.uk/gradschool

Appendix 3

Screens presented in White Noise Task


You are going to hear a number of short noise fragments. These will consist of noise and spoken language. Please rate each fragment separately and indicate your opinion about the spoken language by choosing one of the following options:
1. 1 = I heard something positive;
2. 2 = I heard something negative;
3. 3 = I heard something neutral;
4. 4 = I heard nothing and
5. 5 = I'm not sure.
Listen!
(after each repetition these options given)
1 = I heard something positive;
2 = I heard something negative;
3 = I heard something neutral;
4 = I heard nothing and
5 = I'm not sure.
(after 75 repetitions)
END OF TASK

Appendix 4

Ambiguity of Attribution Task – further information

Glossary for AAT

Taptone synchrony

In each of the conditions (1 -10), there is a precise record and calculation of what happens when the participant carries out the taps – this is called taptone synchrony. The precise recording in each repetition of the task is used to measure the attribution rating against for that particular repetition. For example, there are five repetitions in 'condition 1', but the taptone synchrony of each of these numbers will be slightly different. This means that the independent variable in this task is not strictly speaking categorical, but varying numbers (five in each) placed at ten intervals along a continuum.

Generation of Taptone synchrony

The taptone synchrony was manipulated in the following way: a random number between 0 and 90 was generated on every tap; each condition was associated with a threshold above which tones generated by self would be heard and below which tones generated by other would instead be heard.

Mutual Information

The mutual information variable was calculated by binning the exact data from each participants' taptone synchrony (objective measure) in a grid against the attribution rating (subjective measure). 2) Mutual Information was computed using the following formula : (calculated as entropy of variable 1 plus entropy of variable 2 minus the combined entropy variable 1 and 2: entropy(V1) + entropy(V2) - entropy(V1V2) = mutual information between V1 and V2.

Fuzzy Logic

Fuzzy logic is a form of many-valued logic that deals with approximate, rather than fixed and exact reasoning. Compared to traditional binary logic (where variables may take on true or false

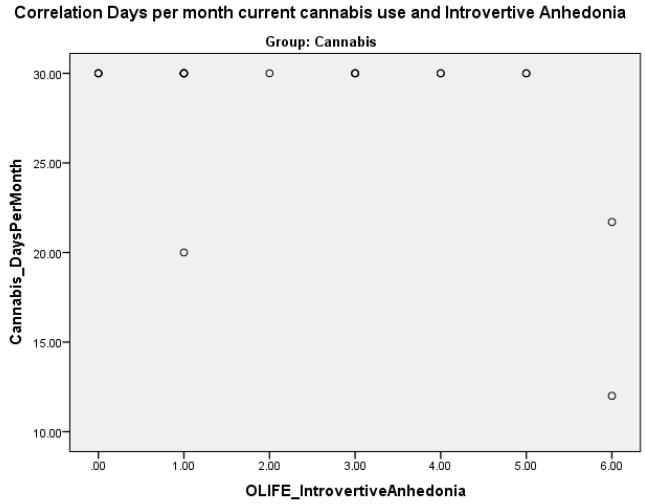
values), fuzzy logic variables may have a truth value that ranges in degree between 0 and 1. Fuzzy logic has been extended to handle the concept of partial truth, where the truth value may range between completely true and completely false. In this task fuzzy logic was used to calculate hit rates and false alarm rates along the continuum.

