Chronic ketamine use and psychotic symptomatology.

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Overview

This thesis examines the effects of chronic use of ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, on subjective experience and cognition. It is important to explore the chronic effects of ketamine as the number of individuals using the drug recreationally is increasing both in the UK and worldwide. There is a paucity of research exploring the *chronic* effects of ketamine. Many studies have shown that acutely ketamine induces psychotic-like symptomatology and specific cognitive dysfunction in healthy, drug-naïve volunteers. For this reason, a ketamine model of the psychoses has been proposed. However the few studies of the effects of chronic ketamine have provided mixed findings.

Part 1 of the thesis comprises a literature review, which investigates the psychotomimetic effects of ketamine, through the synthesis of current research findings, to determine whether ketamine is a useful model of the symptomatology characteristic of the psychoses. It presents an overview of ketamine and its association with the psychoses, before providing a detailed account of the functional psychoses and drug models of the psychoses (namely the dopamine hypothesis, the serotonin hypothesis and the glutamate hypothesis). The review then synthesises the acute and chronic ketamine studies to date, highlighting which states appear to be best modelled (i.e. the pre-psychotic, acute or chronic state experienced by individuals with idiopathic psychoses). Finally, the review briefly considers the treatment implications of the ketamine model of psychoses, and the risk chronic ketamine use poses to users in terms of developing fully-manifest psychotic symptomatology.

In Part 2, an investigation of the chronic effects of ketamine on subjective experiences and cognitive functioning is reported, in order to determine whether chronic ketamine models symptomatology associated with the pre-psychotic state of idiopathic psychoses (where the term idiopathic refers to psychotic symptomatology of unknown aetiology, i.e. that which occurs in the majority of the general population and is not drug-induced). This investigation was part of a joint project conducted with 2 other trainees to investigate the chronic effects of ketamine, cannabis and cocaine on subjective experiences and cognitive functioning (See Appendix 1 for details of the contribution made by each trainee).

The empirical paper reports a between subjects study which compared 21 frequent ketamine users (who used ketamine daily), 20 infrequent ketamine users (who used ketamine a maximum of once or twice a week) and 20 controls (who reported no illicit drug use). On a clinical index of symptomatology (SPI-A), a 'frequency' effect was observed: frequent ketamine users were found to be higher in psychotic-like symptomatology (i.e. basic symptoms) than infrequent users, who in turn were found to be higher in symptomatology than controls. Both groups of ketamine users were also found to be higher in psychosis proneness on a general population index of psychotic-like markers (OLIFE) compared with controls. Furthermore, both groups of ketamine users demonstrated impaired episodic memory and working memory compared to controls. Group differences were found in executive functioning.

Part 3 comprises a critical appraisal of the research. It includes reflections on my experience of the research process and conducting research with the ketamine using population, as well as reflections on clinically relevant observations.

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Part 1: Literature Review

How useful is ketamine as a model of the psychotic and cognitive symptomatology characteristic of idiopathic psychoses?

Abstract

Rationale: A review of the psychotomimetic effects of ketamine was needed because of (i) the increasing population of recreational ketamine users in the UK and abroad, and (ii) ketamine's application to the N-methyl-D-aspartate (NMDA) receptor hypofunction model of the psychoses. To the best of our knowledge, no such review of the literature had previously been conducted.

Method: The PsychInfo database was searched using the following keywords: psychosis, acute, chronic, positive symptoms, negative symptoms, prodrome, early symptoms, basic symptoms, ultra-high risk, mania, bipolar, schizoaffective, ketamine, glutamate, review, and the following authors: Fletcher, Honey, and Kapur. Studies were selected from those published between 1994 and November 2007, and the main exclusion criterion was non-human studies. Additional studies were also identified through those initially reviewed.

Findings: Acute ketamine challenge studies with healthy participants, participants with idiopathic psychoses and acute-on-chronic studies with self-administering ketamine users have found ketamine induces a dose-dependant 'clinical syndrome', characterised by (i) subtle, attenuated positive and negative psychotic-like symptomatology, and (ii) cognitive impairments. Thus, *acute* ketamine appears to be a valid and reliable model of the symptomatology reliably observed in within the pre-psychotic state.

Furthermore, the few studies which have investigated the effects of *chronic* ketamine indicate that it may better represent the chronic state experienced by

individuals with psychoses, where negative symptomatology and specific cognitive symptomatology predominate. However this finding is very tentative due to the paucity of research into the effects of chronic ketamine use.

Conclusions: Currently, it is unclear which state experienced by individuals with psychoses the *chronic* ketamine profile best models. This author suggests that chronic ketamine users may present with subtle psychotic-like symptomatology, which has not been detected by the behavioural measures utilised in previous studies. Directions for further research and treatment implications of the ketamine model of the psychoses for individuals with idiopathic psychoses are discussed. In addition, it is important to communicate the effects of both *acute* and *chronic* ketamine use to recreational users. Ketamine's status as a risk factor for psychotic symptomatology is also discussed.

1. Introduction

1.1 Overview

This review endeavours to investigate the psychotomimetic effects of ketamine, through the synthesis of current research findings. To determine whether ketamine is a useful model of the symptomatology characteristic of the psychoses, the review firstly considers the factors deemed necessary and sufficient for a useful drug model of the psychoses. An introduction to the psychoactive drug, ketamine, is then provided, along with an overview of the functional psychoses and their associated symptomatology. Historical drug models are then briefly explored, and compared with the glutamate hypothesis of the psychoses, which arises in part from the ketamine model. The main body of the review then focuses on evaluating the validity, reliability and specificity of the ketamine model of the psychoses, in order to gain a better understanding of the type of psychotic symptomatology the ketamine profile may best represent. It is suggested that a useful drug model of the psychoses should inform the development of novel interventions for idiopathic psychoses, and indicate higher risk for the precipitation of idiopathic psychoses following repeated use of the drug in question (where the term idiopathic refers to psychotic symptomatology of unknown aetiology, i.e. that which occurs in the majority of the general population and is not drug-induced). The conclusions drawn include a consideration of implications for future research.

1.2 Rationale for the current literature review

The past 15-20 years has seen an explosion of interest regarding the effects of ketamine. This literature mainly focuses on *acute* ketamine-induced effects in healthy, drug-naïve individuals, with some interest in the effects of *acute* dosage with individuals with idiopathic psychoses. However there is a paucity of studies

concerned with *chronic* effects of ketamine, experienced as the result of long-term recreational use. Researchers are becoming increasingly interested in the similarities and differences between ketamine-induced symptomatology, and symptomatology characteristic of idiopathic psychoses.

Just as, for example, the study of amphetamine-induced effects led to the dopamine (DA) hypothesis of psychoses, which proved invaluable for developing our understanding of the neurobiological basis and phenomenology of the psychoses, the study of ketamine-induced effects has contributed to the glutamate hypothesis of psychoses. Novel approaches to the treatment and prevention of drug-induced and idiopathic psychoses, based on the glutamate hypothesis are currently being explored (Anand et al., 2000; Goff et al., 1999; Heresco-Levy et al., 1999; Newcomer et al., 1998, all cited in Newcomer & Krystal, 2001). Indeed, Patil et al. (2007) recently demonstrated that a new, glutamate-acting drug (LY210023), was as effective as olanzapine in attenuating psychotic symptomatology.

If ketamine consistently induces symptomatology similar to that observed in the psychoses, evidence to support the glutamate hypothesis of psychoses would be generated. Therefore, a review of the literature regarding the overlap between ketamine-induced symptomatology and symptomatology characteristic of idiopathic psychoses is crucial. To the best of the author's knowledge, a previous review of this nature is not in existence. Hence, this review is a novel endeavor. In addition, with the growing number of recreational ketamine users both in the UK and abroad (Copeland & Dillon, 2005; McCambridge, Winstock & Mitcheson, 2007; Murphy & Roe, 2007), a review of the psychological and cognitive impact of both acute and chronic ketamine use is overdue.

2. Review Methodology

A search of the relevant literature was conducted using the following keywords: psychosis, acute, chronic, positive symptoms, negative symptoms, prodrome, early symptoms, basic symptoms, ultra-high risk, mania, bipolar, schizoaffective, ketamine, glutamate, review, and the following authors: Fletcher, Honey, and Kapur. The following keywords were entered into the thesaurus application in PsycInfo to ensure all similar relevant terms were searched: psychosis, positive symptoms, negative symptoms, prodrome, mania, bipolar, and schizoaffective. Search terms were combined using the AND/OR applications.

The search was initially conducted using PsycInfo because it's aim was to gather all studies which had investigated ketamine-induced experiences and cognitive dysfunction, rather than studies which primarily focused upon exploring the biological underpinnings of ketamine-induced effects and NMDA antagonism. Studies were selected from those published between 1994 and November 2007. Exclusion criteria were: non-human studies, studies that investigated ketamine for a purpose other than to model psychotic symptomatology, e.g. anaesthetic studies and studies looking at the anti-depressant effects of acute ketamine. The main inclusion criterion was: studies that investigate the link between ketamine and symptomatology characteristic of the psychoses. I grouped the studies into those primarily focusing on glutamatergic pathways, acute ketamine challenge studies, and chronic ketamine studies. Additional studies were also identified through those initially reviewed. PubMed was then also searched using the same criteria to ensure no studies had been missed. No further relevant papers were found.

3. Evaluating drug models of psychoses

3.1 What makes a useful drug model of the psychoses?

Despite the philosophy of science literature containing copious discussion regarding the criteria for a good scientific theory, the question of what makes a useful model remains largely unanswered. In addition, a literature search (criteria: (drug) model / psychosis / schizophrenia) revealed no direct guidance on this matter. Nevertheless, Fletcher and Honey (2006) note several factors on which they evaluated the ketamine and cannabis models of the psychoses, which have provided guidance for this review. In addition, Honey et al. (2005) note that a useful drug model will develop the predictive and explanatory power of theories of the psychoses.

Fletcher and Honey (2006) note that a useful drug model of the psychoses should have clinical and contextual validity. The former refers to the extent to which symptomatology induced by a drug overlaps with psychotic symptomatology. The authors note that no drug model is complete in this respect. The latter refers to the duration and awareness of drug-induced symptomatology in comparison to psychotic symptomatology observed in psychoses. They also note that a useful drug model should be reliable, in that it can repeatedly replicate the syndrome it is attempting to model. Finally, the authors propose a useful drug model should have some degree of clinical, cognitive, transmitter and experimental specificity. Clinical and cognitive specificity refer to the drug's ability to mimic only psychoses-related clinical or cognitive symptomatology. Transmitter specificity relates to the extent to which the drug in question acts upon the specific neurotransmitter system it is claiming to investigate, and thus implicate in psychoses. Experimental specificity refers to the experimental designs utilised when

investigating a drug model of psychoses, which could underlie the differences in results demonstrated in the literature reviewed below. These criteria for a useful drug model of the psychoses will be referred to throughout this review, where relevant.

3.2 Limitations of drug models of the psychoses

The drug models of psychoses have several central limitations. Firstly, drug models adhere to the medical model, which proposes that diagnosable mental health disorders are illnesses, which have biological antecedents, the exact nature of which are awaiting discovery. It has been proposed that the medical model has de-emphasised and obscured the potential role of social and interpersonal factors (e.g. social and educational disadvantage, child abuse and neglect) in the development and maintenance of psychoses, through its dominance in the psychoses research literature (Boyle, 2004). Indeed, thus far drug models have been unable to mimic the full range of symptomatology observed in the psychoses (see section 6 for review), thus indicating that neurotransmitter dysfunction may well not be the whole picture. Furthermore, up to 75% of individuals with psychotic symptomatology still experience significant active psychotic and cognitive symptomatology whilst undergoing atypical antipsychotic therapy (Tamminga, 1998), which have been developed primarily as a consequence of drug model research. Clearly evidence thus far suggests that neurotransmitter dysfunction is certainly not the only explanation for psychotic symptomatology, and may indeed not be the primary explanation. It may be that the dominance of the drug model literature within psychoses research, and the certain nature of the language used in this literature has perpetuated the belief that neurotransmitter dysfunction is key to psychotic symptomatology.

Secondly, as drug models have been developed within the medical model the literature around them automatically takes the position that psychotic symptomatology can be categorised into diagnosable disorders or illnesses, which have biological antecedents, the exact nature of which are awaiting discovery. However as Mary Boyle's (2002; 2004) work suggests, psychoses such as schizophrenia and bipolar disorder are constructs, which encompass organised sets of beliefs that have been propagated by the dominant systems in society, namely medicine and science. This position acknowledges there may be some genetic / biological involvement in psychotic symptomatology (the extent of which is unknown contrary to the belief propagated by medicine and science), but calls into question the appropriateness of categorising individuals with psychotic symptomatology into medically constructed categories (i.e. DSM and ICD diagnoses, such as schizophrenia and bipolar disorder) for which there is no *clear* evidence to confirm a specific brain disease or illness (see Boyle, 2002 for overview). Drug models are therefore limited as they attempt to model specific categorical diagnoses, rather than dimensional symptomatology. A minority of the drug model literature recognises this. For example, Abi-Saab, D'Souza, Moghaddam and Krystal (1998) suggest drug models may prove better at offering insight into psychotic symptomatology in general, rather than specific DSM or ICD diagnoses. Hence, this review has taken the approach of investigating how well the ketamine model models specific psychotic symptomatology associated with different states of the psychoses.

Thirdly, drug models of psychoses are limited because they study the psychotomimetic effects of one recreational drug at a time, which is proposed to predominately act upon one neurotransmitter system. If it is the case that

neurotransmitter dysfunction plays an as yet unclear role in psychotic symptomatology, then this may be an artificial way of modeling such a process. Indeed, it has been proposed that a future model of the psychoses might comprise groups of overlapping genes which correspond to the disruption of *various* neurotransmitter systems, which pose as risk factors for a spectrum of clinical phenotypes, whose expression would be mediated by environmental factors (Craddock & Owen, 2005). For example, a risk factor for the development of positive psychotic symptomatology might be genetic abnormalities in DA and glutamate neurotransmission.

Finally, drug models of psychoses have been developed through both studying drug-induced effects of acute doses and chronic use. As the repeated administration of recreational drugs is unethical, such latter research has relied upon recruiting participants who are already using the investigated drug in their everyday lives. Hence, drug models are limited as their conclusions and theories are in part based upon the findings of naturalistic drug studies, which have a host of common limitations, including poly-drug use, restricted study design and recruitment difficulties (see Curran, 2000 for review).

This author takes the position that drug models can be useful tools in the search for knowledge regarding the aetiology and maintenance of psychotic symptomatology, but that readers should be mindful that they are most helpful to this endeavour when viewed within the context of the above limitations. It is not proposed that drug-induced experiences which mimic psychotic symptomatology are exactly the same as idiopathic psychotic symptomatology, but rather that the striking similarity is of interest and warrants investigation.

4. Ketamine and its association with the psychoses

4.1 Overview

Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, which interferes with the action of excitatory amino acids (EAAs), including glutamate and aspartate (Anis, Berry, Burton & Lodge, 1983, cited in Curran & Monaghan, 2001). The EAAs are the most prevalent excitatory neurotransmitters in the brain and play an important role in cortico-cortical and cortical-subcortical interactions (Cotman & Monaghan, 1987, cited in Curran & Monaghan, 2001). Ketamine is available clinically as a racemic mixture of two enantiomers, the S-isomer and the R-isomer, which have different receptor binding profiles. The former has 2-4 times greater affinity for the NMDA receptor and clinical potency than the latter (Øye, Hustveit, Moberg, Pausen, & Skoglund, 1991; Øye, Paulsen, & Maurset, 1992, both cited in Abi-Saab, D'Souza, Moghaddam, & Krystal, 1998). Although both isomers bind to receptors other than the NMDA receptor (with less affinity), findings suggest the effects of subanaesthetic doses of ketamine are mediated by the NMDA receptors (Abi-Saab et al., 1998; Umbricht et al., 2000). This implies the ketamine model of the psychoses has high transmitter specificity.

Ketamine use began within clinical settings, for the purposes of anesthesia and analgesia. However its use was associated with bizarre post-operative 'emergence phenomena' comprising of vivid dreams, hallucination-like experiences, delusions and confusional states (Siegel, 1978, cited in Curran & Monaghan, 2001). The 'emergence phenomena' resulted in ketamine's withdrawal from use with adults, but ketamine is still used in ambulatory, veterinary and pediatric anesthesia, and more recently in the treatment of chronic pain.

Interestingly, the 'emergence phenomena' have made ketamine the drug of choice for some recreational drug users.

Recreational ketamine use (street names; K, Special K and Vitamin K), became popular in the UK club scene in the early 1990s. The effects of ketamine are dose-specific, therefore at lower doses users may feel euphoric, experience waves of energy, and possibly synaesthesia, whereas at higher doses users might become paralysed, experience hallucinations and alternate realities, and a feeling of dissociation, providing an 'out of body' experience known as the 'K-hole'. These effects are short-lived, due to ketamine's short half-life (Wieber, Gugler, Hengstmann, & Dengler, 1975, cited in Umbricht et al., 2000). In the past couple of years a surge in ketamine use has been observed (DrugScope, 2005). Indeed recently it was found that 0.8% of 16-24 year-olds had used ketamine in the last year (Murphy & Roe, 2007). Furthermore, surveys of club goers have found a much higher incidence of recreational ketamine use (43% of club goers surveyed; Mixmag, 2004). Although data on illicit drug use is not robust, it nevertheless provides an indication of rates of ketamine use in the dance club community. From January 2006, ketamine has been classified a class-C controlled drug in the UK.

4.2 Ketamine as a drug model of the symptomatology characteristic of psychoses

Acute ketamine has been utilised to explore a ketamine model of psychoses. The model proposes glutamatergic dysfunction for symptomatology, and therefore for antipsychotic treatment. In contrast to amphetamine, which mimics only positive psychotic symptomatology (i.e. delusions and hallucinations), studies investigating ketamine-induced effects have found evidence of a full range of symptomatology (positive, negative and cognitive) characteristic of the psychoses. However these studies have never been reviewed.

An important question researchers are beginning to pose is whether *acute* or *chronic* ketamine administration better models the symptomatology which is deemed characteristic of the pre-psychotic, acute or chronic states experienced by individuals diagnosed with psychoses. In this vein, some researchers have suggested that *acute* ketamine-induced effects better model the symptomatology characteristic of the period of time prior to the emergence of fully developed psychotic phenomenology (Corlett et al., 2006 & 2007; Pomarol-Clotet et al., 2006), which some term the prodrome (McGorry et al., 1995, cited in Cornblatt, Lencz, & Obuchowski, 2002). For the purposes of this review, the author differentiates between acute and chronic effects of ketamine. In addition, the author considers the degree of similarity between the *type* of symptomatology ketamine mimics and the symptomatology deemed characteristic of the different states experienced by individuals with diagnoses (i.e. pre-psychotic, acute, chronic), in order to consider which state acute and chronic ketamine models may most closely represent.

5. The functional psychoses

5.1 The continuum model

There is a growing movement within British Psychiatry and Psychology to leave behind what has historically been termed the 'Kraepelinian dichotomy'[2], in favour of a 'dimensional' conceptualisation of functional psychoses. Current diagnostic systems (DSM-IV: APA, 1994; ICD-10: WHO, 1992) attempt to distinguish between schizophrenia and bipolar disorder *categorically*. However

[2] A differentiation held 'true' in Western Psychiatry since Emil Kraepelin (1919), which assumes schizophrenia and bipolar affective disorder are distinct entities with separate underlying neurobiological processes and interventions.

Murray et al. (2004) note that in clinical actuality precise symptomatic distinction between disorders is not possible, (with the category of schizoaffective disorders testifying to this). There is increasing recognition that individuals *across* categorically defined psychoses have *both* key first-rank Schneiderian[3] (FRS), and mood symptomatology (Conus, Bdel-Baki, Harrigan, Lambert, & McGorry, 2004; Murray et al., 2004). Indeed, it has been suggested that FRSs should be considered symptoms of the psychoses rather than symptoms of schizophrenia specifically (Peralta & Cuesta, 1999, cited in Gonzalez-Pinto, 2003a). Evidence from genetic studies also indicates there is not a 'neat' biological distinction between schizophrenia and bipolar affective disorder (see Craddock & Owen, 2005 for key evidence). Thus, a more valid and reliable alternative to this categorical conceptualisation is the dimensional study of the symptomatology of the psychoses, (Andreasen & Olsen, 1982; Crow, 1980; Liddle & Barnes, 1990; Von Knorring & Lindstrom, 1995, all cited in Gonzalez-Pinto et al., 2003b).

In keeping with this movement, this review will not refer to specific diagnostic DSM-IV or ICD-10 classifications (except in section 5.2), but will take the position that psychotic and cognitive symptomatology may be present *across* the psychoses, to differing degrees. The review will refer to symptomatology deemed characteristic of the psychoses, and its relationship with ketamine, rather than specific categorical diagnoses, such as schizophrenia. This approach is in line with Abi-Saab et al. (1998) who suggest drug models may prove better at offering insight into the pathophysiology of psychotic symptomatology in general, rather than specific DSM-IV or ICD-10 diagnoses.

[3] The main first-rank Schneiderian symptomatology (FRSS) consists of delusions, hallucinations and formal thought disorder. For decades FRSS have been considered the core symptomatology of the psychotic condition (Jaspers, 1963, cited in Gonzalez-Pinto et al., 2003a), where the term psychosis has been synonymous with 'schizophrenia'.

5.2 Categorisation of symptomatology characteristic of the psychoses

5.2.1 Why is categorisation important?

If ketamine is to qualify as a useful model of the symptomatology characteristic of the psychoses, it must induce its core symptomatology. Prior to the evaluation of the ketamine model of the psychoses, it is therefore necessary to consider the conceptualisation of this core symptomatology.

Over the years, many theorists have proposed various factor models of the psychoses, ranging from one to eight factors (see Serretti et al., 2001 for overview), which indicate symptomatology is not unidimensional. Serretti and Oliati (2004) note that recently, factorisation has also been introduced to understand other psychoses. The factor model deemed most useful for the purposes of this review is the five-factor model (Lindenmayer, Bernstein-Hyman, & Grochowski, 1994; Lindenmayer, Bernstein-Hyman, Grochowski, & Bark, 1995a; Lindenmayer, Grochowski, & Hyman, 1995b), which has demonstrated validity and reliability across different levels of chronicity, age groups and cultures. This model proposes symptomatology characteristic of the psychoses can be categorised into five separate, but coexisting components: negative and positive psychotic symptomatology, manic symptomatology (excitement, poor impulse control, hostility, tension), depression / anxiety (anxiety, guilt feelings, depression, somatic concern, preoccupation), and cognitive symptomatology (conceptual disorganisation, disorientation, difficulty in abstract thinking, mannerisms and posturing, poor attention). The best replicated of these dimensions are the positive and negative psychotic components, and the manic and depression / anxiety components (Wolthaus et al., 2000), even in populations of individuals with heterogeneous psychoses (Serretti & Oliati, 2004; Ventura, Nuechterlein, Subotnik,

Gutkind & Gilbert, 2000). However cognitive symptomatology is notoriously neglected, despite it being evident in all people with psychoses.

As positive and negative psychotic symptomatology have been recognised as core to the presentation of psychoses from the outset (e.g. Crow's Type I and II schizophrenia, 1980; FRSs, Schneider, 1959), this review will specifically consider ketamine's ability to model them. Further, as there is virtually irrefutable evidence that cognitive dysfunction (not secondary to medication, institutionalisation or symptomatology, and largely stable over time), which manifests years before the development of overt psychotic symptomatology, is a core component of the psychoses (Cornblatt, Obuchowski, Roberts, Pollack & Erlenmeyer-Kimling, 1999; Erlenmeyer-Kimling et al., 2000; Walker, Diforio & Baum, 1999, all cited in Bilder et al., 2006), this review will also specifically consider ketamine's ability to induce such deficits.

5.2.2 Positive psychotic symptomatology

Schneider (1959) advocated an arbitrary checklist of first-rank schizophrenic symptoms, which rapidly gained favour as they were 'positive' (i.e. reflecting an *excess* of 'normal' behavior), and were therefore definable and reliably rateable. These included delusions, hallucinations and formal thought disorder. Mackay (1980) argued that florid, positive symptoms occur in acute psychoses, often appearing at times of stress.

5.2.3 Negative psychotic symptomatology

In the early 20th Century, Kraeplin's psychiatric disorder of dementia praecox isolated a fundamental set of symptomatology with a very poor prognosis and a chronic course. This set of symptomatology is now termed negative symptomatology (reflecting a *loss* of 'normal' behavior). Herbener and Harrow

(2001) note that many studies have demonstrated the presence of negative symptomatology in individuals with heterogeneous psychoses. Although the main features of negative symptomatology are recognised as flat affect, poverty of speech (alogia), and anhedonia (Moller et al., 1994), there is still considerable diversity within the literature regarding its exact definition.

5.2.4 Cognitive symptomatology

There is irrefutable evidence that individuals who experience psychotic symptomatology also present with dysfunction across multiple cognitive domains, including learning and memory, executive functions, attention, language, spatial abilities, and general intelligence (Heinrichs & Zakzanis, 1998, cited in Murray et al., 2004). However neither ICD-10 nor DSM-IV criteria include a measure of cognitive dysfunction. Although there is debate regarding the onset of cognitive dysfunction, there is general agreement that this neurodevelopmental variance is present early in life, and that by the time of the first episode, deficits are large[4]. Cognitive impairments provide a superior predictor of a range of functional outcomes (e.g. ability to maintain social relationships, keep a job and function independantly), in comparison to psychotic symptomatology (Elvevag & Goldberg, 2000, cited in Selva et al., 2007).

5.3 Different states experienced by individuals with psychoses

The psychoses literature has attempted to determine the pattern of positive and negative psychotic symptomatology, and cognitive dysfunction which best characterises and differentiates between a pre-psychotic, acute and chronic state experienced by individuals with idiopathic psychoses. Therefore, as well as considering they type of symptomatology mimicked by ketamine (i.e. positive,

[4] Bilder et al. (2000) approximate neurodevelopmental deficits at first episode to equal 1.5 standard deviations, compared to healthy comparison groups.

negative and cognitive), this review will *also* consider whether acute and chronic ketamine reliably induced symptomatology which appears characteristic of any of the above states. This endeavour is in line with Abi-Saab et al. (1998), who suggested '...different drug models might more accurately portray a subgroup of symptoms at different stages and / or specific phases of the illness', (pg 105).

This endeavour is complex as the states described below are *constructs* created by medicine and science on the basis of characteristic patterns of symptomatology. Similar symptomatology is present within each state, and hence the states are not clearly separable categories. The subsections below (5.3.1 & 5.3.2) will consider how each state has been defined (i.e. the symptomatology that is deemed *characteristic* of the state) in the literature, and will indicate how the literature proposes the states can most usefully be differentiated.

5.3.1 Pre-psychotic state

There is widespread recognition of a state prior to the emergence of fully-manifest psychotic symptomatology, often referred to as 'the prodrome' (McGorry et al., 1995, cited in Cornblatt et al., 2002). Whether this state should be termed the 'prodromal state' is a theoretical matter beyond the scope of this review. For the purposes of this review this state will be termed the 'pre-psychotic' state (in line with Marneros, Pillmann, Haring, Balzuweit, & Bloink, 2005), so as to be inclusive of the two most significant approaches used to define the prodrome; the 'basic symptom' (Huber, 1980; Klosterkötter, Hellmich, Steinmeyer & Schultze-Lutter, 2001), and 'ultra-high risk' (Yung & McGorry, 1996; Yung et al., 1998) approaches. Indeed, these 2 approaches are increasingly being combined in the 'prodrome of psychoses' literature, such as in the German Research Network on Schizophrenia studies (Häfner, Maurer & Ruhrmann, 2004, cited in Simon et al.,

2007), and the European Prediction of Psychosis studies (Klosterkötter, Ruhrmann, Schultze-Lutter, Salokangas & Linszen, 2005, cited in Simon et al., 2007).

It is proposed that 'basic symptoms' describe the earliest, subtle, sub-clinical and self-experienced disturbances of thought processes, perception, motivation and affect, which initially occur during the pre-psychotic state. It has been argued the 'ultra-high risk' criteria capture unusual experiences occurring further into the development of fully-manifest psychotic symptomatology (Simon et al., 2007), and can include intermittent and attenuated positive symptomatology. Basic symptoms and unusual experiences captured by the ultra-high risk criteria are proposed to be *characteristic* of the pre-psychotic state alone. Although *some* basic symptoms may also be apparent during the chronic state, once idiopathic psychoses have been diagnosed (Gross, 1997), this latter state is *characterised* by negative psychotic symptomatology, a significant degree of cognitive impairment, and a history of fully-manifest positive psychotic symptomatology, not the presence of basic symptoms. Furthermore, it is argued that a much higher level of basic symptoms is experienced during the pre-psychotic state in comparison to the chronic state. As noted above, the states experienced by individuals with idiopathic psychoses are constructs which share symptomatology. Therefore, it is unsurprising that there may be some overlap of symptomatology between states. This review is not a critique of the state constructs, and so further consideration of this matter is beyond the scope of this paper.

The pre-psychotic state can last between 1-5 years (Yung et al., 2003), and is *characterised* by sub-clinical, attenuated positive and negative symptomatology, mood changes, cognitive dysfunction and functional impairments (Yung & McGorry, 1996). For example, Schultze-Lutter, Ruhrmann, Hoyer, Klosterkotter

and Leweke (2007) found evidence for disturbances of attention, thought, perception, and motor action in a sample of outpatients without any diagnosis, who went on to develop psychotic symptomatology, in comparison to a clinical control group. Both prospective and retrospective studies have shown attenuated negative symptomatology is *characteristic* of the pre-psychotic state (e.g. Häfner, Loffler, Maurer, Hambrecht & Heiden, 1999; Klosterkötter, Gross, Huber & Steinmeyer, 1997; Tsuang et al., 2000, all cited in Cornblatt el al, 2002), very often developing over months and years before positive symptomatology is observed. Theorists believe a progressive pathway of deterioration exists, whereby initial non-specific, attenuated negative symptomatology and cognitive dysfunction are followed by the development of attenuated positive symptomatology, which gradually increase in intensity, until they reach a psychotic level (Cornblatt et al., 2002). Indeed, it has been suggested that attenuated positive symptomatology is *characteristic* of those individuals closest to developing fully-manifest psychotic symptomatology (Simon et al., 2006). Furthermore, many studies have suggested a trend, which indicates that individuals with first-episode psychosis are significantly more cognitively impaired than individuals in a 'pre-psychotic period' (e.g. Keefe et al., 2006; Niendam et al., 2006).

Initially, sub-clinical symptomatology may only be perceptible by the individual (Gross, 1997). As the attenuated symptomatology becomes more pronounced they may also then be observed in behaviour (e.g. more frequent thought blocking can start to interfere with participation in conversations). The pre-psychotic symptomatology fluctuates in occurrence and severity, and is dependant on demands and stress (Gross, 1997). The symptomatology experienced during this state is proposed to be the early stages of the corresponding full-blown

symptomatology of the psychoses (Klosterkötter, Ebel, Schultze-Lutter, F & Steinmeyer, 1996).

There is a growing interest in understanding the pre-psychotic state, and its ability to predict the development of psychotic symptomatology. Traditional treatment for the psychoses aims to reduce the duration of untreated active psychotic symptomatology, through the speedy provision of antipsychotic drugs following diagnosis. In contrast, current opinion is increasingly proposing the treatment of individuals in the pre-psychotic state, in the hope of attenuation, delay or even prevention of fully-manifest psychotic symptomatology. If ketamine were able to reliably model the construct of the pre-psychotic state as defined in the literature (which some authors have proposed), it may further understanding in this area. A caveat regarding this approach is the high 'false-positive' rate. Drake and Lewis (2005) estimate only 25 - 40% of those who present with brief or attenuated psychotic symptomatology progress to fully-manifest psychotic symptomatology within the year, whilst some never do.

5.3.2 Acute and chronic states

The presence of an acute, relatively short-lived, but potentially relapsing state *characterised* by positive psychotic symptomatology has been recognised since the beginning of the 20th Century. Crow (1980) provided one of the first attempts to theoretically differentiate this acute state from a chronic state of deterioration. He proposed two distinct syndromes; Type I, characterised by positive psychotic symptomatology, an acute course and good prognosis, and Type II, characterised by negative (Moller et al., 2002) and cognitive symptomatology, a chronic course, and poor outcome. Crow (1980) argued that these syndromes represented different dimensions of pathology, but can occur together.

There is a large body of literature which suggests chronic states of psychotic symptomatology are associated with particularly evident cognitive deficits (Murray et al., 2004), however studies have also demonstrated cognitive deficits in individuals with acute states of psychotic symptomatology (Murphy et al., 1999; Qureshi & Frangou, 2002; Sweeney, Kmiec & Kupfer, 2000, all cited in Murray et al., 2004). In particular, memory and specific executive function deficits are characteristic of both acute and chronic states of psychotic symptomatology (Chan, Kwok, Chiu, Lam, Pang & Chow, 2000; Fossati, Amar, Raoux, Ergis & Allilaire, 1999). The literature shows a mixed picture regarding the temporal stability of cognitive deficits, with some studies (including longitudinal ones) providing evidence that the neuropsychological profile remains stable (see Goldberg et al., 1993a; Nopoulos, Flashman, Flaum, Arndt & Andreasen, 1994, all cited in Gur, Ragland & Gur, 1997), whereas others indicate declining cognitive function over time (Sweeney, Haas & Li, 1992, cited in Gur et al., 1997). Studies clearly provide mixed results.

Critiques of this cognitive research include the proposition that psychotic symptomatology compromises cognitive functioning (e.g. emotional and motivational deficits can affect performance on cognitive tasks), for which many studies do not directly control. Nevertheless, Mortimer (1997) argued that the influence of psychotic symptomatology on cognition is not so clear, citing cross-sectional studies which found equivalent levels of cognitive impairment in different groups of people with psychotic symptomatology, with a wide range of 'illness' duration (Goldberg et al., 1993b; Heaton, Paulsen & McAdams, 1994; Hyde, Nawroz & Goldberg, 1994), and studies which demonstrated comparable levels of cognitive deficit in people with first-episode and chronic psychotic symptomatology

(Hoff, Riordan, O'Donnell, Morris & De Lisi, 1992). Furthermore, first-onset psychosis typically coincides with an age when it adversely affects educational attainment, and individuals with a more chronic presentation of any psychoses will have received more antipsychotic medication, which may contribute to further cognitive dysfunction.

Currently, most authors agree on demarcating acute states of the psychoses from some form of chronic, mostly deteriorating state (Pillmann & Marneros, 2003). The current British differentiation between acute and chronic states of psychotic symptomatology mainly rests upon the relative chronicity of the presentation. It is suggested that both states involve FRS delusions and / or hallucinations, however chronic states involve deterioration from a premorbid level of functioning and continuous signs of disturbance for more than 6 months (Van Os et al., 1995).

Recently, this distinction has been further delineated as the presence of 'acute and transient psychotic disorders' (ATPD; ICD-10: WHO, 1992), and its DSM-IV equivalent, 'brief psychotic disorder' (BPD; DSM-IV: APA, 1994) have been proposed. These diagnoses refer to acute states with rapid onset and resolution, and an atypical course (Pillmann & Marneros, 2003). Despite potential relapse to the acute state, there is often full remission in between, with no transition to a chronic degenerative presentation. Nevertheless significant proportions do develop more chronic presentations (Kuruvilla, Thangadurai, Gopalakrishnan, Kurien & Jacob, 2006). Therefore it appears there may be a core group of individuals with ATPD, whilst others given this diagnosis are developing more chronic presentations. Interestingly, the positive symptomatology experienced by individuals diagnosed with ATPD differs to that experienced in other psychoses.

For example, the former experience significantly fewer hallucinations and bizarre delusions (such as thought insertion, thought broadcasting, delusions of control), and much more rapidly changing delusions, in comparison to the latter (Marneros, Pillmann, F., Haring, A., Balzuweit, S., & Bloink, 2003).

For the purposes of this review, the term acute state will be used to refer to a period of time, characterised by positive psychotic symptomatology, with a relatively brief duration (in line with Van Os et al., 1995). This acute state may be (although is not necessarily), embedded within a more chronic state, characterised by cognitive and negative psychotic symptomatology.

6. Drug models of the psychoses

6.1 Historical models

6.1.1 The dopamine hypothesis of the psychoses

Interest in the role of neurotransmitters in the cause and treatment of psychotic symptomatology developed in the 1950s. The classic dopamine (DA) hypothesis of the psychoses (Carlsson & Lindqvist 1963, cited in Kegeles et al., 2000), which suggests that disturbed and hyperactive dopaminergic function is a central aspect of the pathogenesis of FRS positive symptomatology, is one of the earliest and most influential of the theories. The DA hypothesis was developed on the basis of several consistent observations within the literature (For summaries see Baumeister & Francis, 2002; Kahn & Davidson, 1995). Initially, it was observed that recreational use of amphetamine and cocaine (particularly after larger doses and / or prolonged use) produces a transient, psychotic-like state in healthy participants, dominated by positive symptomatology, such as auditory hallucinations and akathisia (Angrist, Sathananthan, Wilk & Gershon, 1974;

Janowsky & Risch, 1979; Sherer, Kumor, Cone & Jaffe, 1988, all cited in Krystal et al., 2005). In a systematic review, Curran, Byrappa and McBride (2004) found that single, moderate doses of dopamine agonists resulted in brief increases in positive psychotic symptomatology in 50-70% of participants with pre-existing psychotic symptomatology, especially those with a history of positive symptomatology. It has been found that dopamine agonists increase dopaminergic transmission mainly due to increased DA release in the mesolimbic pathway (O'Connor, 1998).