Appendix 5

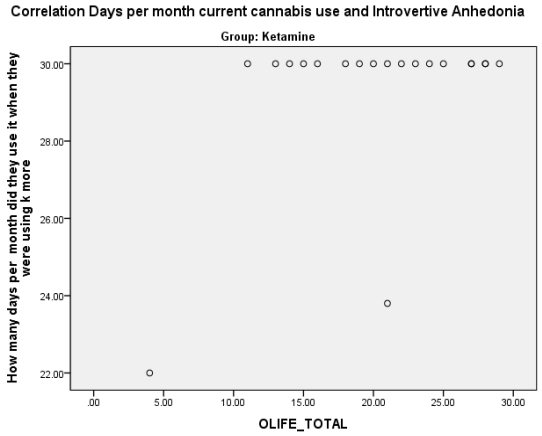
Scatter Plots for correlations

Appendix 3 Scatter plots

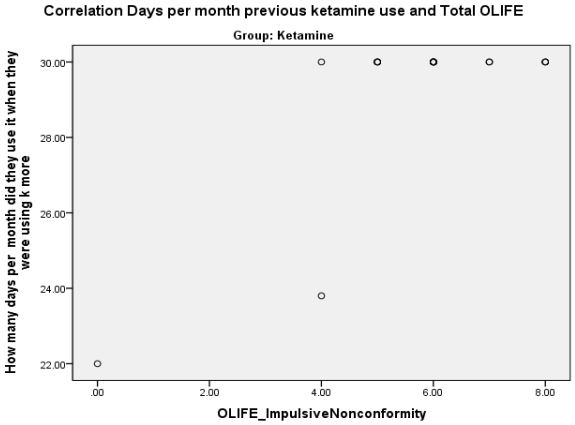
Figure 3c



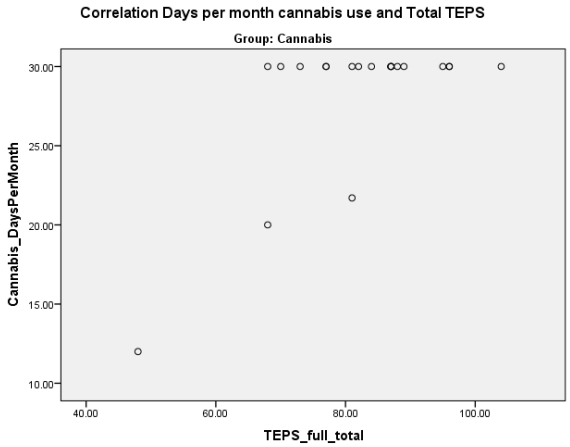
3d



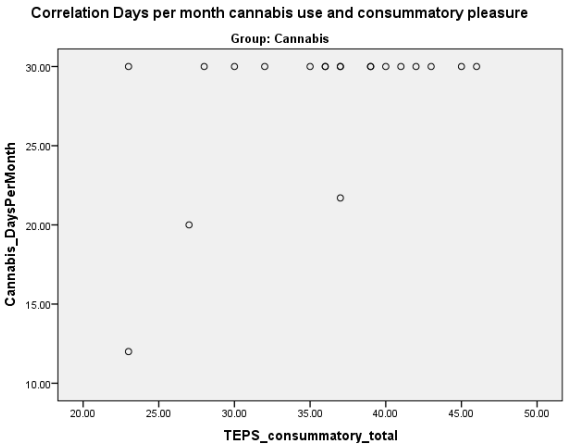
3e



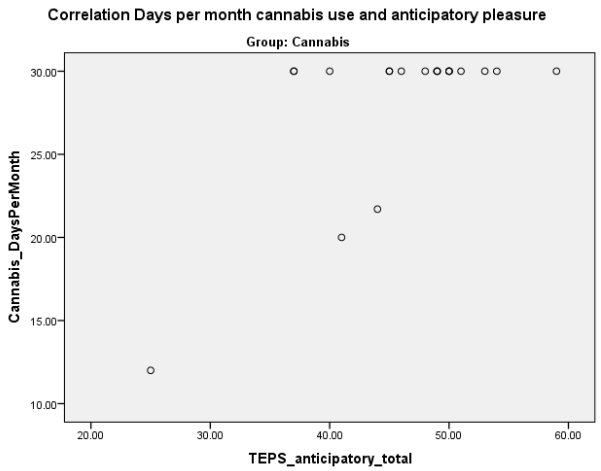
3f



3g



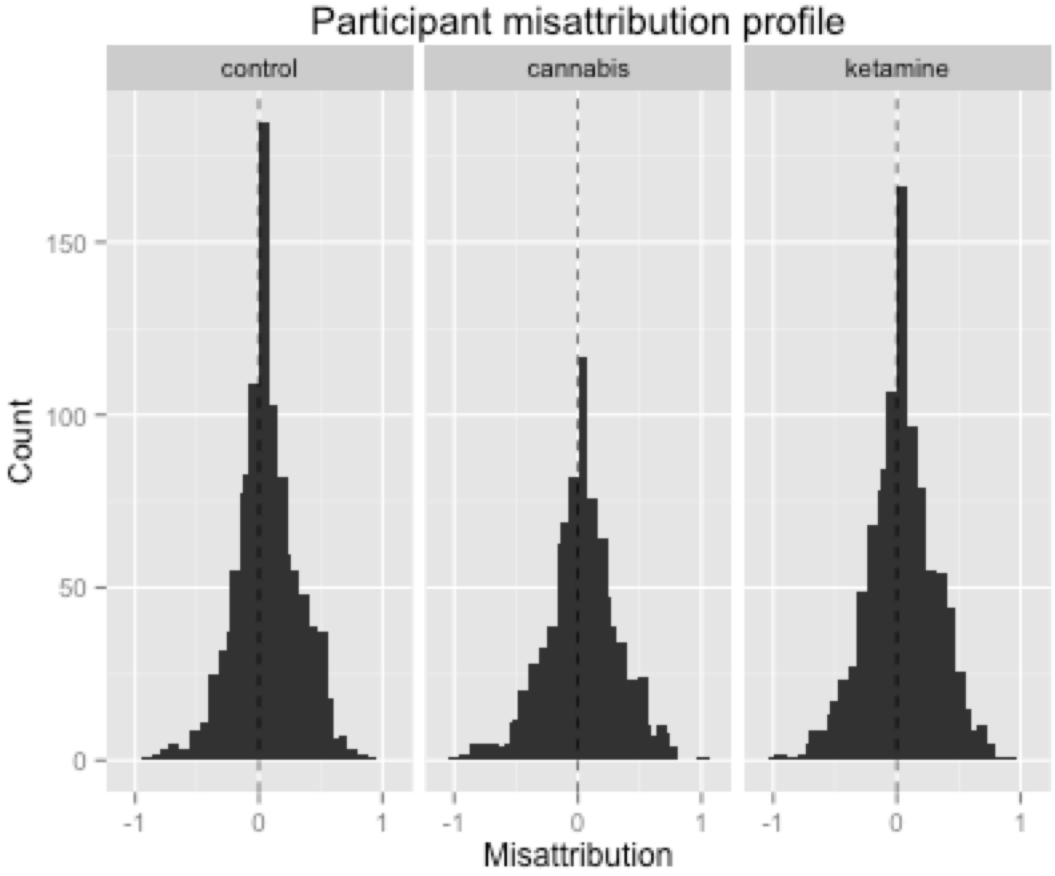
3h



In the ketamine group there was a significant correlation between current days of use and MI scores r = -0.512, p = 0.025. There were also significant correlations between previous number of days using ketamine regularly and i) Total O-LIFE scores r=0.453, p=0.045 and ii) 'Impulsive Non-Conformity' scores r =0.753, p<0.001. In the cannabis group, there was a significant negative correlation between days of use and O-LIFE 'Introvertive Anhedonia' scores r = -0.446, p=0.49. There were also significant correlations between number of days use and i) TEPS Total r =0.665, p<0.001; Figure 3f, ii) 'Consummatory' r = 0.508, p=0.022, and iii) 'Anticipatory' r = 0.668, p=0.001. Scatter plots showing that these correlations were driven by outliers are given in Appendix X.

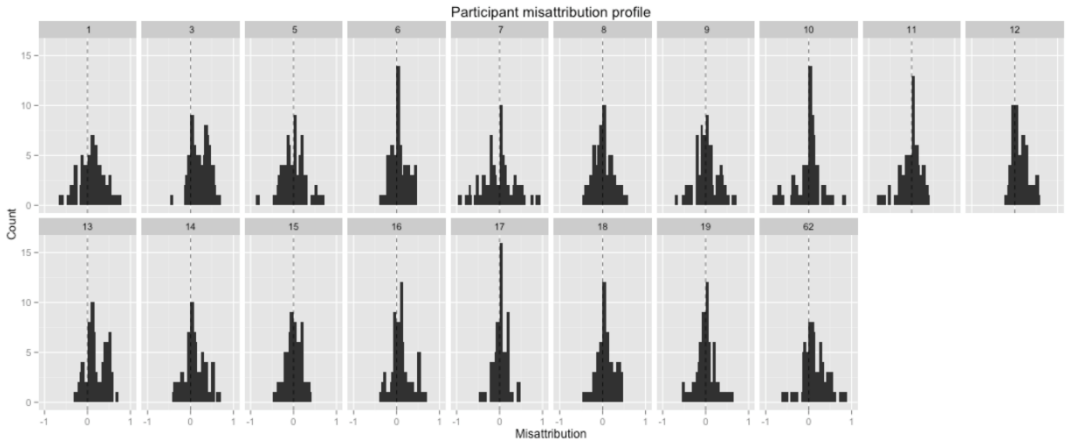
Appendix 6

Misattribution bar charts by group

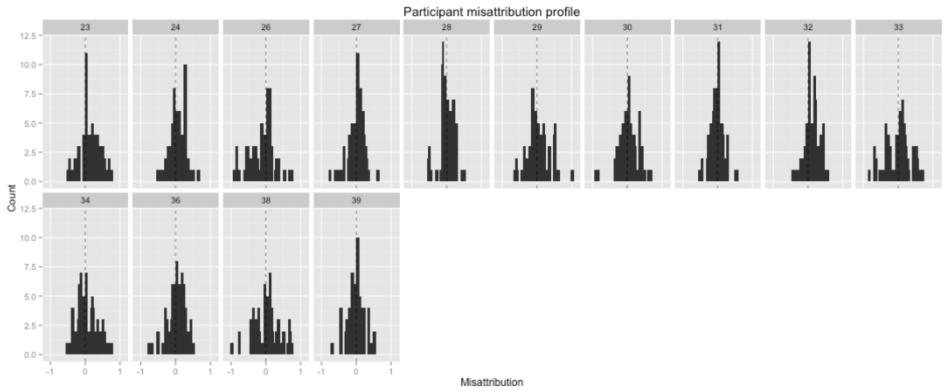


Misattribution by group.