The classic DA hypothesis was strengthened by the observation that drugs that blocked DA receptors (DA antagonists, which formed the basis of atypical antipsychotics such as haloperidol and chlorpromazine), effectively controlled positive psychotic symptomatology, whether naturally occurring or chemically induced, despite having limited or no efficacy with negative symptomatology (O'Connor, 1998). In addition, studies investigating DA's metabolite, homovanillic acid, in plasma (pHVA), indicated that when participants with psychotic symptomatology discontinue atypical antipsychotics, an increase in pHVA level is observed, concurrent with a worsening of symptomatology. As atypical antipsychotics are especially effective at improving positive symptomatology, and as pHVA may primarily reflect striatal DA activity, increased DA activity in the striatum may be associated with the positive symptoms of psychosis (Kahn & Davidson, 1995).

Although this theory dominated for more than 3 decades, the DA hypothesis in its original form cannot account for all the core symptoms of psychosis, which include not only positive psychotic symptomatology, but also negative and cognitive symptomatology. Theorists therefore attempted to modify the DA hypothesis, on the basis of studies (Kahn & Davidson, 1995 for summary), which

indicated negative and cognitive symptomatology may be associated with decreased DA function in the prefrontal cortex. It was hence proposed the psychoses may be characterised by chronic dopaminergic deficiency (associated with negative and cognitive symptomatology), which under environmental stress precipitates episodes of acute DA overactivity (associated with positive symptomatology), involving different DA receptor systems (Mackay, 1980).

Boeijinga, Soufflet, Santoro and Luthringer (2007) note the DA hypothesis is still unable to satisfactorily account for negative symptomatology, a chronic state of deterioration after repeated relapses, and cognitive dysfunction observed in the multitude of psychotic presentations. Further challenge to the DA hypothesis stemmed from the advent of atypical antipsychotics which do not act solely upon dopamine neurotransmitters, and are more efficacious than typical (older), DA specific antipsychotics. According to Mackay (1980), 'It would be naïve and counterproductive to suggest that (DA) is the only, or even the most important abnormality', (p. 382).

6.1.2 The serotonin hypothesis of the psychoses

In 1954, it was first observed that Lysergic acid diethylamide (LSD) possessed hallucinogenic properties. As a result, a similarity was proposed between these properties and psychotic symptomatology. As LSD has a mainly serotonergic action (5-hydroxytryptamine, 5HT), it was proposed that its psychotropic effects were associated with a relative serotonin (5HT) dysfunction. In addition, controlled studies with individuals diagnosed with chronic psychoses demonstrated that a selective 5HT receptor antagonist (ritanserin), alleviated psychotic symptomatology, showing specificity for negative symptomatology. Such findings formed the basis of the serotonin hypothesis of psychosis, which proposed negative

psychotic symptomatology could be explained serotonergically (Woolley & Shaw, 1954, cited in Baumeister & Hawkins, 2004).

The original hypothesis was soon revised, due to numerous contradictory findings. By 1956, Woolley & Shaw proposed both a deficit and an excess of 5HT were equally plausible explanations of psychotic symptomatology (Baumeister & Hawkins, 2004). Further research provided varied findings (Iqbal & van Praag, 1995 for review), and therefore the hypothesis was cast aside during the 1960s and 1970s. The development of 'atypical' antipsychotics (currently the antipsychotics of choice within British psychiatry, e.g. olanzapine, risperidone, clozapine), which have both serotonin and DA actions, renewed interest in the hypothesis, and more importantly has led to a combined 5HT / DA hypothesis of the psychoses.

6.2 The interaction of dopamine and serotonin systems

Evidence strongly supports a 5HT / DA interaction (Iqbal & van Praag, 1995). For example, atypical antipsychotics have had a profound impact on the management of psychotic symptomatology, as 5HT antagonist action appears to augment the actions of DA receptor antagonists, thus demonstrating an improved efficacy in managing negative symptoms (Meltzer, 1992, as cited in Tamminga, 1998). Indeed, O'Connor (1998) notes that serotonin antagonism of DA activity in the prefrontal cortex may be the key to alleviating the negative psychotic symptomatology. Although atypical antipsychotics have the potential to attenuate both positive and negative symptomatology, up to 75% of individuals with psychotic symptomatology still experience significant active psychotic and cognitive symptomatology whilst undergoing atypical antipsychotic therapy (Tamminga, 1998). Therefore, it is evidence that the DA / 5HT interaction may not provide the whole picture.

6.3 The glutamate hypothesis of the psychoses

The glutamate hypothesis of the psychoses originated from observations that glutamate releasers (e.g. phencyclidine and ketamine), appear to induce symptomatology resembling that observed in the psychoses better than other compounds (Carpenter, 1999). Individuals with idiopathic psychoses report that experiences on PCP more closely resembled their individual acute psychotic symptomatology than any other psychoactive drugs (Ban, Lohrenz & Lehmann, 1961; Luby, Cohen, Rosenbaum, Gottlieb & Kelley, 1959, both cited in Carpenter, 1999). Induced effects include perceptual changes and delusions, poverty of speech and thought, negative symptomatology, agitation and memory disturbance (Newcomer & Krystal, 2001 for review). Due to these effects, and the recognition that other drug models cannot account for the full range of symptomatology observed in the psychoses, the ability of PCP and ketamine to provide a more compelling drug model of the psychoses has been of increasing interest.

Initially, the anaesthetic phencyclidine (PCP) was investigated but due to its toxicity (Rothman & Olney, 1987, cited in Abi-Saab et al., 1998), researchers turned to its structural analogue, ketamine, which causes reactions similar to, but not as severe as those caused by PCP. The 'clinical syndrome' produced by PCP and ketamine led to the glutamatergic hypothesis of the psychoses, which proposes glutamatergic NMDA receptor hypofunction (which ketamine and PCP induce), may be responsible for the psychotic symptomatology and cognitive dysfunction observed in the psychoses (Bunney, Bunney & Carlsson, 1995; Coyle, 1996; Javitt & Zukin, 1991; Olney & Farber, 1995, all cited in Abi-Saab et al., 1998). Newcomer and Krystal (2001) suggest the mechanism itself might involve NMDA receptor dysfunction, or upstream / downstream effects which can be reproduced by

blocking NMDA receptors. The glutamate hypothesis is currently one of the leading neurochemical theories of the psychoses.

Further evidence for the hypothesis comes from pharmacological, post-mortem and clinical studies, which implicate the glutamatergic NMDA receptor in the pathophysiology of psychotic symptomatology (Javitt & Zukin 1991; Olney & Farber 1995, both cited in Boeijinga et al., 2007). For example, postmortem studies reveal NMDA receptor expression and function is altered in the brains of individuals with psychotic symptomatology (see Millan, 2005 for studies, cited in Large, 2007). Furthermore, PCP triggers acute psychotic symptomatology in stabilised individuals with chronic psychotic symptomatology, lasting up to several months (Stelzer, Simon, Kovacs & Rai, 1994, cited in Newcomer & Krystal, 2001), whereas LSD causes only a brief hallucinogenic state which does not last longer in individuals with psychotic symptomatology than in healthy controls (Domino & Luby, 1981, cited in Newcomer & Krystal, 2001). Some, but not all, genetic data suggests an association between NMDA receptor gene polymorphisms and psychotic symptomatology (Itokawa et al., 2003; Makino, Shibata, Ninomiya, Tashiro & Fukumaki, 2005, both cited in Large, 2007).

The above findings suggest the psychotic and cognitive symptomatology experienced by individuals with idiopathic psychoses cannot be fully explained by the DA hypothesis, or indeed the interaction between DA and serotonin systems. Furthermore, as atypical antipsychotics cannot attenuate or eliminate all psychotic symptomatology, glutamatergic NMDA receptors are increasingly important in the development of novel antipsychotic medication, as their dysfunction may be a central feature of the psychoses.

6.4 The interaction of glutamate and dopamine systems

It has been proposed that NMDA receptor antagonists induce psychotomimetic effects via an interaction with the DA system (Boeijinga et al., 2007), however the neurobiology of this relationship remains unclear (Rabiner, 2007 for review). It is both suggested that primary abnormalities in DA transmission might reduce glutamate release onto NMDA receptors (Olney & Farber, 1995, cited in Newcomer & Krystal, 2001), or NMDA receptor hypofunction may secondarily alter DA transmission (Adams & Moghaddam, 1998; Grace, 1991, both cited in Newcomer & Krystal, 2001). Kegeles et al. (2000) found evidence for the latter theory, with acute ketamine administration, which causes NMDA blockade, significantly increasing the effect of amphetamine on striatal dopamine release. This study was limited by its small sample and an apparent lack of randomisation.

7. A review of acute and chronic ketamine-induced effects

7.1 Methodological issues

There are several methodological limitations which constrain the interpretation of data from ketamine studies. Firstly, the majority of studies use a crossover design, which does not control for tachyphylaxis (i.e. a developed tolerance for ketamine, after repeated administration). Secondly, the majority of studies (certainly those conducted in the 1990s), investigating the psychotomimetic effects of ketamine utilised the Brief Psychiatric Rating Scale (BPRS: Overall, 1974, cited in Newcomer et al., 1999a), which is not specific or selective for symptomatology characteristic of the psychoses. In addition, using less sensitive measures may have prevented the detection of more subtle ketamine-induced

effects. More recently authors have attempted to overcome this limitation (e.g. Pomarol-Clotet et al., 2006). Finally, prior to Newcomer et al.'s studies in 1999, ketamine plasma levels were not monitored, which limits the interpretations based upon this data.

7.2 Ketamine as a model of positive and negative psychotic symptomatology: Does the ketamine model of the psychoses have clinical validity and specificity?

7.2.1 The effects of acute ketamine in healthy participants

The majority of investigations into the effects of acute ketamine have been completed using challenge studies with healthy participants. Such studies involve the investigation of symptomatology through the transitory manipulation of NMDA receptor function with an acute, subanaesthetic dose of ketamine, in a controlled environment. Krystal et al. (1994) and Malhotra et al. (1996) were the first to use this methodology to explore acute ketamine-induced effects.

They found ketamine induced a 'clinical syndrome', characterised by positive and negative psychotic-like symptomatology (including thought disorder, blunted affect, emotional withdrawal), as well as perceptual alterations similar to dissociative states (e.g. altered body perception, depersonalisation, derealisation and distorted sensory perception). As the phenomenological profile resembled a range of psychotic symptomatology so closely, acute ketamine was proposed as a drug model of the psychoses. Therefore the acute ketamine model of the psychoses appeared to have good clinical validity. Initially, it appeared the model had limited clinical specificity, as clinical phenomena, not typical of the psychoses, were also noted (e.g. mood elevation and dissociation). With very limited data, the question of

whether the *acute* ketamine model was reliable remained; could it consistently model symptomatology characteristic of the psychoses in further studies?

Using visual analog scales, Radant, Bowdle, Cowley, Kharasch and Roy-Byrne (1998) observed dose-dependant effects of ketamine in 10 healthy young men in a randomised, single-blind, placebo-controlled crossover design. Findings indicated significant evidence of ideas of reference, hearing voices, perceptual alterations (including changed environmental perception, body perception, and passage of time), difficulties controlling thoughts, and feelings of unreality (evidence of dissociative effects). In a benchmark crossover study (utilised to minimise systematic bias between the groups), Newcomer et al. (1999a) also found dose-dependant, fully reversible and time-limited effects of ketamine. Results indicated that as time progressed from baseline to infusion, to post-washout, scores on both the negative subscale (blunted affect, emotional withdrawal, & motor retardation) and positive subscale (hallucinations, conceptual disorganisation & unusual thought content) of the abbreviated BPRS rapidly increased and then decreased after the infusion, within the high dose (0.27mg/kg: replication of higher dose in Krystal et al., 1994), and moderate dose (0.081mg/kg) conditions, thus indicating the psychotomimetic properties of higher doses of ketamine. In addition, evidence of dose-dependant avolition, apathy, anhedonia, asociability and affective flattening were found on the Scale for the Assessment of Negative Symptoms (SANS: Andreasen, 1982). The design of this study was robust, and thus its findings can be taken as indicative of the model's reliability. Hence it initially seemed that the *acute* ketamine model best represented the acute state experienced by individuals with idiopathic psychoses, as positive and negative psychotic symptomatology appeared to be reliably experienced when measured by the BPRS.

Prior to Newcomer et al. (1999a), ketamine challenge studies were confounded by a lack of steady-state infusion, limited dose conditions, and / or failure to measure plasma ketamine and metabolite levels during the study (which meant levels could be above or below that stated). Newcomer et al. (1999a) overcame these obstacles. Nevertheless, their study did have some limitations, including an exclusively young male cohort of participants, a relatively small sample size (increasing the probability of Type II error), and one dropout after randomisation.

Similarly designed crossover trials have since replicated Newcomer et al.'s (1999a) dose-dependant findings, (Anand et al., 2000; Boeijinga et al., 2007; Hetem, Danion, Diemunsch & Brandt, 2000; Morgan, Mofeez, Brandner, Bromley & Curran, 2004a), providing further evidence for the reliability of the ketamine model of the psychoses. Even low doses of ketamine (0.27 mg/kg over the first 10 min, followed by 0.12 mg/kg over 50-min), have been found to significantly increase positive and negative psychotic-like symptomatology, in comparison to placebo (Parwani et al., 2005). This study also investigated levels of perceptual alteration following a low dose of ketamine. Qualitatively, they noted participants reported alterations in body perception (e.g. floating sensation, being pulled), self-perception (i.e. reports of depersonalisation and a sense of unreality), environmental perception (e.g. things falling away from beneath them, objects appearing distorted), motor retardation (e.g. feeling heavy), and unusual thought content (e.g. jumbled thoughts). Interestingly, the perceptual alterations induced by acute ketamine (e.g. impaired body perception, environmental perception, time perception, and feelings of unreality), are *characteristic* of the pre-psychotic state rather than the acute state (Hamilton, 1985, cited in Anand et al., 2000).

Adler, Goldberg, Malhotra, Pickar and Breier (1998) conducted a double-blind, randomised, placebo-controlled crossover study which aimed to extend previous findings that *acute* ketamine appeared to induce thought disorder. Their study utilised a more valid measure of formal thought disorder (Scale for the Assessment of Thought, Language and Communication, TLC: Andreasen, 1978, cited in Adler et al., 1998), than had previously been used (i.e. BPRS). Findings indicated significant formal thought disorder during ketamine infusion, following a loading dose of 0.12mg/kg, in comparison to placebo. Using the Positive and Negative Syndrome Scale (PANSS: Kay, Opler & Lindenmayer, 1989), Krystal et al. (2005) also found evidence of several aspects of thought disorder (conceptual disorganisation, difficulties in abstract thinking and poor attention), with low dose ketamine administration (0.23mg/kg), in comparison to placebo. Other ketamine-induced effects included psychotic-like delusions, and negative psychotic-like symptomatology (blunted affect, emotional withdrawal, and motor retardation). Thus the picture developing thus far appeared to suggest *acute* ketamine best models the acute state.

Acute ketamine-induced speech disturbances (including disorganised speech), have also been found, resembling formal thought disorder observed in the psychoses (Abi-Saab et al., 1998; Krystal et al., 2003). For example, Covington et al. (2007) analysed speech samples from two prior experiments, (a between-groups study of individuals diagnosed with psychosis and comparable healthy controls, and a within-subjects challenge study with healthy participants), using software they developed. Results indicated acute ketamine resulted in significantly more repetitious speech in healthy participants, which was comparable to the significant level of repetitious speech detected in participants with idiopathic psychoses.

Interestingly, repetitious speech was observed more frequently following acute ketamine, than in individuals with idiopathic psychoses. These results should be interpreted with caution, as the study used small-scale experiments, and was the first to utilise this novel computer speech analysis technique. Nevertheless, findings were in line with Adler et al. (1999), who also found a larger increase in repetitiousness following acute ketamine, than in individuals with idiopathic psychoses.

Diverse speech disturbances are core to the psychoses (McKenna & Oh, 2005 for review), as they are proposed to form part of formal thought disorder, a FRS. The most marked disturbances tend to be failure to follow a discourse plan, repetition / perseveration, or drifting aimlessly, thus failing to convey the originally intended information. Evidence of such speech disturbances following *acute* ketamine use further add weight to the suggestion that *acute* ketamine best models the *acute* state.

The majority of earlier studies investigating acute ketamine-induced effects did not assess symptomatology in great detail, often relying on the BPRS (not specific for measuring psychotic symptomatology), to capture the participants' presentation. Therefore, the validity of the conclusions based upon the findings of earlier studies (which predominantly utilised the BPRS) have more recently been called into question. As a result, Pomarol-Clotet et al. (2006) attempted to provide a more comprehensive account of ketamine's effects, using measures other than the BPRS. Evidence of ideas, or even partially held delusions of reference were observed in approximately half their sample, supporting previous findings (see above). Self-reported experiences approximating dissociation (both depersonalisation and derealisation), were also described. Negative psychotic-like

symptomatology was observed (poverty of speech and affect flattening), however the authors suggested this may be due to ketamine's general depressant effect on the central nervous system, and recommended further study into this issue. The study failed to find evidence of formal thought disorder, which contradicts previous studies (Adler et al., 1998; Krystal et al., 1994, 2005). These results need to be interpreted with caution, due to the study's phenomenological design preventing statistical comparisons between the effects of ketamine and placebo.

Interestingly, perceptual alterations (specifically of the body, time, and the environment), but not hallucinations were detected. These findings were in line with Stone, Erlandsson & Arstad (2006, cited in Stone & Pilowsky, 2006), who found wide ranging ketamine-induced perceptual alterations but no true hallucinations. Rather, several participants reported eidetic imagery, and most reported visual illusions. This highlights an important point regarding the clinical validity of the *acute* ketamine model of the psychoses. Although several studies have reported the presence of ketamine-induced 'hallucinations', this may in fact be a product of the measure utilised (BPRS), rather than a 'true' finding, as the BPRS rates perceptual alterations on the same scale as hallucinations. Whereas the former are frequently induced by acute ketamine, ketamine rarely induces auditory hallucinations, frequently associated with the psychoses, but does (at high doses), induce complex visual hallucinations, which are relatively uncommon in the psychoses (Honey et al., 2006). Any reported ketamine-induced auditory hallucinations appear to differ from true hallucinations (Honey et al., 2006). This methodological confound may have propagated the belief that ketamine routinely induces hallucinations (Lahti, Weiler, Michaelidis, Parwani & Tamminga, 2001).

The dose-dependant visual and auditory perceptual distortions and (at higher doses) hallucinatory-like experiences are very similar (in form but not always in content), to attenuated positive psychotic symptomatology. The former are reported during the pre-psychotic state (Freedman & Chapman, 1973, cited in Abi-Saab, 1998), whereas hallucinations form one of the main criteria for the acute state of psychoses, in idiopathic psychoses. Pomarol-Clotet et al.'s (2006) findings therefore appear to provide evidence of limited clinical validity if the acute ketamine model is proposed to reproduce the acute state, as hallucinatory experiences do not appear to be reliably replicated with doses of the drug administered in challenge studies. The model does appear to have superior clinical validity if deemed to represent the pre-psychotic state, as acute ketamine repeatedly induces perceptual alterations and ideas of reference (similar to delusions), both characteristic symptomatology of this state of the idiopathic psychoses.

Neither perceptual alterations nor hallucinations can be explained solely by changes in external sensory stimuli, which suggests an internal brain mechanism must be involved in the generation of these phenomena. Pereira and Johnson (2003) proposed the neurobiological genesis involves the NMDA receptor channel, which functions as a coincidence-detection mechanism for afferent and reentrant signals, supporting conscious perception, learning, and memory formation. The findings of ketamine challenge studies support this hypothesis. The detailed neurobiology of this genesis is beyond the scope of this review, and readers are directed to Pereira and Johnson (2003) for more information concerning the genesis of ketamine-induced perceptual distortions and hallucinatory-like experiences, and thus the potential genesis of idiopathic psychotic perceptual distortions and hallucinations. Interestingly, Drake and Lewis (2005) propose specific symptomatology

experienced during the pre-psychotic state is predictive of an imminent transition to fully-manifest psychotic symptomatology. They noted these include ideas of reference, unusual thought content, (e.g. magical thinking), perceptual abnormalities, marked and rapid functional decline, and social withdrawal, all of which are induced by subanaesthetic doses of acute ketamine.

The paranoia induced by acute ketamine in healthy participants rarely reaches delusional proportions, presenting rather as 'suspiciousness' (Bowdle et al., 1998; Malhotra et al., 1997a), evidenced by participants believing others are talking about them or researchers are against them, with intact awareness that this may be drug-induced (Abi-Saab et al., 1998), and ideas of reference (Bowdle et al., 1998; Krystal et al., 1994 & 1998; Radant et al., 1998). This attenuated positive psychotic symptomatology is observed in the pre-psychotic state, providing further evidence that acute ketamine may best model this state. Indeed, during this state, individuals with developing psychotic symptomatology report experiencing alterations in visual and auditory perception, and attentional changes, such that attention is drawn to non-salient, irrelevant environmental stimuli (Freedman, 1974; Freedman & Chapman, 1973; Hemsley, 1994; McGhie & Chapman, 1961, all cited in Corlett et al., 2006). Furthermore, the ability to form associations (between perceptions, thoughts, stimuli, and events), is heightened, so much so that associations are often formed where none exist (Miller, 1989 & 1993; Schneider, 1930, all cited in Corlett et al., 2007). It is suggested that attempts to account for these strange experiences result in the invention of bizarre, causal structures to explain them, which manifest clinically as delusions (Kapur, 2003; Kapur, Mizrahi & Li, 2005).

Many studies have indicated acute ketamine induces perceptual alterations, theoretically proposed to be involved in delusion formation. These include changes

in the perception of one's own body, time, auditory and visual stimuli, (Krystal et al., 1994; Newcomer et al., 1999a; Pomarol-Clotet et al., 2006; Radant et al., 1998; Stone et al., 2006). There is a paucity of research investigating the effects of ketamine on association formation, its effects on attention are mixed (see cognitive section below). Nevertheless, in a randomised, placebo-controlled crossover study, Corlett et al. (2006) found evidence of heightened association formation (measured by prediction error), following a low dose of ketamine. Furthermore, using a regression analysis, it was found that participants' drug-naïve responses to prediction error (suggested to provide an indication of subjects' sensitivity to prediction error), were significantly predictive of subsequent perceptual alterations, as well as ideas and delusions of reference.

Thus, although earlier studies appeared to indicate that *acute* ketamine may best represent the acute state, more recently it has been suggested that this may have in part been the result of the measures utilised in these earlier studies (i.e. BPRS) confounding interpretations. Indeed *acute* ketamine does not appear to *reliably* induce fully-manifest core FRSs, namely hallucinations, delusions, and formal thought disorder, but rather *reliably* induces perceptual alterations (associated with hallucinations and delusions), ideas of reference, delusional ideas and unusual thought content. Therefore, more recently it has been argued that acute ketamine appears to model symptomatology *characteristic* of the pre-psychotic state, rather than the acute state. This matter is still unclear, and only further acute ketamine studies utilising more sensitive and specific measures will assist in determining which state *acute* ketamine best models, in terms of the psychotic symptomatology it induces.

7.2.2 The effects of acute ketamine in individuals with idiopathic psychotic symptomatology

Several investigations have also assessed the effects of *acute* ketamine in participants with idiopathic psychoses. However these studies are limited, partly due to ethical issues surrounding the administration of an agent which has the potential to exacerbate psychotic symptomatology and cognitive deficits both acutely and long-term (Carpenter, 1999 for review of ethical considerations). Nevertheless, the consistent finding that subanaesthetic, acute doses of ketamine induce a mild, dose-related, short-lived increase in positive psychotic symptomatology provides further evidence for the clinical validity and reliability of the ketamine model of the psychoses (Lahti, Koffel, LaPorte & Tamminga, 1995; Lahti et al., 2001; Malhotra et al., 1997a).

Lahti et al. were the first group to conduct ketamine challenge studies with individuals with idiopathic psychoses. Initially, Lahti et al. (1995) reported that 9 stable in-patients with psychoses experienced a significant, but short-lived increase in total BPRS scores 20 minutes after a ketamine infusion of 0.3mg/kg and 0.5mg/kg. This significant increase was mainly accounted for by a significant increase in their BPRS 'psychosis' subscale scores, indicating the presence of significant ketamine-induced positive symptomatology. Specifically, it was noted that the themes and content of the ketamine-induced positive psychotic symptomatology were very similar to symptomatology experienced by the participants during acute episodes of their psychoses. This was true for delusions, thought disorder, and hallucinations. For example, 2 participants with a history of extensive paranoid delusions reactivated part of these specific delusions with ketamine. Some participants with a history of thought disorder became disorganised

following the administration of ketamine, in ways characteristic of their own presentation of thought disorder. Furthermore, visual hallucinations were frequent for all participants. Whereas some of these had the quality of previous symptomatology, other hallucinations had more of a 'dream-like' quality. Therefore, Lahti et al.'s (1995) findings appeared to indicate that an *acute* dose of ketamine causes the re-emergence of an *acute* state, in individuals with chronic, stable psychoses.

After a period of between 4-8 weeks, in which participants were free of antipsychotics, 6 of the original 9 participants consented to undertake the same challenge study. Interestingly, Lahti et al. (1995) found that when these participants were haloperidol-free, they did not experience a significant increase in their total BPRS scores, nor in their 'psychosis' BPRS subscale scores, despite the former scores showing a non-significant trend ($p< 0.07$) towards worsening mental state. This lack of significant findings may be due to a smaller sample size, a higher baseline level of psychotic symptomatology, and / or pharmacokinetic factors. Furthermore, when the authors compared the total BPRS scores of only the 6 participants who completed both sets of challenge studies, no significant difference in scores was found.

In contrast, Malhotra et al. (1997a) completed a study which found acute ketamine (0.12mg/kg), significantly increased both positive and negative psychotic symptomatology (measured by BPRS), in comparison to placebo, in 13 antipsychotic-free individuals with idiopathic psychoses and 16 healthy controls, with no differences between groups in terms of the size of these increases. Both groups also demonstrated significantly increased thought disturbance, withdrawal and motor retardation. Qualitative observations also indicated conceptual

disorganisation. In line with Lahti et al.'s (1995) data, observations of participants with idiopathic psychoses indicated a re-activation of their individual psychotic symptomatology, following acute ketamine. In this respect, ketamine differs to amphetamine. The latter tends to induce new symptomatology, that is not typical of the individual's previous psychotic presentation (Tamminga, Lahti, Medoff, Gao, & Holcomb, 2003, cited in Large, 2007). Auditory hallucinations were observed in 50% of the diagnosed group with a history of hallucinations, and increased suspiciousness was observed in 75% of the diagnosed group with a history of paranoid symptoms. This pattern was not observed in controls. However the study was limited by a small sample size, a lack of ketamine plasma level monitoring, and the use of bolus administration rather than infusion (as in Lahti et al., 1995), which may not have been as accurate a technique. Indeed, the differences between this study's findings and those of Lahti et al. (1995) may have been due to the differing methods of ketamine administration, and / or differences in study design, participant selection, and differing ketamine doses.

More recently, Lahti et al. (2001) conducted a placebo-controlled crossover study which further supported previous data. They found that 20 minutes after a ketamine bolus, 17 participants with active, but stable idiopathic psychotic symptomatology (resulting in a diagnosis of schizophrenia), experienced a significant increase in total BPRS scores, and BPRS 'psychosis' subscale scores, in comparison to placebo. Lahti et al. (2001) noted that the similarity between ketamine-induced symptomatology experienced by individuals with idiopathic psychoses and their own positive psychotic symptomatology suggested that ketamine provided a unique model of the psychoses.

Taken together these results appear to speculate that an *acute* ketamine model may best represent the *acute* state. This is in line with the findings of earlier studies with healthy, drug-naïve participants. However it is in contrast with the conclusions of later studies with healthy, drug-naïve participants, which appear to suggest acute ketamine induces symptomatology *characteristic* of the pre-psychotic state. It may be that individuals with stable, chronic idiopathic symptomatology have a low threshold and / or an increased susceptibility for the emergence of fully-manifest psychotic symptomatology, as a result of previous experience of such symptomatology. Indeed, Krystal et al. (1999) note that individuals with idiopathic psychoses appear to exhibit an increased sensitivity to some, but not all the ketamine-induced effects observed in healthy participants. For example, they comment that hallucinatory experiences, but not delusional responses are even more prominent and developed in individuals with idiopathic psychoses, in comparison to healthy participants. Further investigation is required to elucidate this matter.

7.2.3 The effects of acute and chronic ketamine in recreational users

The methodology of challenge studies only enables the investigation of *acute* effects of NMDA-antagonism through ketamine. This leaves a gap in the literature regarding the *chronic* effects of ketamine, despite suggestions that *chronic* ketamine use may provide a useful model of the chronic state (Ellison, 1995; Jentsch & Roth 1999, both cited in Uhlhaas, Phillips & Silverstein, 2007). Ketamine's medicinal use as a one-off anaesthetic, as well as its range of cognitive and psychotic-like side-effects, ethically prohibits administering repeated doses to healthy participants under experimental conditions. Therefore, studies investigating the effects of *chronic* ketamine rely on recruiting from a population of individuals who use ketamine recreationally. This small body of research is subject to the many

limitations of naturalistic drug research (e.g. poly-drug use interactions, pre-existing population differences, varying doses and purity of the drug).

Curran and Morgan (2000) were the first authors to use this naturalistic population to study the psychotomimetic effects of *chronic* ketamine. In terms of acute ketamine-induced effects observed in a sample of *chronic* ketamine users (termed acute-on-chronic use), findings indicated ketamine (approximately 2 mg/kg within 30 minutes of testing), induced significant psychotic-like symptomatology (measured by a *state* schizotypal symptomatology questionnaire developed by Curran & Morgan specifically for this study), in comparison to poly-drug controls. On this measure, magical ideation, perceptual distortions and thought disorder were found to be significantly increased. Subjectively rated effects of ketamine included perceptual alterations (including visual, auditory, temporal and body perception), lack of coordination and unsteadiness, out of body experiences, and altered reality. Pronounced dissociative states (depersonalisation, derealisation and amnesia, measured by an adapted version of the CADSS), were also observed, in comparison to controls. Three days after acute ketamine use, following abstinence from alcohol and other recreational drugs, despite generally lower scores on measures, ketamine users still experienced significantly more psychotic-like symptomatology and dissociation than controls, although other subjectively rated effects did not differ from controls.

These findings closely replicate the *acute* dissociative and psychotomimetic effects of ketamine in challenge studies with healthy, drug-naïve participants, (see 7.2.1). As the measures used in these studies were more specific for psychotic symptomatology than the BPRS, it was possible to determine that the psychotomimetic effects appear to be those *characteristic* of the pre-psychotic state

(i.e. attenuated psychotic symptomatology). This therefore suggests that the *acute* ketamine model may best represent the acute state. Interpretation of the data gained for Day 3 is more complex. One possibility is that the symptomatology observed is due to long-term, *chronic* effects of ketamine. It is conceivable that residual effects of acute ketamine use on Day 0 gave rise to the symptomatology, or pre-existing group differences. This study was limited by a high dropout rate, and a lack of biometric confirmation of drug intake.

A further study of similar design (Curran & Monaghan, 2001), compared frequent (greater than twice a month), and infrequent (ketamine twice a month or less), users of ketamine. Results indicated very high levels of psychotic-like symptomatology (including perceptual alterations, unsteadiness and lack of coordination, bodily numbness, mental confusion), and dissociation following an acute dose of ketamine (acute-on-chronic) in both groups, yet no evidence of significant residual effects, 3 days later. These findings were supported by Morgan, Riccelli, Maitland and Curran (2004c). The lack of psychotic-like symptomatology 3 days after acute ketamine administration (Curran & Monaghan, 2001; Morgan et al., 2004c), indicates the *chronic* ketamine model may not be a reliable nor valid model of the *acute* state. It is proposed that as *chronic* ketamine has *not* thus far been found to induce fully-manifest negative psychotic symptomatology, it may not be an appropriate model for the *chronic* state of the psychoses, despite its detrimental effects on cognition (see section 7.3). Rather, it may be that *chronic* ketamine users present with subtler psychotic-like symptomatology, which the behavioural measures utilised by Morgan et al. (2004c; 2006), are not sensitive or specific enough to detect. The author of this review hence suggests the *chronic* ketamine model may better represent the pre-psychotic state, which is *characterised*

by *attenuated* positive and negative psychotic symptomatology. This proposition is supported by the findings of Uhlhaas et al. (2007), who observed higher levels of delusional ideation 3 days after ketamine use, in a sample of *chronic* ketamine users, and Morgan et al. (2004d) who found higher levels of schizotypal symptomatology and perceptual distortions in a sample of ketamine users who had substantially reduced their ketamine use, compared with poly-drug controls.

Recently, the processes involved in delusion formation have been investigated in chronic ketamine abusing participants (Uhlhaas et al., 2007). Results indicated significantly impaired contextual processing (measured by a contour integration task), and thus impaired perceptual organisation, following a non-standardised, *acute* dose of ketamine (participants recruited in vivo at a party), in comparison to poly-drug controls, and no significant residual effects 3 days later. This finding supported Umbricht et al. (2000), who found acute ketamine induced deficits in perceptual organisation in both auditory and visual domains, in 20 healthy, drug-naïve participants.

Uhlhaas et al. (2007) argued that such impairments in perceptual organisation might, in part, account for the perceptual alterations observed in ketamine challenge studies, and thus may be related to delusion formation. Indeed, similar impairments in stimulus-driven contextual processing are observed in studies with individuals with idiopathic psychoses (Silverstein, Kovics, Corry & Valone, 2000; Uhlhaas, Phillips, Mitchell & Silverstein, 2006, both cited in Uhlhaas et al., 2007). Whilst some perceptual organisation deficits have been observed in chronic schizophrenia (Dakin, Carlin & Hemsley, 2005, cited in Uhlhaas et al., 2007), it has been suggested that individuals in the pre-psychotic and acute psychotic stages experience marked deficits in visual perception, as found above

(Uhlhaas, Phillips & Silverstein, 2005). It has also been proposed that NMDA receptors are involved in perceptual organisation (see Phillips & Silverstein, 2003). This provides further indication that an *acute* ketamine model may best represent either the pre-psychotic or acute state.

7.3 Ketamine as a model of cognitive symptomatology: Does the ketamine model of the psychoses have clinical validity and cognitive specificity?

Abi-Saab et al. (1998) note ketamine-induced effects extend beyond psychotic-like symptomatology, to include other types of symptomatology associated with idiopathic psychoses. Indeed, there is a considerable body of evidence demonstrating cognitive dysfunction induced by NMDA receptor blockade, as a result of both acute and chronic ketamine administration. It has been proposed that such dysfunction is a consequence of ketamine inhibiting the induction of long-term potentiation, (LTP) a neuronal learning process (Harris, Ganong & Cotman, 1984, cited in Curran & Morgan, 2000). Indeed, NMDA receptors are densely localised throughout the cerebral cortex and the hippocampus, areas important for memory and cognition. Contrary to the historical proposition that cognitive deterioration observed in people with psychotic symptomatology is related to fixed structural abnormalities, it has been suggested that neurochemical dysfunction may be responsible for this process (Mortimer, 1997).

Despite a wealth of literature regarding the cognitive dysfunction experienced by individuals with idiopathic psychoses, there is still no agreement regarding the 'neuropsychological profile' of individuals who experience psychotic symptomatology. Memory dysfunction in various systems is considered as core symptomatology in individuals with idiopathic psychoses (Aleman, Hijman, de

Haan & Kahn, 1999; Gold, Randolph, Carpenter, Goldberg & Weinberger 1992; Heinrichs & Zakzanis, 1998, all cited in Honey et al., 2005). Thus, in order for the ketamine model of psychoses to possess clinical validity, ketamine administration should reproduce similar memory system dysfunction.

Prior to reviewing the literature regarding cognitive deficits induced by ketamine, it is necessary to note caveats. Firstly, no one cognitive task taps any single cognitive process or memory system exclusively (Wheeler, Stuss & Tulving, 1997, cited in Curran & Morgan, 2000). Studies have therefore based interpretations on the principal memory system thought to be tapped by the tasks employed. Secondly, the behavioural effects of ketamine may impair attention and executive functions, which are required for all memory tasks. Therefore, if these cognitive processes are not controlled for in studies, impaired performance on memory tasks may actually be due to deficits in attention and executive functioning, which will confound findings. Results from studies which are not mindful of these potential confounds have been interpreted with caution.

7.3.1 The effects of acute ketamine in healthy participants

7.3.1.1 Declarative memory systems (episodic and semantic memory)

Early ketamine challenge studies consistently demonstrate transient deficits in various memory systems (Ghoneim, Hinrichs, Mewaldt & Peterson, 1985; Harris, Biersner, Edwards & Bailey, 1975; Krystal et al., 1994; Malhotra et al., 1996). Specifically, declarative memory (consisting of episodic and semantic memory) is consistently impaired by *acute* ketamine in healthy participants. A large number of studies have shown acute ketamine (at a range of doses), induces verbal episodic memory impairment (Anand et al., 2000; Krystal et al., 1994). Disruption of episodic memory has been found in recognition tasks (Hetem et al. 2000), recall

of passages of prose (Morgan et al., 2004a; Newcomer et al., 1999a); and recall of high- and low-frequency word lists (Hetem et al., 2000; Malhotra et al., 1996).

For example, Newcomer et al. (1999a) found dose-dependant effects of ketamine on immediate and delayed verbal episodic memory. The authors noted that after placebo, healthy participants' total correct recall score (immediate – delayed recall scores), on a free recall task was 18.6% better than their performance after a high dose of ketamine (0.27mg/kg). Similarly, statistically significant differences were found between the low ketamine dose (0.0243mg/kg) and high ketamine dose conditions, on a non-verbal episodic memory task. This study was robust as it controlled for attention and working memory deficits. However a caveat; the sensitivity of different tasks could have contributed to the apparent selectivity of ketamine's effect. These findings provide further evidence for the clinical validity of the acute ketamine model of the psychoses, as episodic memory dysfunction represents a core cognitive deficit in individuals with idiopathic psychoses.