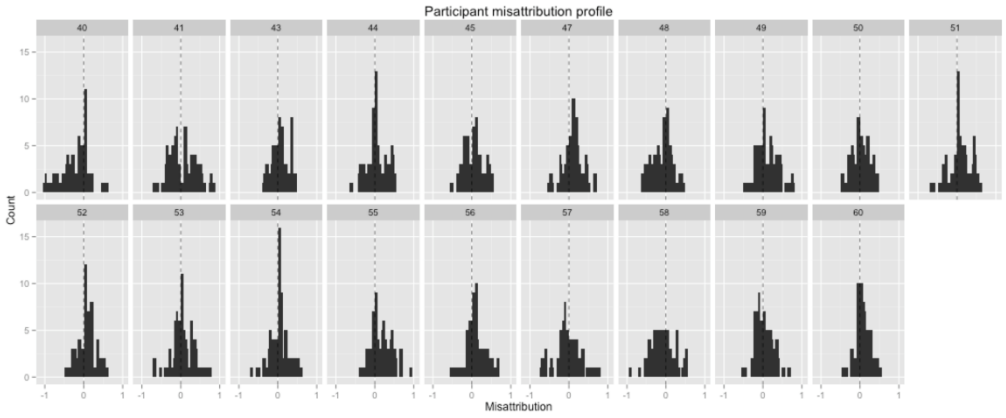
Control



Cannabis



Ketamine



Part 3

Critical appraisal

Reflecting on the Research Process

Making use of the data from Ketamine users

During the initial stages of the research progression, Alyssa, Val and I had several discussions about how to best capture the data in a study recruiting chronic ketamine-users. This was partly related to needing to think about the length of tasks and concentration required to carry out hours of testing and questionnaire filling. However, much of the consideration also related to the idea that sometimes the self-report questionnaires, or quantitative data collected from tasks did not adequately convey subjective experience of certain symptoms or phenomenology associated with experiences connected with ketamine use. I had initially been keen to include a qualitative aspect to the research, in keeping with the previous study carried out in the Pharmacology department into subjective experiences of ketamine users (Muetzfeldt et al, 2008). Unfortunately, due to the nature of combining three studies into one data capturing event, there was not time to carry out in depth interviews with participants.

Reflecting on this during and after the data collection, Alyssa and I felt that there was a missed opportunity. We had been granted access to a niche sub-group of chronic drug-users, all of whom appeared to be very keen to share their experiences with the three researchers involved (Myself, Alyssa and Will). This appeared to be partly motivated by the idea that their stories and experiences could be used for the benefit of other people. Several of the participants in the ketamine group shared extremely distressing and challenging information about the pain and health problems they had experienced as a consequence of having used sometimes up to 14 grams of ketamine a day. They also reported voluntarily on the effect that their drug use had had on their parents, families and close non-drug using friends. Several participants in this group mentioned losing loved ones to drug-related deaths. Whilst the ketamine participants were cooperative and willing to go along with the line of questioning

involved in the interviews about drug use and associated experiences, they were more likely than controls or cannabis users to elaborate on their experiences by providing information in anecdotal stories or examples of specific experiences which had either been distressing or unusual.

Unfortunately, these stories, anecdotes and explanations of the difficulties encountered in having to give up a drug involuntarily due to the ketamine drought, were not recorded. The use of computer tasks, and the short questionnaires we employed in the study, in no way captured the full essence of these participants. There was a sense of these individuals 'needing' to share their experience. Several participants commented on the fact that this research 'may help other people,' which is why they had agreed to take part. Whilst the Ambiguity of Attribution task did identify a subtle distinction in ketamine users in the responding style to the task, and inferences can be drawn from this, the scope of this finding felt minimal in comparison to the wealth of experience and information ketamine users wanted to share with us as researchers.

This imbalance is something that needs to be given consideration in the future. Whilst we received ethical approval prior to the study, and all participants had a chance to ask questions before taking part or giving their consent, there was still a sense that those who chose to be involved in the study did so out of both a personal need to share their own experience of ketamine dependency (as a therapeutic outlet) but also to cascade information about the possible dangers of chronic ketamine use to a wider audience, in order to prevent future distress for other individuals. This study did not focus directly on the daily experiences of ketamine use; rather it utilised ketamine-users dependency as a model for development of psychosis. Whilst it could be argued that ethically, the research was attempting to understand and prevent the onset of another type of chronic illness, Psychosis, or Schizophrenia, more focus could have been put into the reported experience of dependency on ketamine, and how

this led to depression, serious physical illness, and sometimes under extreme conditions death.