Furthermore, Morgan et al. (2004a) gained similar findings, observing significant impairment in episodic memory in a group of 18 healthy participants (measured by a prose recall task), in comparison to placebo, following an acute, high dose of ketamine (0.8mg/kg), in the face of preserved attentional and executive performance. Interestingly, the high dose selectively impaired encoding of information into episodic memory, but not retrieval, indicating a dissociative effect on episodic memory, in that ketamine impairs encoding rather than retrieval.

Further robust research supports these early findings (Honey et al., 2005; Malhotra et al., 1996; Newcomer et al., 1999b; Parwani et al., 2005). For example, in a placebo-controlled crossover study Hetem et al. (2000) found ketamine

infusion (steady-state of 0.5mg/kg), generated significant impairment in free recall and recognition of 2 lists of 40-words learnt *during* infusion, in 26 healthy participants, compared with placebo. No evidence of impairment was identified for free recall or recognition for words encoded *prior* to ketamine administration. Interestingly, individuals with idiopathic psychoses appear to experience impairments in encoding and retrieval of information, also utilising free recall and recognition tasks, as in ketamine challenge studies (Chan et al., 2000), although some suggest a retrieval-specific deficit in the psychoses (Calev, Venables & Monk, 1983, cited in Chan et al., 2000).

Although participants within a pre-psychotic state do not show the same level of cognitive impairment as that observed in individuals with first-episode psychoses (Keefe et al., 2006; Pukrop et al., 2006, cited in Niendam et al., 2007), or multiple episodes of psychosis (Hawkins et al., 2004, cited in Niendam et al., 2007), it appears their most pronounced cognitive deficits are very similar to those experienced by individuals with fully-manifest psychotic symptomatology. One of the most reliably replicated deficits in participants deemed to be in the pre-psychotic state is impairment in verbal episodic memory (Eastvold, Heaton & Cadenhead, 2007; Niendam et al., 2006).

Evidence for acute ketamine-induced impairment in semantic memory has been found in some (Abel, Allin, Hemsley & Geyer, 2003, cited in Morgan et al., 2006; Adler et al. 1998; Krystal et al., 1994), but not all (Krystal et al., 1999; Morgan et al., 2004a; Newcomer et al., 1999a) studies. This difference may be the result of methodological issues, however as these studies all accessed semantic memory using the category fluency task. The semantic memory system can more appropriately be studied using semantic priming tasks, which involve the

facilitation of responding to a word (e.g. table), when it is preceded by a semantically related word (e.g. chair), as compared with an unrelated word (e.g. sheep).

Morgan et al. (2006) used a semantic priming task to assess semantic memory dysfunction, following acute ketamine administration in healthy participants. Findings indicated only a high dose of ketamine (200ng/ml of plasma), significantly impaired the controlled processes of semantic priming (expectancy and semantic matching), in comparison to placebo. Indeed, the high dose of ketamine caused 'inverse priming,' i.e. faster reaction times to unrelated rather than related words. The authors proposed this finding may be the result of a deficit in on-line contextual processing of semantic information, a process in which NMDA receptors have been implicated (Phillips & Silverstein 2003, cited in Morgan et al., 2006).

The above findings suggest that the *acute* ketamine model has some clinical validity and cognitive specificity for the cognitive symptomatology of the psychoses, as it has been proposed that early, prominent impairment in episodic and semantic memory systems is frequently observed within the psychoses (Green, 1996, cited in Newcomer et al., 1999a; Mortimer, 1997). Indeed, several researchers have suggested semantic memory deficits are central to the cognitive impairment observed in the psychoses (e.g. Moritz et al., 2001, cited in Morgan et al., 2006; Rossell, Shapleske & David, 2000). Furthermore, it has been suggested that impairments in episodic memory are the most severe of all cognitive disturbances associated with the psychotic symptomatology (Heinrichs & Zakzanis 1998, cited in Hetem et al., 2000). Evidence that ketamine impairs episodic memory at levels equal to and below plasma concentrations associated with psychotic-like symptomatology (Honey et al., 2005; Newcomer et al., 1999a), suggests ketamine

may best model either the pre-psychotic or chronic state, as both these states are *characterised* by cognitive impairment. Newcomer & Krystal (2001) argued that *acute* ketamine may best model memory impairment during the pre-psychotic state. As *acute* ketamine does not reliably induce fully-manifest negative psychotic symptomatology (see section 7.2.3), which is *characteristic* of the *chronic* state, this proposal appears well founded. They suggest that gradually increasing levels of NMDA receptor hypofunction may be associated with increasingly impaired cognition in the psychoses. Indeed, verbal episodic memory deficits are a consistent finding in neuropsychological research with individuals in the pre-psychotic state (Eastvold et al., 2007; Niendam et al., 2006; Pukrop et al., 2007). Interestingly, a significant impairment in verbal episodic memory has been found to be predictive of an imminent transition from a pre-psychotic state to fully-manifest psychotic symptomatology (Brewer et al., 2005; Lencz et al., 2006, both cited in Eastvold et al., 2007).

The type of 'conscious state' experienced when accessing verbal episodic memory also appears to be affected by ketamine. Morgan and Curran (2006) differentiate these types of 'conscious state' as remembering information about past episodes, independantly of self-reference (recognition memory), and the ability to remember contextual information about those episodes, such as who was present and who said what (source memory). Robust studies have found acute ketamine significantly impairs both abilities in healthy participants (Honey et al., 2005, 2006; Morgan, Mofeez, Brandner, Bromley & Curran, 2004b). A comparable study found no evidence of a selective impairment of source memory, as a result of a 60-minute ketamine infusion (Hetem et al., 2000).

Honey et al.'s (2005) study showed acute ketamine administration at encoding significantly increased guessing bias (a tendency to guess words had been encoded under shallow, rather than intermediate or deep levels of processing), in comparison to placebo. The authors proposed this indicated a greater proportion of words were responded to on the basis of their familiarity, rather than 'true' recollection of encoding (i.e. source information), thus leading to increased use of the guessing strategy. However this study was limited by a small sample size and design insensitivities, which possibly resulted in subtle ketamine-induced effects being missed.

A further double-blind, placebo-controlled, randomised study by the same group found that following acute ketamine administration, healthy participants demonstrated impaired performance when deciding if they or an external agent (i.e. the experimenter), generated responses to specific words, if they had previously not been able to recall information from source memory about operations performed on the word (Honey et al., 2006). This is a particularly intriguing finding, as it is at odds with source memory deficits experienced by individuals with idiopathic psychoses, whose core deficit is an increased tendency to externalise. Indeed, it is suggested that such dysfunction is central to some of the positive psychotic symptomatology of the psychoses, including auditory hallucinations, passivity phenomena, thought insertion, and delusions of control (Brebion, Gorman, Amador, Malaspina & Sharif, 2002; Frith, 1987; Frith & Done, 1989, all cited in Honey et al., 2006), and their response to treatment (Keefe, Poe, McEvoy & Vaughan, 2003, cited in Honey et al., 2006).

When administered at encoding, the effects of acute ketamine are generally consistent with studies which report source memory dysfunction, in individuals

with idiopathic psychotic symptomatology (Brebion et al., 2000, 2002; Keefe, Arnold, Bayen & Harvey, 1999; Keefe, Arnold, Bayen, McEvoy & Wilson, 2002; Morrison & Haddock, 1997; Vinogradov et al., 1997, all cited in Honey et al., 2005). It has been suggested that this observed source memory dysfunction best fits with cognitive impairment within the *acute* state, because individuals with more chronic presentations display a selective impairment in source memory, with intact recognition memory (Hetem et al., 2000).

The *acute* ketamine model may lack cognitive specificity in this area, as source accuracy was not measurably impaired as a consequence of ketamine, which conflicts with findings with individuals with psychotic symptomatology (Honey et al., 2005). Furthermore, the increased tendency to internalise in agency source monitoring tasks is at odds with the pattern of source memory deficits in individuals with idiopathic psychoses. Honey et al. (2006) argued that this latter finding may simply indicate the acute ketamine model better represents cognitive deficits associated with paranoia / suspiciousness and delusions of reference (the type of positive psychotic-like symptomatology induced by ketamine), rather than the source monitoring deficits experienced by individuals with idiopathic passivity phenomena and auditory hallucinations (which are not typically induced by ketamine). They therefore conclude that 'in short, ketamine may mimic some aspects of the psychopathology of schizophrenia but not others', pg 421. They propose that as *acute* ketamine appears to induce subtler cognitive symptomatology than that experienced by individuals with fully-manifest psychotic symptomology, it may best model the pre-psychotic state.

7.3.1.2 Executive functioning and working memory

Poor executive functioning is repeatedly observed in individuals with idiopathic psychoses, even in cases where there is no general cognitive deterioration (Hughes et al., 2003; Liddle & Morris, 1991, cited in Mortimer 1997). Whilst some studies have indicated acute ketamine impairs executive functioning (Adler et al., 1998; Hetem et al., 2000; Krystal et al., 1994), others have not (Harborne, Watson, Healy & Groves, 1996, cited in Morgan & Curran, 2006; Morgan et al., 2004b; Newcomer et al., 1999a; Radant et al., 1998), and most have gained mixed results (Honey et al., 2003; Krystal et al., 2000; Morgan et al., 2004a). The basis for these differences is not clear. Nevertheless it is clear that individuals both in the pre-psychotic state and with fully-manifest psychoses do experience notable deficits in verbal executive functions (Eastvold et al., 2007; Gschwandtner et al., 2003; Hawkins et al., 2004; Hoff et al., 1992, all cited in Niendam et al., 2007; Pukrop et al., 2007; Simon et al., 2006), even though the deficits experienced by the former are less prominent than those experienced by the latter (Hawkins et al., 2004, cited in Niendam et al., 2007; Keefe et al., 2006; Pukrop et al., 2006).

A more consistent finding is that of a specific working memory (WM - an element of executive function), deficit in healthy participants, following acute ketamine. Morgan and Curran (2006) note the main observed trend within studies is that *acute* ketamine affects manipulation rather than maintenance of information in WM. For example, forward digit span and performance on the spatial delayed response task (both measures of the maintenance of material in working memory), have been found to be intact following ketamine administration (Abel et al., 2003; Ghoneim et al., 1985; Newcomer et al., 1999a; Rowland et al., 2005). Intact backwards digit span (measure of the manipulation of information in working

memory), has been observed in some (Ghoneim et al., 1985; Rowland et al., 2005) but not other (Abel et al., 2003) studies. In an RCT, Honey et al. (2003) also found that a low dose of ketamine (100ng/ml), significantly impaired performance on a WM task, specifically impairing the manipulation of information in WM, in the presence of intact maintenance processes. Interestingly, WM deficits in psychoses appear to be characterised by greater impairment in manipulation, rather than maintenance (Kim, Glahn, Nuechterlein & Cannon, 2004; Perry et al., 2001, both cited in Fletcher & Honey, 2006), suggesting the acute ketamine model has clinical validity in this domain.

The N-back task has also been used to investigate verbal WM dysfunction, following ketamine. This task involves an attentional component (0-back), in which participants simply respond to a number/letter, and two other components with increasing WM load. Robust studies have demonstrated significant ketamine-induced impairment on the WM components of this task, with intact 0-back (attentional) ability (Adler et al., 1998; Morgan et al., 2004b; Newcomer et al., 1999b).

It has been proposed that the cognitive dysfunction observed above, at subdissociative levels of ketamine, are not representative of either the deficits in the acute or chronic state because in the chronic state, such subtle cognitive effects may be swamped by the extent of cognitive impairment present, and in the acute state the extent of psychotic symptomatology could potentially be masking such subtle patterns of cognitive impairment (Honey et al., 2003). They therefore argue that the patterns of cognitive impairment observed in *acute* ketamine challenge studies may more appropriately represent precursors to the full cognitive impairment apparent in individuals with idiopathic psychoses.

This author therefore suggests that the cognitive dysfunction outlined above mimics the very earliest changes (i.e. during pre-psychotic state), present in those with idiopathic psychoses.

Many studies have found that individuals considered as being within a pre-psychotic state display deficits in WM and executive functions (Eastvold et al., 2007; Simon et al., 2006; Wood et al., 2003, cited in Pukrop et al., 2007). These earlier studies were limited by a significant proportion of 'false-positives' (i.e. participants deemed to be in the pre-psychotic state, but who do not develop psychoses). Nevertheless, Pukrop et al. (2007), whose study overcame this limitation, found significant impairments in WM and verbal executive function when 'true-positives' (i.e. participants deemed to be in the pre-psychotic state, who did develop psychoses) were compared to healthy controls. Indeed, Simon et al. (2007) concluded that the most pronounced cognitive deficits experienced by individuals in the pre-psychotic state are impairments in executive function and WM. Furthermore, significant impairment in spatial working memory has been found to be predictive of an imminent transition to fully-manifest psychotic symptomatology (Brewer et al., 2005; Lencz et al., 2006, cited in Eastvold et al., 2007).

Indeed, based upon the pattern of WM and episodic memory impairment following acute ketamine, Fletcher and Honey (2006) argue that *acute* ketamine shows promise in mimicking characteristic cognitive impairment associated with the pre-psychotic state, and therefore appears to have good clinical validity and promising clinical reliability. However the cognitive specificity of the acute ketamine model is not that strong, as evidence of procedural memory impairment (Morgan et al., 2004b) and preserved executive functions (for review see Morgan &

Curran, 2006) contrast with the presentation of individuals with psychotic symptomatology (Perlstein, Carter, Noll & Cohen, 2001, cited in Morgan et al., 2004b), and in a pre-psychotic state (Niendam et al., 2006; Pukrop et al., 2007).

7.2.1.3 Attentional processes

There is limited evidence for ketamine-induced attentional deficits as a result of an acute dose in healthy participants. Whereas some studies have found ketamine is associated with deficits in sustained attention (Krystal et al., 1994; Malhotra et al., 1996; Umbricht et al., 2000), others have indicated no impairment (Heekeren et al., 2007; Krystal et al., 1999; Newcomer et al., 1999a; Radant et al., 1998), whilst others have found mixed results (Oranje et al., 2000). It therefore appears the *acute* ketamine model is not particularly reliable in replicating the loss of the selective function of attention experienced by those with idiopathic psychotic symptomatology (Baribeau-Braun, Picton & Gosselin, 1983; McGhie & Chapman, 1961, both cited in Oranje et al., 2000), including those in the pre-psychotic state (Pukrop et al., 2007).

These findings also bring into question the cognitive specificity of the acute ketamine model as in a review, Gur et al. (1997) noted attentional dysfunction is a primary deficit experienced by people with idiopathic psychoses.

7.3.2 The effects of acute ketamine in individuals with idiopathic psychotic symptomatology

Limited ketamine challenge studies investigating cognitive dysfunction have been conducted with individuals with idiopathic psychoses. Malhotra et al. (1997a) found ketamine caused significantly impaired free recall and recognition memory, with intact attentional function, in a group of 13 antipsychotic-free individuals with a psychoses diagnosis, in comparison to placebo. Interestingly, episodic memory

was significantly more impaired in participants with a psychoses diagnosis, in comparison to healthy controls, following ketamine. However an early study by LaPorte, Lahti, Koffel and Tamminga (1996) found no evidence of episodic memory impairment or WM deficits in a very small sample of 7 participants with a psychoses diagnosis, following 0.5mg/kg of ketamine. The authors suggested this lack of significant ketamine-induced cognitive deficits may have been the direct result of the design of the study, which was unusual and had several limitations. Ketamine (or placebo), was administered *after* the learning procedure. Hence, the study's findings suggest ketamine-induced episodic memory impairment is specific to encoding, rather than retrieval of information.

7.3.3 The effects of acute and chronic ketamine in recreational users

A major limitation of the above research into ketamine-induced cognitive dysfunction is its focus on ketamine's *acute* effects. As a result, theorists have begun to investigate cognitive dysfunction in recreational ketamine users, in order to further our understanding of the *chronic* effects of ketamine, paralleling investigations into *chronic* psychotic-like symptomatology. Early anecdotal evidence suggested ketamine users experience memory deficits and attentional dysfunction (Jansen, 1990; Siegel, 1978, both cited in Curran & Morgan, 2000).

A few studies have examined the effects of ketamine on the cognition of recreational users, on the night of drug use (acute-on-chronic effects), and then 3 days later (chronic effects), following abstinence from alcohol and other recreational drugs. Firstly, Curran and Morgan (2000) found on the night of drug use (Day 0), *acute* ketamine induced a broad spectrum of cognitive impairments (episodic, semantic, working memory and focused attention), in comparison to poly-drug controls. These findings replicated data from previous challenge studies

with healthy volunteers (see above). However working memory was measured utilising the serial sevens task, therefore findings from this task may have been confounded by numeracy skills and working memory abilities prior to any ketamine use.

Three days later, when compared to polydrug using controls, ketamine users still presented with significantly impaired episodic and semantic memory. The authors noted however that a lack of practice on the specific cognitive task, due to acute amnesic effects of ketamine on Day 0 was possibly responsible for the former, but not the latter impairment in memory. Errors made in the category fluency task (which taps semantic memory), included rhyming (e.g. for the category "fruit" one ketamine user began "melons, Helens ...") and semantic errors (e.g. another began "oranges, juice, vitamins, goodness ..."). Such errors are similar to those reported in acute schizophrenia (McKenna, Mortimer & Hodges, 1992, cited in Curran & Morgan, 2000).

It could however be argued that the cognitive dysfunction observed on Day 3 was not due to *chronic* effects of ketamine, but rather was the result of pre-existing group differences in cognitive functioning. Curran and Monaghan (2001) conducted a further study (with similar design), to investigate this possibility. They compared two groups of ketamine users, frequent and infrequent, the former differing to the latter on the basis of more frequent intake, and larger doses of ketamine. At Day 0 (acute-on-chronic effects), both frequent and infrequent ketamine users were significantly impaired on tasks tapping episodic, semantic and working memory and focused attention. Three days later, frequent ketamine users still experienced impaired episodic and semantic memory systems, whereas infrequent users were performing at significantly higher levels on all previously

impaired cognitive tasks. These findings suggest that the patterns of memory impairment on Day 3 are a consequence of the *chronic* use of ketamine. This conclusion is strengthened by the observation that an acute dose of ketamine does not cause residual cognitive impairments 3 days later, in healthy participants (Morgan et al., 2004a).

The above studies indicated episodic memory impairment as a result of both acute and chronic ketamine use. As in ketamine challenge studies, the type of 'conscious state' experienced when accessing verbal episodic memory also appears to be affected by chronic ketamine use. Morgan et al. (2004c) were the first group to examined source and recognition memory in chronic ketamine users. They found on the night of drug use (acute-on-chronic effects), both source and recognition memory were impaired in ketamine users, which supports most findings in healthy participants (Honey et al., 2005, 2006; Morgan et al., 2004b). Three days later (chronic effects of ketamine), source memory was selectively impaired alongside intact recognition. This pattern of impairment has been suggested to fit more closely with a chronic state than the findings from acute ketamine challenge studies (Huron et al., 1995, cited in Hetem et al., 2000). Interestingly, an *acute* dose of ketamine on Day 0 (acute-on-chronic), induced a similar degree of source memory impairment to healthy participants infused with a high level of ketamine, whereas *chronic* effects of ketamine 3 days later induced a source memory impairment similar to healthy participants infused with a low dose of ketamine (Morgan et al., 2004b).

In a robust study, Morgan et al. (2006) found chronic ketamine use significantly impaired the controlled processes of semantic priming, specifically for low but not high frequency words, in comparison to poly-drug controls. As with healthy participants observed in this study, this effect was characterised by

'inversed priming'. The authors suggested the priming impairment for low-frequency words might be indicative of degradation in the semantic store. These results indicate a chronic ketamine model may be more appropriate than an acute model for representing the pattern of impaired semantic priming observed in individuals with more idiopathic psychoses, where a degradation of the semantic store has also been suggested (Rossell, Bullmore, Williams & David, 2001; Rossell & David, 2006, both cited in Morgan & Curran, 2006).

8. Treatment implications

8.1 Clinical specificity

In order for drug models of the psychoses to be utilised ethically and successfully in the development of pharmacological treatments for idiopathic psychoses, it is imperative for them to possess good clinical specificity. If the drug model is not specific, then the development of treatments based on its neurobiological methods of action will likely prove fruitless, or worse potentially harmful. Although current opinion in the pre-psychotic state and first-episode literature suggests that the early identification of attenuated or fully-manifest psychotic symptomatology and subsequent early intervention could provide the best outcome for individuals, it is vital to be mindful of the high rate of individuals identified as experiencing pre-psychotic symptomatology and cognitive dysfunction, who do not develop a subsequent psychoses (i.e. false-positives). For early intervention to succeed, an accurate definition of the pre-psychotic state is essential (Simon et al., 2007). This issue raises ethical concerns about the pharmacologic treatment of individuals who are identified as in a pre-psychotic state, who may never actually develop a psychoses (Corcoran, Malaspina &

Hercher, 2005; Haroun, Dunn, Haroun & Cadenhead, 2006; McGorry, Yung & Phillips, 2001, all cited in Eastvold et al., 2007) who at baseline assessment, using current criteria, are indistinguishable from those who do go on to develop psychotic symptomatology. Improved predictive accuracy for distinguishing individuals at imminent risk for developing psychoses is required for the earliest possible interventions to be disseminated ethically. If the acute and / or chronic ketamine model does appear to best mimic the symptomatology *characteristic* of the pre-psychotic state, it may play a pivotal role in the development of a more robust definition of the pre-psychotic state, with far greater predictive accuracy.

As a drug model of the psychoses, ketamine appears to have reasonable clinical specificity. Both acute and chronic ketamine intake are able to model a variety of psychotic-like and cognitive symptomatology, potentially associated with the psychoses. Whereas the *acute* ketamine model appears to induce psychotic-like symptomatology which is *characteristic* of either the pre-psychotic or acute states, it currently appears that the *chronic* ketamine model may best induce psychotic-like symptomatology *characteristic* of the pre-psychotic state (however research into the *chronic* effects of ketamine is sparse).

The majority of studies demonstrate subanaesthetic doses of acute ketamine also frequently induce significant dissociation (Anand et al., 2000; Curran & Morgan, 2000; Krystal et al., 1994; Malhotra et al., 1996; Pomarol-Clotet et al., 2006; Uhlhaas et al., 2007) and euphoria (Anand et al., 2000; Krystal et al., 2005). The former type of symptomatology is not specific to the psychoses, and is present in several other DSM-IV diagnoses, such as various anxiety disorders and post-traumatic stress disorder. Although it could be argued that the latter experience does not fall within a factor of psychotic-like symptomatology, it may well be akin to the

elevated and expansive mood experienced within the 'manic symptomatology' factor (Lindenmayer, Bernstein-Hyman & Grochowski, 1994; Lindenmayer, Grochowski & Hyman, 1995a; Lindenmayer, Bernstein-Hyman, Grochowski & Bark, 1995b). Interestingly, ketamine-induced euphoria can be observed in the presence of dysphoria, predominantly due to tension or anxiety, (e.g. Krystal et al., 2005), which is in line with the controversial proposal that depressive symptomatology may co-exist with manic symptomatology (Cassidy, Forest, Murry & Carrol, 1998; Dilsaver, Chen, Shoaib & Swann, 1999, both cited in Gonzalez-Pinto et al., 2003b). Finally, although there are several aspects of cognitive disruption (Honey et al., 2005), and altered sensorimotor functioning (Oranje et al., 2000; Weiler, Thaker, Lahti & Tamminga, 2000) which may differentiate ketamine-induced symptomatology from that of idiopathic psychoses, overall the ketamine model still appears to have reasonable clinical specificity.

8.2 Pharmacologic interventions

Despite not having complete clinical specificity, the ketamine model does appear to have good clinical validity. Therefore, based on the hypothesis that NMDA receptor hypofunction contributes to the pathophysiology of the psychoses, pharmacological treatments that facilitate NMDA receptor function have been developed (Tuominen, Tiihonen & Wahlbeck, 2005 for review). For example, a recent RCT investigated the efficacy of an oral selective agonist for mGlu2 and mGlu3 receptors, termed LY210023 (Patil et al., 2007) in a cohort of 118 drug-free participants, with high levels of psychotic symptomatology. Results indicated that LY210023 was safe and well tolerated by participants. They found both LY210023 (40mg twice daily), and olanzapine (15mg once daily), displayed a rapid onset of efficacy, as after week 1, both groups scored significantly lower on the PANSS than

placebo. This improvement was maintained until the end of the trial (4 weeks later). Furthermore, the LY210023 group showed significantly less psychotic symptomatology on both the positive and negative sub-scales of the PANSS. In addition, LY210023 participants did not show increased prolactin levels, worsening extrapyramidal symptoms or weight gain, unlike individuals using more commonly prescribed antipsychotics. The authors suggested their findings supported a potential alternative antipsychotic monotherapy for psychoses. However a high level of dropout limited this study.

Generally, clinical trials of glutamate agonists have generated mixed results (for review see D'Souza, Charney & Krystal, 1995, cited in Abi-Saab et al., 1998), and thus despite glutamate transmission dysfunction being implicated in psychoses, there still remains an absence of treatments acting on these pathways. Interestingly, lamotrigine (300mg administered 2 hours prior to a ketamine infusion) has been found to significantly decrease ketamine-induced psychotic-like positive and negative symptomatology, dissociation, semantic memory deficits and elevated mood (Anand et al., 2000). A recent paper suggested lamotrigine might be usefully utilised as an adjunct to conventional and atypical antipsychotic treatment of psychotic symptomatology, in particular positive symptomatology (Kremer et al., 2004, as cited in Patil et al., 2007).

The efficacy of current antipsychotic medication for attenuating acute ketamine-induced symptomatology in clinical populations has also been investigated. These few studies indicate that single doses of haloperidol (Krystal et al., 1999; Lahti et al., 1995), or olanzapine (Anand et al., 2000; Lahti, Holcomb, Gao & Tamminga, 1999), do not significantly attenuate ketamine-induced psychotic-like symptomatology, despite evidence that haloperidol can reduce

ketamine-induced impairment of executive function in healthy participants (Krystal et al., 1999). A caveat to be mindful of here is that individuals with idiopathic psychoses frequently require weeks or even months of drug treatment for symptom resolution to be achieved. Clozapine is one of the most effective drug treatments for psychotic symptomatology (Davis & Chen, 2004, cited in Large, 2007) and therefore has been used in the validation of all drug models of psychoses. This atypical antipsychotic significantly blunts ketamine-induced positive symptomatology (Malhotra et al., 1997b), which again provides evidence for the validity of the ketamine model.

9. Chronic ketamine use - risk factor for psychotic symptomatology?

This review has thus far focused upon the 'idiopathic hypothesis' of the psychoses, which proposes psychotic symptomatology is precipitated by gradually evolving, endogenous receptor dysfunction. The 'exogenous hypothesis' of psychoses will now be considered briefly. This hypothesis suggests the consumption of external pharmacological agents, in this case glutamate antagonists (PCP or ketamine), may constitute a risk factor for the development of psychotic symptomatology, through mechanisms that are extrinsic to the pathophysiology of 'naturally occurring' psychoses. To the author's knowledge, there is no published data concerning the rates of subsequent psychoses in chronic ketamine users. Although it has been noted that PCP induces symptomatology virtually indistinguishable from that observed in idiopathic psychoses, such that chronic PCP users may be misdiagnosed as experiencing a psychoses (Pearlson, 1981; Smith, Wesson, Buxton, Seymour & Kramer, 1978, both cited in Abi-Saab et al., 1998), such findings have not been reported for ketamine use.

Ketamine has been found to mimic relapse to an acute state in individuals with well-controlled, stable chronic psychoses (Lahti et al., 1995, 2001; Malhotra et al., 1997a). However induced symptomatology is mild and short lived. Interestingly it does appear that there are qualitative differences in the symptomology re-experienced by individuals with idiopathic psychoses when given an acute dose of ketamine, and symptomatology experienced by healthy participants when given the same acute dose of ketamine. Typically, lower doses of ketamine have been found to induce illusions, perceptual alterations, thought disorder and suspiciousness in drug-naïve, healthy participants, rather than fully-manifest hallucinations. This is in contrast to individuals with idiopathic psychoses, who experience ketamine-induced fully-manifest psychotic symptomatology, including hallucinations. Furthermore, the hallucinatory experiences induced by *high* doses of ketamine in drug-naïve, healthy participants are mainly visual in form (Vollenweider, Leenders, Oye, Hell & Angst, 1997). Complex visual hallucinations are relatively uncommon in individuals with idiopathic psychoses. In contrast, there is a higher rate of ketamine-induced auditory hallucinations (e.g. 50% of the sample with a history of auditory hallucinations; Malhotra et al., 1997a) experienced by those with idiopathic psychoses, in comparison to healthy participants. This form of hallucinatory experience is much more common to idiopathic psychoses presentations. It has been proposed this may be due to a reduction in threshold, as the result of increased sensitivity for psychotic symptomatology, therefore making the re-activation of previously experienced psychotic symptomatology more likely.

It is therefore tentatively hypothesised that these findings suggest acute ketamine induces fully-manifest psychotic symptomatology. Due to the short duration of this psychotic symptomatology, and as only specific aspects of the

psychoses are replicated, it is argued that acute ketamine does not cause transition to an *acute* state. However participants in the above studies were only provided with between 1 to 3, low doses of ketamine, so caution should be used in applying these data to recreational use. It is therefore apparent that a gap in the literature exists with regard to the effects of *chronic* ketamine use, and subsequent rates of ketamine-induced psychoses.

10. Conclusions – how useful a model of the psychoses is ketamine?

10.1 Clinical validity and reliability

10.1.1 Acute ketamine model of the psychoses

In summary, the acute ketamine model appears to have good clinical validity and reliability for the pre-psychotic state. Challenge studies with healthy participants, participants with idiopathic psychoses and acute-on-chronic studies with self-administering ketamine users have found ketamine induces a dose-dependant 'clinical syndrome', characterised by subtle positive and negative psychotic-like symptomatology (including unusual thought content, blunted affect, emotional withdrawal), as well as dissociative effects (non-core symptomatology sometimes observed in psychoses). Attenuated negative symptomatology associated with the psychoses has not been reported using other drug models. Acute ketamine does not appear to reliably induce 'true' delusions or hallucinations, but rather causes perceptual alterations and suspiciousness. It is proposed these perceptual alterations best model the processes involved in delusion and hallucination formation, and therefore are indicative of pre-psychotic processes. Honey et al. (2006) propose that as ketamine appears to induce subtler symptomatology than that

experienced by individuals with fully-manifest psychotic symptomology, it may best model the pre-psychotic state.

Furthermore, it has been proposed that the cognitive deficits induced by *acute* ketamine may better reflect the cognitive disturbances seen in the pre-psychotic state (Fletcher & Honey, 2006), in which cognitive symptomatology is subtler. Evidence that ketamine impairs episodic memory at levels equal to and below plasma concentrations associated with psychotic-like symptomatology (Honey et al., 2005; Newcomer et al., 1999a) also suggests ketamine may best model the pre-psychotic state.

10.1.2 Chronic ketamine model of the psychoses

It currently unclear which state of the psychoses the *chronic* ketamine model best represents, the pre-psychotic or the chronic state. The lack of psychotic-like symptomatology 3 days after acute ketamine administration observed in the majority of *chronic* ketamine studies (e.g. Curran & Monaghan, 2001; Morgan et al., 2004c), indicates the *chronic* ketamine model is probably not a reliable nor valid model of the *acute* state. It is proposed that as *chronic* ketamine has *not* thus far been found to induce fully-manifest negative psychotic symptomatology, it is not an appropriate model for the *chronic* state of the psychoses either, despite its detrimental effects on cognition. Rather, it is proposed that *chronic* ketamine may best mimic the attenuated psychotic symptomatology *characteristic* of the pre-psychotic state. This hypothesis is supported by the findings of Uhlhaas et al. (2007), and Morgan et al. (2004d), however further investigation is needed into this matter as so few chronic ketamine studies have been completed. At this stage, it is not possible to differentiate between these possibilities, as research has not

investigated the presence of subtle, pre-psychotic symptomatology in chronic ketamine users.

Chronic ketamine has been proposed to best model the semantic and episodic memory impairments associated with the psychoses (Morgan & Curran, 2006). However it is unclear which state *chronic* ketamine-induced cognitive impairments most resemble. The finding that *chronic* ketamine use specifically impairs source memory, in the presence of intact recognition memory is suggested to fit more closely with a *chronic* state (Huron et al., 1995, cited in Hetem et al., 2000), but the picture is an unclear one, as there is simply not enough available research evidence yet in the literature to make an informed decision. Further research is thus required to investigate the chronic effects of ketamine on cognition.

10.2 Contextual validity

Ketamine has a relatively short plasma half-life of 2-4 hours (Copeland & Dillon, 2005), therefore its acute effects are short lived, and fully reversible. Recreational users usually administer ketamine intranasally, which has an estimated duration of effect of up to 1 hour (Siegel, 1978). In a session, ketamine users will frequently self-administer several sequential doses to maintain psychotropic effects over time. The short half-life of ketamine would mean it would be eliminated from the body within 24 hours (Curran & Monaghan, 2001). This is not the case with psychotic and cognitive symptomatology characteristic of the acute and chronic states of psychoses, where symptomatology may be present for weeks, months and even years. It thus appears the acute ketamine model has much less contextual validity than the chronic model, in which ketamine-induced effects also take a chronic course. It may be that the acute ketamine model better mimics the pre-

psychotic state, as within this state symptomatology can be transitory and relatively short in duration (Yung & McGorry, 1996).

Furthermore, both healthy participants and recreational ketamine users are reliably able to report the subjective effects of ketamine, whereas it is controversially reported that frequently those with idiopathic psychoses 'lack insight' into their symptomatology. Indeed, the DSM-IV-TR states that 'a majority of individuals with schizophrenia lack insight regarding the fact that they have a psychotic illness'. This further suggests the ketamine model has limited contextual validity.

10.3 Clinical and cognitive specificity

All drug models of the psychoses have only partial specificity, inducing some but not all aspects of symptomatology. Therefore, it is unlikely that acute or even chronic administration of a pharmacological agent would reproduce all the symptomatology, specifically related to the psychoses, which arise through a complex interplay of genetic, developmental, and environmental factors.

The ketamine model appears to have limited clinical specificity. For example, complex visual hallucinations have been reported at high doses of acute ketamine (Vollenweider et al., 1997), which are relatively uncommon in idiopathic psychoses. However auditory hallucinations, which are common to the psychoses, are not usually elicited by ketamine. Furthermore, acute ketamine is subjectively rewarding (Morgan et al., 2004a), induces euphoria, and disruption of some aspects of sensorimotor function (see above), which are not typically associated with the psychoses. In addition, it has been suggested that the acute ketamine model may have limited clinical specificity for negative symptomatology, as it is confounded

by the presence of significant levels of sedation (Abi-Saab et al., 1998). Further studies are required to address this problem.

The cognitive specificity of the acute ketamine model is also limited, as evidence of procedural memory impairment (Morgan et al., 2004b) and preserved executive functions (Morgan & Curran, 2006 for review) contrast with the presentation of individuals with psychotic symptomatology (Perlstein et al., 2001, cited in Morgan et al., 2004b), and those in a pre-psychotic state (Eastvold et al., 2007; Niendam et al., 2006; Pukrop et al., 2007). In addition, the accuracy of source memory does not appear to be measurably impaired by acute ketamine, which contrasts with findings with individuals with psychotic symptomatology (Honey et al., 2005). Finally, the cognitive specificity of the ketamine model is brought into question as although attentional dysfunction is a primary deficit experienced by people with idiopathic psychoses (Gur et al., 1997), mixed findings have been gathered regarding ketamine-induced attention impairments.

10.4 Transmitter specificity

It has been demonstrated that ketamine has high transmitter specificity (Abi-Saab et al., 1998 for review), and thus antagonism at the NMDA receptor is thought to account for ketamine-induced effects observed in the studies above.

10.5 Experimental specificity

The vast majority of the studies reported in this review were randomised, placebo-controlled, crossover studies, and thus their findings are deemed relatively robust. However the ketamine challenge studies mostly had a crossover design, which is limited by tachyphylaxis (i.e. a developed tolerance for ketamine, after repeated administration). This suggests that acute ketamine studies in the main may be underestimating the level of symptomatology experienced by individuals infused

with acute ketamine. This confound may in part explain the difficulty with determining whether the *acute* ketamine model best mimics symptomatology characteristic of the pre-psychotic or acute states. Furthermore, the experimenters in the majority of acute ketamine challenge studies were not blind to the condition participants were undertaking. It is impossible to blind experimenters in chronic ketamine studies. The ketamine literature is therefore potentially confounded by bias, which could be introduced as a result of experimenters knowing the participants' level of ketamine infusion or recreational consumption.

11. Ideas for future research

As any useful literature review should, this paper has reliably indicated direction for future research needs. In particular, it is evident that research investigating the *chronic* ketamine model of the psychoses is limited, and requires pursuing. Specifically, studies involving the recreational ketamine population are in their infancy, and require further development.

It is unclear whether the *chronic* ketamine model best mimics symptomatology *characteristic* of the pre-psychotic or chronic state. This author has proposed that chronic ketamine users may in fact present with subtle, attenuated psychotic-like symptomatology, which is undetected by the behavioural measures utilised by the few *chronic* ketamine studies which have been published. Indeed, it is hypothesised that chronic administration may give rise to ketamine-induced attenuated positive and negative psychotic symptomatology and cognitive dysfunction *characteristic* of the pre-psychotic state.