From another perspective, ethically it felt as if we were positioned as experts in the field of research into ketamine, and therefore there was a duty to listen to and respond with information about ketamine users' personal experiences, either with some kind of reassurance, or with information about what they could expect in the future in terms of their mental capacity and psychological wellbeing. This was definitely challenging at times, as it required a stepping out of the researcher role, to respond in a compassionate manner to individuals' concerns about their physical or mental health, as a result of their drug use. Several participants asked us if they would be able to access the results of the research. They also wanted to know if they would have personal feedback about their own performance, and if we would be able to assess whether or not there had been long term impact on their cognitive processing faculties or their mental health. At the time, we suggested that there may be opportunity for a feedback session on the research, maybe carried out in conjunction with a contact we made from Bristol Drugs Project. As yet, this has not been arranged, but is something that may be well received, based on the eagerness of ketamine participants to understand more about changes in functioning due to their ketamine use.

The Ketamine Drought – Limitation or Strength

Our initial recruitment drive led us to encounter stories of the 'ketamine drought' where even careered ketamine users in this niche sub-group in Bristol reported having had to substantially reduce their use of the drug non-voluntarily. They described how what was available to buy as 'k' was actually Creatine – a body-building powder – cut with amphetamine, or other unknown substances. As a result of the drought, several 'k-users' had

substantially increased their intake of other substances, most often hash, valium, cocaine or speed. Several ketamine users also described how they had increased their alcohol consumption also, as they missed the sedative effects of ketamine.

The ketamine drought initially held up the recruitment process, as several potential participants for this group had to be excluded at screening on the basis of their use of other drugs used as replacements ('dependence' according to SDS criteria on cocaine, crack, valium, speed, mephedrone) were all mentioned by potential participants. This was rather frustrating at times, as it meant that individuals, who under different circumstances would have been ideal for the study, were no longer able to be included. Whilst it was important to recruit participants who were not dependent on drugs other than ketamine, we did have to exercise flexibility with these criteria, so that dependence on alcohol, tobacco and cannabis were not exclusion criteria for the study, as long as ketamine dependence was rated as the most severe.

Although most ketamine users described still feeling 'dependent' on the drug, admitting that they would still be regularly using it if it was readily available, they also acknowledged that the ketamine drought had been an unplanned intervention in the course of their drug use. A few people described it as possibly having 'saved their life.' In a recent report by the BBC (Hatton, 2015) into the long term harms of ketamine use, Jim Bartlett from Bristol Drugs Project reflected on the ketamine drought, and how it had inadvertently created space for long-term chronic users to reduce their use, and address these harms once detoxed from the drug. It is unlikely that participants in this research would have shown the same enthusiasm as they did for the project, had they still been heavily using. In this sense, perhaps having had a positive experience of taking part in research may influence participants to contribute their experiences to research again in the future.

Interpretations – Are drug models sound, and/or useful to the evidence-base?

This study was by nature complex in design, due to the theoretical positioning of chronic ketamine and cannabis users as a model for individuals who may be experiencing early psychosis. Whilst this theoretical model has been explored previously, the use of novel tasks, and a combination of different measures meant that this was a unique research project. There were challenges in carrying out research with a drug model at its core. Firstly, the ethical implications of recruiting chronic drug-users, and the associated levels of distress described to us were not given full attention due to the nature of the study. Secondly, any significant results, where cannabis or ketamine groups performed differently in tasks, or scored more highly in measures, by nature of the model had implications for both dependency and early psychosis constructs. This was at times difficult to navigate, especially when making interpretations of the results. Fortunately, working with Alyssa, and colleagues from the Clinical Psychopharmacology Unit helped to clarify the possible implications and meanings of results. As everyone involved in jointly analysing the data had a wealth of experience investigating both drug use, and psychosis constructs, this process was enriching in terms of broadening my understanding about how these constructs may be interrelated.

Initially, we had hoped to recruit ketamine users who were still using daily, as previous studies had suggested that the chronic ketamine use model of psychosis was more likely to provide a representative model of the subtleties of the onset of psychosis (Freeman et al, 2012). Conversely, the more obvious effects observed in studies where drug-induced psychosis states are brought on by acute administration of ketamine in laboratory settings have limited validity in terms of understanding inherent psychological profiles of individuals at risk for developing psychosis (Morgan, et al. 2006) They point more to a neurobiological marker for the onset of psychosis.

Future Studies

We initially set out to in some way replicate findings from the the Morgan et al study (2012). However, they compared data from non drug-using and recreational drug-using controls, chronic daily users of cannabis and ketamine with data from the SPI-A for a prodromal group of individuals (Schultze-Lutter et al, 2008). In future studies, it may be interesting to compare a clinical group of help-seeking individuals who meet criteria for UHR for psychosis, but who are not meet substance dependency criteria, with both *current* chronic users of ketamine and cannabis, and *previous* users of both drugs, to further clarify which drug-using groups are most similar to this prodromal group.

It may also be interesting to further investigate whether acute drug models of psychosis relate more closely to florid or first episode psychosis, rather than the more subtle presentations in the Ultra High Risk individuals. Again, this might be helpful in mapping the trajectory of development from low-level symptoms such as moderate clinical depression or anhedonia, into the more disturbing and pronounced symptoms such as delusions and severe paranoia which manifest later in First Episode Psychosis.

Joint Working

Working jointly on the thesis with Alyssa was a very positive experience. I felt extremely lucky to be working alongside someone who shared not only an interest in the area, but also shared values about how best to approach the work, and what considerations needed to be made in order to work effectively to produce a meaningful research project. This was also complemented by the ongoing input from members of the Psychopharmacology Unit, with regular meetings throughout the research process. Working in collaboration with others requires organisation and commitment from all involved, but I feel it really enriched the research process. From the initial conceptualising of the research study, through to the writing up process, having colleagues to consult and brainstorm with definitely made the process more enjoyable and I believe was a huge benefit to the resulting work. For example, I was able to recruit participants for the drug-using populations through associates from my

previous job as a drugs worker, Alyssa had previous experience with working as a researcher and had good advice on specific practicalities, and Will was incredibly organised with collating data quickly into spreadsheets to organise our thinking. This teamwork made the whole research process much more efficient and proactive than it may have been otherwise, and I was grateful to work with dedicated partners on the research.

Objective and Subjective data – The end of task interview

As a researcher, I am interested in how individuals respond to the process of taking part in research, and the level of insight or self-awareness of different individuals. Unfortunately, we were unable to formally make use of the qualitative data captured in the interviews about the testing process. Many participants had limited responses to these questions, and after over two hours of completing questionnaires and computer tasks, they were keen to finish up. However, sound bytes from each of the participants gave some indication of how they may have approached the tasks. I have included some examples below to finish off the thesis. I would encourage researchers who are interested in using computer based tasks to make use of some sort of interview alongside them in their research, as I believe it provides a window into the subjective experience participants endure, which may offer a different perspective on their 'performance' in tasks when analysing the data.

- *In response to the question – How did they the Ambiguity of Attribution Task make them feel?*

a) *Control Group: "frustrated", "just bored", "annoyed", "disorientated – I found it stupid."*
b) *Cannabis Group: "Comfortable, but got annoying." "Tedious,""I was just keeping the rhythm, it was my technique."*
c) *Ketamine Group: "Frustrated and confused", "It all went a bit blurred for me…", "Found it quite easy, I had a tactic, it was like when I play the drums." "Interested…It held my attention and was challenging."*

References

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Morgan, C. J., Muetzelfeldt, L., & Curran, H. V. (2009). Ketamine use, cognition and psychological wellbeing: a comparison of frequent, infrequent and ex-users with polydrug and non-using controls. *Addiction*, *104*(1), 77-87.

Freeman, D., Startup, H., Dunn, G., Černis, E., Wingham, G., Pugh, K., ... & Kingdon, D. (2014). Understanding jumping to conclusions in patients with persecutory delusions: working memory and intolerance of uncertainty.*Psychological medicine*, *44*(14), 3017-3024.

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