In order to investigate this hypothesis it would be necessary to utilise a robust and sensitive measure of the earliest signs of developing psychoses. This

would be a novel approach to research conducted with the ketamine using population. Given a suitable sample size, it would thus be possible to determine whether ketamine users experience pre-psychotic symptomatology, and if so explore the degree to which such symptomatology is experienced, and the meaning afforded such symptomatology. Potential measures that could be utilised to assess pre-psychotic symptomatology in the recreational ketamine population include the Schizophrenia Prediction Instrument – Adult version (SPIA: Klosterkötter et al., 2001), and the Scale of Prodromal Symptoms (SOPS; McGlashan, Miller, Woods, Hoffman & Davidson, 2001) and its companion interview manual, the Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2003). The former has been developed from a hierarchical cluster analysis of the BSABS (Gross, Huber, Klosterkötter & Linz, 1987), and includes 10 'basic symptoms' that were recently reported by Klosterkötter et al. (2001). The latter measures (usually used in combination), are proposed to assess for the later pre-psychotic symptomatology, just prior to the emergence of fully-manifest psychotic symptomatology, and are based upon Yung et al.'s (2005) pre-psychotic state criteria. In order to further evaluate the clinical validity and reliability and cognitive specificity of the chronic ketamine model of the psychoses, it would be necessary to conduct further studies investigating the cognitive profile of recreational ketamine users, to determine if previous findings could be replicated.

A factor to consider in such studies would be the frequency with which ketamine is being administered recreationally. It may be possible to compare cohorts of recreational ketamine users who take ketamine at differing frequencies, to explore any potential significant differences.

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Part 2: Empirical Paper

Chronic ketamine use and pre-psychotic symptomatology

Abstract

Background: Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, with psychotomimetic properties. An *acute* dose of ketamine induces psychotic-like symptomatology, dissociative effects and pronounced cognitive dysfunction, thus ketamine is used as a 'model' of the psychoses. Recreational use of ketamine is rapidly increasing but there is limited research on ketamine's *chronic* effects.

Aims: Researchers have suggested that ketamine may better model the psychotic symptomatology and cognitive dysfunction associated with the pre-psychotic state (prodrome), however this has not been systematically investigated. The present study aimed to determine the extent to which the *chronic* effects of ketamine overlap with the symptomatology characteristic of the pre-psychotic state.

Participants: Sixty-one participants, 35 men and 26 women aged 18 to 46 years, completed the study.

Design: A between subjects design was used to compare three groups: 21 frequent ketamine users (who used ketamine daily), 20 infrequent ketamine users (who used ketamine a maximum of once or twice a week), and 20 control participants (who reported no illicit drug use). Participants completed an interview (Schizophrenia Prediction Instrument – Adult Version: SPI-A), self-report questionnaires (including O-LIFE; Peter's Delusion Inventory, PDI; Dissociative Experiences Scale, DES) and a battery of cognitive tasks tapping episodic memory, working memory and executive functioning.

Results: Both ketamine groups reported higher levels of psychotic-like symptomatology on the clinical index of symptomatology (SPI-A) and the general population index of psychotic-like markers (O-LIFE). On the former index a 'frequency' effect was observed: frequent users were found to experience more psychotic-like symptomatology (i.e. basic symptoms) than infrequent users. Frequent ketamine users were also found to score higher on measures of dissociation, and both groups of ketamine users experienced higher delusional ideation compared with controls. Furthermore, both groups of ketamine users demonstrated impaired episodic and working memory compared to controls. Group differences were also found in verbal fluency.

Conclusion: The findings lend support to the ketamine model of the psychoses, and suggest that glutamatergic disturbances may contribute to the pre-psychotic state because symptomatology proposed to be *characteristic* of the pre-psychotic state was observed in *chronic* ketamine users. These findings have important clinical implications for the growing numbers of ketamine users in this country and elsewhere.

Key words: chronic effects, basic symptoms, ketamine, pre-psychotic symptomatology, psychoses, psychosis proneness; schizotypy

INTRODUCTION

"It's so much like a party in your own head that eventually you are isolated and in a world of your own. Your brain 'fraggles'; there's disconnection and loose ends in your mind, like its full of live wires." (infrequent user 5)

"I get very distracted by spiritual interactions. I don't think ketamine causes these experiences, but rather it is a catalyst for these experiences, for spiritual activity. The spirits are breaking the boundary of this world and the other side. It (ketamine) helps you to tune in, like tuning a radio dial. People need to understand that." (frequent user 2)

Ketamine – an overview

Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, which interferes with the action of excitatory amino acids (EAAs), including glutamate and aspartate (Anis, Berry, Burton & Lodge, 1983). The EAAs are the most prevalent excitatory neurotransmitters in the brain and play an important role in cortico-cortical and cortical-subcortical interactions (Cotman & Monaghan, 1987). Ketamine use began within clinical settings, for the purposes of anesthesia and analgesia. As a result of the bizarre post-operative 'emergence phenomena' it induced (vivid dreams, hallucination-like experiences, delusions and confusional states: Siegel, 1978), it was withdrawn from anaesthetic use with adults. Interestingly, these 'emergence phenomena' have made ketamine the drug of choice for an increasing number of recreational drug users.

Recreational ketamine use (street names; K, Special K and Vitamin K), became popular in the UK club scene in the early 1990s. In the past few years a surge in

ketamine use has been observed (DrugScope, 2005). Indeed recently it was found that 0.8% of 16-24 year-olds had used ketamine in the last year (The British Crime Survey: Murphy & Roe, 2007). Furthermore, surveys of club goers have found a much higher incidence of recreational ketamine use (43% of club goers surveyed: Mixmag, 2004). In January 2006, ketamine was classified a class-C controlled drug in the UK.

Ketamine use and psychotic-like symptomatology and cognitive dysfunction

The *acute* effects of ketamine in healthy volunteers have been widely investigated. Findings indicate that *acute* ketamine has dose-specific effects, reliably inducing unusual thought processes and speech disturbances (mimicking formal thought disorder), blunted affect, emotional withdrawal, perceptual alterations, dissociation and cognitive impairment, such as deficits in episodic, semantic and working memory (Anand et al., 2000; Boeijinga, Soufflet, Santoro & Luthringer, 2007; Covington et al., 2007; Hetem, Danion, Diemunsch & Brandt, 2000; Krystal et al., 1994; Malhotra et al., 1996; Morgan, Mofeez, Brandner, Bromley & Curran, 2004a; Newcomer et al., 1999; Pomarol-Clotet et al., 2006). The psychotomimetic effects of *acute* ketamine appear to include symptomatology deemed core to the psychoses (i.e. positive and negative psychotic-like symptomatology, and marked cognitive impairment). These studies support a 'ketamine model' of the psychoses, which has led to the glutamatergic hypothesis of the psychoses (Olney & Farber, 1995). This hypothesis proposes that glutamatergic NMDA receptor hypofunction (which ketamine induces), may contribute to the psychotic symptomatology and cognitive dysfunction observed in the psychoses.

However there is a paucity of research investigating the *chronic* effects of ketamine, and to this author's knowledge there are only 8 published studies (Curran & Monaghan, 2001; Curran & Morgan, 2000; Morgan et al., 2006; Morgan, Monaghan & Curran, 2004b; Morgan, Riccelli, Maitland & Curran, 2004c; Muetzelfeldt et al., 2008; Narendran et al., 2005; Uhlhaas, Millard, Muetzelfeldt, Curran & Morgan, 2007). The increasing number of recreational ketamine users in the UK and worldwide, and the growing evidence of ketamine-induced psychotic-like experiences requires this gap in our knowledge to be addressed. Ketamine's medicinal use as a one-off anaesthetic, as well as its range of cognitive and psychotic-like side effects ethically prohibit administering repeated doses to healthy participants under experimental conditions. Therefore, the only window on *chronic* effects is through individuals who use ketamine recreationally.

Curran and Morgan (2000) were the first authors to use this naturalistic population to study the psychotomimetic effects of *chronic* ketamine. They found ketamine users experienced higher levels of psychotic-like symptomatology, including magical ideation, perceptual distortions, unusual thought content and dissociation than poly-drug controls, three days after an acute dose of ketamine (following abstinence from alcohol and other recreational drugs). They also noted significantly impaired episodic and semantic memory. Their findings closely replicated the acute dissociative and psychotomimetic effects of ketamine in challenge studies with healthy, drug-naïve participants. Similarly, Uhlhaas et al. (2007) found higher levels of delusional ideation 3 days after ketamine use, and Morgan et al. (2004b) found higher levels of schizotypal symptomatology and perceptual distortions in a

sample of ketamine users who had substantially reduced their ketamine use, compared with poly-drug controls.

However other studies have found no evidence of psychotic-like or dissociative symptomatology in ketamine users, in comparison to poly-drug controls (Morgan et al., 2004c, 2006). Nevertheless, these studies did find evidence of cognitive deficits, including episodic memory dysfunction, with selective source memory (memory for contextual information about episodes) impairment alongside intact recognition. Furthermore, Curran and Monaghan (2001) found no differences in psychotic-like symptomatology between frequent and infrequent ketamine users, yet did find frequent users exhibited impaired episodic and semantic memory, 3 days after acute ketamine use.

The findings of these *chronic* ketamine studies are clearly mixed. It could be argued this is because the psychotic-like symptomatology and cognitive dysfunction observed are not due to *chronic* effects of ketamine, but rather were the result of pre-existing group differences. However Curran and Monaghan's (2001) findings provide support against this interpretation because three days after acute ketamine use, frequent ketamine users still experienced impaired episodic and semantic memory, whereas infrequent users performed at significantly higher levels on all previously impaired cognitive tasks. This conclusion is strengthened by the observation that an acute dose of ketamine does not cause residual cognitive impairments 3 days later, in healthy participants (Morgan et al., 2004a).

If it is taken that ketamine does have chronic effects, why has an absence of psychotic-like symptomatology been observed in several studies when users are drug free (Curran & Monaghan, 2001; Morgan et al., 2004c, 2006)? Differences across studies may have been the result of the varying frequency with which ketamine was taken by users, and the differing amounts taken. This interpretation of findings lacks evidence, as groups of ketamine users who used with very similar frequency (e.g. 3.1 & 4.4 times per month) showed differing symptomatology (Curran & Morgan, 2000; Morgan et al., 2006 respectively). A key problem is that the measures utilised to assess psychotic-like symptomatology in previous studies (namely the Schizotypal Symptomatology Questionnaire: SSQ, and Subjective Effects Scales: SES) may not have been sensitive or specific enough to detect the *chronic* phenomenological effects of ketamine, resulting in mixed findings. Indeed, it may be that the symptomatology induced by *chronic* ketamine use (i.e. unusual thought patterns, perceptual distortions and delusional ideation) more closely represents *attenuated* positive and negative psychotic symptomatology, deemed *characteristic* of the 'pre-psychotic' state (e.g. Corlett et al., 2006; Schultze-Lutter, Ruhrmann, Hoyer, Klosterkotter & Leweke, 2007a).

The pre-psychotic state

There is widespread recognition of a state experienced by those diagnosed with idiopathic psychoses, prior to the emergence of fully manifest psychotic symptomatology, often referred to as 'the prodrome' (McGorry et al., 1995, cited in Cornblatt, Lencz & Obuchowski, 2002). For the purposes of this paper this state will be termed the 'pre-psychotic' state (in line with Marneros, Pillmann, Haring, Balzuweit & Bloink, 2005), so as to be inclusive of the two most significant

approaches used to define the prodrome: the 'basic symptom' (Huber, Gross, Schuttler & Linz, 1980; Klosterkötter, Hellmich, Steinmeyer & Schultze-Lutter, 2001), and 'ultra-high risk' (Yung et al., 1998; Yung & McGorry, 1996) approaches. Indeed, these two approaches are increasingly being combined in the 'prodrome of psychoses' literature, such as in the German Research Network on Schizophrenia studies (Häfner, Maurer & Ruhrmann, 2004), and the European Prediction of Psychosis studies (Klosterkötter, Ruhrmann, Schultze-Lutter, Salokangas & Linszen, 2005).

Basic symptoms describe the earliest, most subtle, sub-clinical and self-experienced disturbances of thought processes, perception, motivation and affect, which initially occur during the pre-psychotic state. Basic symptoms are thought to be central to the behavioural disturbances and functional disability experienced during the pre-psychotic period and fully manifest psychoses. However whereas psychotic symptomatology is externally observable by others on the basis of behaviour and expression, it is proposed that during the pre-psychotic period, basic symptoms are often only perceived by the person affected.

Gross (1997) suggests the basic symptom construct can be subdivided into 2 groups: level 1 (nonspecific) and level 2 (characteristic) basic symptoms, with the former developing prior to the latter. She explains that level 2 symptoms consist of cognitive thought disturbances (e.g. thought blocking, disturbance of expressive speech), perceptual disturbances (e.g. hypersensitivity to light and visual stimuli), and action symptoms (i.e. subjectively experienced disorder of movement and action, such as loss of automatic skills), and notes that cognitive thought

disturbances have been found to be indicative of a forthcoming transition to fully-manifest psychotic symptomatology. Furthermore, the presence of basic symptoms does not necessarily indicate that an individual will develop a psychotic disorder in years to come, as some individuals demonstrate patterns of spontaneous remission.

It is proposed that although *some* basic symptoms are intermittently present during the acute and chronic states experienced by individuals with psychoses (Gross, 1997), these state are *characterised* by different symptomatology. The acute state is deemed to be *characterised* by positive psychotic symptomatology, and the chronic state is deemed to be *characterised* by negative psychotic symptomatology, a significant degree of cognitive impairment, and a history of fully-manifest positive psychotic symptomatology. Furthermore, it is argued that a much higher level of basic symptoms is experienced during the pre-psychotic state in comparison to the acute and chronic states.

Aims and hypotheses

No study has yet investigated the possibility that *chronic* ketamine induces attenuated positive (and potentially negative) psychotic symptomatology, deemed *characteristic* of the pre-psychotic state. If chronic ketamine use does mimic symptomatology characteristic of the pre-psychotic state, then attenuated negative symptomatology should be observed (e.g. Häfner, Loffler, Maurer, Hambrecht & Heiden, 1999; Klosterkötter, Gross, Huber & Steinmeyer, 1997; Tsuang et al., 2000, all cited in Cornblatt el al, 2002). This study therefore aimed to inform the ketamine model, and thus the glutamate hypothesis of the psychoses, which proposes glutamatergic NMDA-receptor hypofunction (which ketamine induces),

may be responsible for the psychotic symptomatology and cognitive dysfunction observed in the psychoses (Javitt & Zukin, 1991; Olney & Farber, 1995; Coyle, 1996, all cited in Abi-Saab, D'Souza, Moghaddam & Krystal, 1998). It also aimed to expand the literature regarding the potential long-term effects of ketamine use, so as to inform the ketamine using population.

The current study intended to explore the presence of basic symptoms in a sample of frequent and infrequent ketamine users in comparison with healthy controls. The use of an assessment tool which examines basic symptoms ensured a high level of sensitivity and selectivity for pre-psychotic symptomatology, which other chronic ketamine studies have not used. Given the previous research on chronic ketamine use, the central focus of this study was on the psychotomimetic effects of ketamine. Although dissociation is not a symptom specific to the psychoses, it occurs under ketamine use. Therefore, a measure of dissociation was included. A standard scale was also used to monitor mood. Effects on cognition were also of interest, given the cognitive deficits widely observed during the pre-psychotic state. Cognitive assessments were selected so as to examine cognitive systems reliably observed as impaired in participants deemed to be in the pre-psychotic state, including verbal episodic memory, verbal executive functioning and working memory (Niendam et al., 2006, 2007; Eastvold, Heaton, & Cadenhead, 2007; Pukrop et al., 2007).

On the basis of previous acute and chronic ketamine studies, the following predictions were made:

Subjective effects

1) It is predicted that ketamine users will display higher levels of psychotic-like symptomatology, psychotic proneness and delusional ideation in comparison to controls (Curran & Morgan, 2000; Morgan et al., 2004b; Uhlhaas et al., 2007). It is also hypothesised that frequent ketamine users will show higher levels than infrequent users.

2) Based upon Curran and Morgan (2001), Morgan et al. (2004b, 2004c) and Morgan et al. (2006), it is hypothesised there will be no group differences in level of dissociative symptomatology.

Cognitive effects

1) Executive functioning: Ketamine users will show more deficits in category fluency compared with controls, but no difference in verbal fluency (Curran & Morgan, 2000; Morgan et al., 2004d). Category fluency will be more impaired in frequent ketamine users compared with infrequent users (Curran & Monaghan, 2001).

2) Episodic memory: Prose recall will be more impaired in frequent compared with infrequent ketamine users, who in turn will be more impaired than controls (Curran & Morgan, 2000; Curran & Monaghan, 2001).

3) Working memory: As no study with recreational ketamine users has used digit span as a measure of working memory, this aspect of the present research is exploratory. It is tentatively hypothesised that if chronic ketamine use provides a model of the psychoses, then manipulation rather than maintenance of information in working memory will be selectively impaired (Morgan & Curran, 2006), as is the

general finding with individuals with psychoses (Kim, Glahn, Nuechterlein & Cannon, 2004; Perry et al., 2001).

METHOD

Power calculation

The power calculation was based upon prose recall results (means and SD) reported by Curran and Monaghan (2001), who compared frequent ketamine users with infrequent ketamine users. Statistical power analyses using a programme located at http://www.dssresearch.com estimated a sample of 18 participants per group, in order to gain statistically significant findings at a power level of 0.90, with an alpha level of 1%. This number of participants is in line with previous ketamine studies completed by the Curran & Morgan UCL consortium.

Participants and Design

A between-subjects design was utilised to compare frequent ketamine users, infrequent ketamine users and controls who reported no illicit drug use. Participants were recruited through advertisement and via snowball sampling (Solowij, Hall & Lee, 1992). Participants were paid for their participation and all completed a written, informed consent form. The inclusion criteria were: aged 18-50 years, native English speakers or fluent in English as a second language. Infrequent ketamine use was defined as use of ketamine between 3-12 days in a month; frequent ketamine use as every day.

Joint thesis

This thesis was part of a joint project, completed alongside 2 fellow trainee clinical psychologists, Suzanna Hunt (UCL: Prodromal symptoms in daily skunk users) and Lisa Monaghan (Royal Holloway: Chronic Cocaine use and prodromal symptoms of schizophrenia). See Appendix 1 for details of the contribution made by each trainee.

Ethics

The study was approved by the UCL Graduate School Ethics Committee (See Appendix 2).

Procedure

On the testing day participants were again provided with a volunteer information sheet to read (See Appendix 3) and were then asked to give written, informed consent (See Appendix 4 for consent form). Then they gave details of their current and historical drug use and only ketamine using participants answered further questions specifically about their ketamine use.

Assessments

Tests were selected to assess a range of human memory functions, dissociative and psychotogenic symptoms, and mood effects. Tests were administered in the following order: DES, The Spot-the-Word Test, Short O-LIFE, BDI, prose recall immediate, phonological fluency, semantic fluency, prose recall delayed, PDI, LES, Digit Span. Prose recall was delayed by 15 minutes. This delay was filled with the fluency tasks listed above and another cognitive assessment not reported in this paper. Order of testing was the same for each participant.

Semi-structured Interview - Symptomatology Assessment

Schizophrenia Prediction Instrument – Adult Version (SPI-A; Schultze-Lutter, Klosterkötter & Addington, unpublished). Pre-psychotic symptomatology was assessed using the SPI-A. This assessment was chosen in order to provide a clinical index of symptomatology. Interrater reliability was established through the development of a semi-structured interview schedule (See Appendix 5), based upon the SPI-A manual (Schultze-Lutter et al., unpublished). The trainee clinical psychologists who developed the interview schedule (SD, SH, and LM) practised completing the schedule with each other and piloted the schedule with drug users, in order to improve reliability. Furthermore, SPI-A item self-rating cards were developed for participants, to improve rating reliability (See Appendix 6). However formal assessment of interrater reliability was not conducted.

The SPI-A was developed from a hierarchical cluster analysis of the Bonn Scale for the Assessment of Basic Symptoms (BSABS; Gross, Huber, Klosterkötter & Linz, 1987). It comprises 7 subscales (A-F, & O):

A) Affective-Dynamic Disturbances (experiences associated with changes in mood and emotional responsiveness).

B) Cognitive-Attentional Impediments (experiences such as reduced concentration and attention, and increased distraction).

C) Cognitive disturbances (experiences associated with unusual thought processes and language disruption).

D) Disturbances in Experiencing Self & Surroundings (experiences such as emotional confusion, thought pressure and unstable ideas of reference).

E) Body Perception Disturbances (experiences associated with strange or unusual bodily sensations).

F) Perception Disturbances (experiences associated with visual and acoustic perceptual alteration).

O) Optional Extras (a range of items chosen from a potential list of 11 items to include pre-psychotic symptomatology suggested to be that most predictive of transition to fully-manifest psychotic symptomatology by Klosterkötter et al., 2001).

Sample items from these subscales of the SPI-A include:

A: Impaired tolerance to certain social everyday situations, and Decrease in positive emotional responsiveness towards others.

B: Feeling overly distracted by stimuli, and Slowed-down thinking.

C: Thought interference, Thought blockages and Disturbances in expressive speech.

D: Decreased ability to discriminate between different kinds of emotions and Unstable ideas of reference.

E: Bodily sensations of numbness and stiffness and Bodily sensations of being electrified.

F: Hypersensitivity to light / optic stimuli and Hypersensitivity to sounds / noise.

O: Thought perseveration, Decreased ability to discriminate between ideas and perception, pure fantasy and true memories, Captivation of attention by details of the visual field, Derealisation and Motor blockages.

In total, it featured 34 main items (within subscales A-F), and 5 Optional Extra items. Each item could be rated a score between 0 (absent) and 6 (extreme). Three

SPI-A subscales contained 5 items (A, D, O), and four subscales contained 6 items (B, C, E, F). Total SPI-A subscale scores were calculated by summing the individual scores for each subscale, and then summing the subscale scores. The maximum total SPI-A score was 234 points. Prior to undertaking the SPI-A interview, ketamine users were instructed to rate *only* subjective day-to-day experiences (i.e. chronic effects of ketamine), not intoxicated experiences resulting from acute effects of the drug. Participants were also informed to *only* rate experiences that had developed since they started using ketamine and experiences that had *changed* since starting ketamine. An SPI-A score sheet was created for recording results (Appendix 7).

Subjective rating scales

Dissociative Experiences Scale (DES: Bernstein & Putnam, 1986). This subjectively rated, 28-item measure is designed to index trait dissociation ranging from everyday experiences (e.g. riding in a car and not remembering all the trip), to more pathological experiences (e.g. standing outside your body watching yourself). It was decided to assess dissociation as it is commonly observed in the psychoses, despite not being necessary or specific for a DSM or ICD diagnosis of psychotic disorder. Acute ketamine studies have indicated that acute ketamine reliably induces dissociation, and it was therefore deemed useful to look at whether such symptomatology was present in chronic ketamine users. Sample items include:

- Some people find that sometimes they are listening to someone talk and they suddenly realise they did not hear part or all of what was said.
- Some people are told that they sometimes do not recognise friends or family.

- Some people have the experience of feeling that other people, objects, and the world around them are not real.
- Some people sometime find that they hear voices inside their hear that tell them to do things or comment on things that they are doing.

For each of the 28 items, the respondent is able to score a percentage value of how much they agree with each statement. These percentage values start at 0% and finish at 100%, and are fixed at increments of 10%. A total score reflecting current dissociation is obtained by summing across all items. Therefore, the maximum total DES score is 2800.

The Spot-the-Word Test: Version B (Baddeley, Emslie & Nimmo-Smith, 1993). This test was used to estimate premorbid verbal intelligence. It was required as it is well documented that intelligence impacts upon performance on cognitive tasks. It was therefore desirable to have such a measure so that groups of participants could be matched for premorbid intelligence, and the relationship between scores on cognitive tasks and premorbid intelligence could be determined for the sample of participants in this study.

Participants were required to choose the real word from 60 pairs of words / non-words (e.g. slank-chariot, sterile-palth, grottle-strumpet, chalper-camera) by ticking the item in each pair they believed to be the real word. A total score reflecting premorbid IQ is obtained by summing all correctly identified words, therefore the maximum total score was 60. This task has been shown to give a measure of IQ that

is correlated 0.69 with the National Adult Reading Test (NART; Crawford, Dreary, Starr & Whalley, 2001).

Short Oxford-Liverpool Inventory of Feelings and Experiences Questionnaire (Mason, Claridge & Jackson, 2005). This is a self-report measure consisting of 43 items, and is based upon an analysis of what is probably the largest single dataset of schizotypal measures (Claridge et al., 1996). The measure is utilised to determine the level of 'psychosis proneness' in non-clinical samples of individuals. Psychosis proneness (Claridge, 1987) is a construct which indicates that certain individuals in the general population have similar experiences to the positive symptomatology of the psychoses, while remaining functioning members of society. This is in line with the dimensional conceptualisation of functional psychoses, which suggests that psychotic symptomatology is the severe expression of a disposition to the psychoses, which is present throughout the general population. This assessment was chosen in order to provide a general population index of psychotic-like markers. The O-LIFE has high internal consistency (Mason et al., 1995) and test-retest reliability (Burch, Steel & Hemsley, 1998).

Sample items of included in the Short O-LIFE include:

- Are you easily confused if too much happens at the same time?
- Do you think you could learn to read other's minds if you wanted to?
- Can some people make you aware of them just by thinking about you?
- Have you ever felt the urge to injure yourself?
- Are your thoughts sometimes so strong that you can almost hear them?
- Do you feel very close to your friends?

For each item the participant responds either yes or no. To score the items, a value of 1 is given to yes responses, and a value of 0 to no responses, for the majority of items. For items 4, 9, 17, 27, 30, 37, 39, 41 (reverse items) scoring is reversed. To obtain the total O-LIFE score, all item scores are summed. The Short O-LIFE consists of four subscales. These are attained by grouping scores for specific items, as follows:

1) Unusual Experiences subscale (representative of positive psychotic-like symptomatology akin to hallucinatory and delusional experiences): 12 items (3, 5, 6, 8, 10, 13, 19, 23, 26, 29, 34, 35).

2) Cognitive Disorganisation subscale (conceptualised as disorganised psychotic-like symptomatology relating to thought disorder-like experiences and attentional difficulties): 11 items (1, 7, 12, 16, 20, 24, 31, 33, 36, 38, 42).

3) Introvertive Anhedonia subscale (representative of negative psychotic-like symptomatology, and concerned with the inability to derive pleasure from experiences): 10 items (4, 11, 15, 17, 22, 25, 27, 30, 32, 41).

4) Impulsive Nonconformity subscale (index of impulsivity and risk-taking behaviour): 10 items (2, 9, 14, 18, 21, 28, 37, 39, 40, 43).

The first three factors are comparable to the three factor model of the psychoses proposed by Liddle (1987); Unusual Experiences, Cognitive Disorganisation, Introvertive Anhedonia. The fourth factor, Impulsive Nonconformity, is based on Eysenck's Psychoticism scale (Eysenck & Eysenck, 1975) and is the least well related to psychosis proneness. Subscale scores are obtained by summing the scores for items within that subscale.

The Beck Depression Inventory (BDI-II: Beck, Steer, & Brown, 1996). The BDI-II is a 21-item self-report instrument intended to assess the existence and severity of symptoms of depression as listed in the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV: APA, 1994). A measure of symptoms of depression was required as it is well documented that low mood impacts upon performance on cognitive tasks. It was therefore desirable to have such a measure so that the relationship between mood and scores on cognitive tasks could be determined for the sample of participants in this study.

The instrument requires participants to rate themselves on measures of sadness, pessimism, past failure, loss of pleasure, guilty feelings, punishment, self-dislike, self-criticalness, suicidal thoughts or wishes, crying, agitation, loss of interest, indecisiveness, worthlessness, loss of energy, changes in sleeping pattern, irritability, changes in appetite, concentration difficulty, tiredness and/or fatigue, and loss of interest in sex. For each item participants have a choice of 4 optional Likert-scale responses, scored from 0 (item is not applicable) to 3 (severe). For example for the first item sadness response options are:

(0) I do not feel sad

(1) I feel sad much of the time

(2) I am sad all the time

(3) I am so sad or unhappy that I can't stand it

A total score reflecting severity of depression is obtained by summing across all BDI items, so that the maximum total score is 63. In addition, the Inventory entails two subscales: the Cognitive subscale (8 items: pessimism, past failures, guilty

feelings, punishment, self-dislike, self-criticalness, suicidal thoughts or wishes, and worthlessness) and the Somatic subscale (13 items: sadness, loss of pleasure, crying, agitation, loss of interest, indecisiveness, loss of energy, changes in sleep pattern, irritability, change in appetite, concentration difficulty, tiredness and/or fatigue, and loss of interest in sex). The total subscale scores are calculated by adding individual item scores specific to that subscale.

Peters Delusion Inventory (Peters, Joseph & Garety, 1999). This self-report inventory is designed to assess delusional ideation in the general population. A measure of delusional ideation was required because the study aimed to investigate the ability of chronic ketamine to model symptomatology characteristic of the pre-psychotic state, in which delusional ideation is observed. The PDI is a 21-item measure, which includes items such as:

- Do you ever feel as if things in magazines or on TV were written especially for you?
- Do you ever feel as if you were being persecuted in some way?
- Do you ever feel that you are a very special or unusual person?
- Do you ever feel as if the world is about to end?

Participants answer 'yes' if they have experienced the thought or belief described. A total PDI score is then calculated by summing the number of 'yes' responses. Furthermore, if participants answer yes to an item, they then also rate the degree of distress this thought or belief induces (on a 1-5 Likert-scale where 1= not at all distressing, and 5= very distressing), and their level of preoccupation with (on a 1-5 Likert-scale where 1= hardly ever think about it, and 5= all the time), and

conviction in (on a 1-5 Likert-scale where 1= don't believe it's true, and 5= absolutely true) the thought or belief the experience. A total 'Distress' score is calculated by summing the distress ratings and dividing this score by the number of items to which the participant responded yes. A total 'Preoccupation' score is calculated by summing the preoccupation ratings and dividing this score by the number of items to which the participant responded yes. A total 'Conviction' score is calculated by summing the conviction ratings and dividing this score by the number of items to which the participant responded yes.

The Life Experiences Survey (LES: Sarason, Johnson & Siegel, 1978). This questionnaire assesses the number of significant life experiences (both positive and negative) encountered by participants in the 12-month period prior to testing, and their severity. This measure was chosen as it is widely recognised that stressful life events can precipitate the development of fully-manifest psychotic symptomatology, and changes in mood. It was therefore deemed necessary to explore whether life events in the preceding 12 months were significantly related to SPI-A and BDI-II scores.

The participant responds by rating the severity of relevant life events, from a list of 43 items, using a seven point Likert scale (where –3= 'Extremely negative', and +3= 'Extremely positive').

Sample items from the survey include:

- Marriage
- Death of a spouse

- Major change in distance form family (increased or decreased)

- Major personal illness or injury

There are 3 open-ended items at the end of the questionnaire for the participant to include and rate the severity of additional life experiences which may have occurred in the last 12 months, but which are not in the main body of the survey.

Four scores can be derived from the LES:

1) Number of negative life events: sum the total number of negative life events responded to.

2) Number of positive life events: sum the total number of positive life events responded to.

3) Mean rating of negative life events: sum the severity scores for all the negative life events (removing any negative signs), and divide this total by the number of negative life events responded to.

4) Mean rating of positive life events: sum the severity scores for all the positive life events (removing any negative signs), and divide this total by the number of positive life events responded to.

Cognitive Tasks

Cognitive tasks were selected so as to examine cognitive systems reliably observed as impaired in participants deemed to be in the pre-psychotic state, including verbal episodic memory, verbal executive functioning and working memory (Niendam et al., 2006, 2007; Eastvold, Heaton, & Cadenhead, 2007; Pukrop et al., 2007).

Episodic Memory

Prose recall

Prose recall was chosen to measure episodic memory because there is much previous research with acute ketamine users utilising this measure so findings could be directly compared, and it has been found to provide the best laboratory test predictor of everyday memory performance (Sunderland, Watts, Baddeley & Harris, 1986). Participants were played a taped passage of prose from the Rivermead Behavioural Memory Battery (RBMB: Wilson, Cockburn & Baddeley, 1985), and were then required to verbally recall it (i) immediately and (ii) after a 15-minute delay, filled with other cognitive assessments. Recall was scored in terms of 'idea units' recalled, with one point for each exact synonym and half a point for incomplete recall or a close synonym (maximum score is 21).

Executive functioning

Fluency

Phonological and semantic fluency tasks were chosen as simple and quick measures of frontal lobe function and to tap retrieval from semantic memory. In phonological fluency, participants were given a single letter prompt (i.e. F) and required to generate as many words beginning with that letter in 60 seconds (excluding proper nouns and many words beginning with the same prefix). In semantic fluency, participants were provided with a super-ordinate category member (i.e. musical instruments) and asked to generate as many members of that category as possible again in 60 seconds. The number of correct exemplars and number of errors were recorded for both fluency tasks. Verbal and category fluency total scores were

calculated by summing the number of correct responses. Error scores were calculated by summing the total number of errors for each task separately.

Working Memory

Digit Span Forwards (Version A)

Digit span was used to measure working memory because it is a quick measure that would not fatigue participants greatly, given the previous amount of work they had undertaken. It was also chosen because it provided a way to differentiate the ability to maintain information in working memory from the ability to manipulate information, a pattern of impairment reliably observed in the psychoses literature (Fletcher & Honey, 2006).

Participants were presented with number strings of increasing length, which they had to memorise and immediately verbally repeat (e.g. 8-2-9, 3-8-4-7-5-1-6). Digit span forwards total score was calculated by summing the number of number strings the participant recalled correctly. This task taps the phonological loop component of working memory (Baddeley, 2000), which is involved in rehearsal and temporary maintenance of auditory verbal information.

Digit Span Backwards (Version A)

Participants were again presented with number strings of increasing length, which they had to memorise, and immediately verbally repeat *in reverse order*. Digit span backwards total score was calculated by summing the number of number strings the participant recalled correctly. This task taps the central executive component of working memory (Baddeley, 2000), which is suggested to be a limited-capacity

supervisory attentional mechanism (Shallice, 1982), responsible for the maintenance and manipulation of information.

Statistical Analyses

All statistical analyses were performed using Statistical Package for Social Sciences (SPPS Version 11.5). Group differences were examined using one-way ANOVAs and, where data were nonparametric, the Kruskall-Wallis test. Bonferroni post hoc tests and Bonferroni corrected Mann-Whitney U tests were used to explore simple effects where a significant effect of group was revealed. Independant samples t-tests and, where data were nonparametric, Mann-Whitney U tests were used to compare ketamine groups on ketamine use variables and general drug use variables. Chi-squared tests were used to explore dichotomous data. The prose recall immediate and delayed data were analysed using 3×2 repeated measures analyses of variance (RMANOVA) with delay (immediate, delayed) as the within-subjects factor and group (control, infrequent ketamine, frequent ketamine) as the between-subject factor. Post-hoc comparisons (simple effects) were again Bonferroni corrected.

Correlations (one-tailed) were conducted using Spearman's rank order correlation, and all correlations conducted were hypothesis driven. Correlations were only conducted on measures showing significant group differences to minimise the chance of Type I errors. Correlations were conducted within each of the two ketamine groups for degree of ketamine use and SPI-A total and subscale scores, and DES total scores. Within each of the two ketamine groups SPI-A total and subscale scores were also correlated with BDI, Digit Span backwards, and BDI total scores were correlated with negative life events on the LES. Where no significant

differences between frequent and infrequent ketamine users were obtained, correlations were conducted across both ketamine groups. To minimise Type I error, the α-level for correlations was set at 0.01.

RESULTS

1. Demographics & reported drug use (Tables 1, 2 & 3)

There were 61 participants in total: 20 infrequent ketamine users (ten females), 21 frequent ketamine users (nine females), and 20 non-drug using control participants (seven females). The respective numbers of individuals of different ethnicity in the infrequent / frequent ketamine user groups, and non-drug using control participants were; Asian (0/0/3), Black British (0/0/1), White British (13/13/13), White Other (4/8/2), Other – mixed race (3/0/1). Two participants were Italian by birth, and one Eastern European. There were no significant group differences in gender or ethnic background (comparing White British with Other ethnic background). The highest level of educational qualification attained by infrequent / frequent ketamine user groups, and non-drug using control participants respectively were; GCSEs (2/7/4), College diploma / NVQ (1/6/0), AS/A levels (3/3/7), Undergraduate degree (11/3/7), Diploma of higher education (3/2/0), Masters (0/0/2). The current employment status of infrequent / frequent ketamine user groups, and non-drug using control participants respectively was: Unemployed (4/8/2), Employed (12/10/18), Student (4/3/0).

The three groups did not differ in age but did differ in pre-morbid IQ ($\chi 2 = 7$, $P = 0.03$), although Bonferroni corrected Mann-Whitney U tests showed no differences between any 2 groups.

Groups differed in BDI total score ($\chi 2 = 23.19$, $P < 0.001$), BDI Somatic subscale score ($\chi 2 = 23.38$, $P < 0.001$), and BDI Cognitive subscale score ($\chi 2 = 18.2$, $P < 0.001$). Frequent ketamine users scored higher on all 3 BDI scales than both infrequent ketamine users (BDI Overall & Somatic: $P < 0.001$; BDI Cognitive: $P = 0.002$) and controls ($P < 0.001$). In the frequent ketamine user group, 14 individuals were found to have clinically significant levels of depression (BDI depression category: 6 'mild', 3 'moderate', 5 'severe').

There were no differences in the number of positive life experiences encountered by participants in the year prior to testing. However differences were found between groups for the degree of positivity of the positive experiences encountered ($F(2, 57) = 6.43$, $P = 0.003$), reflecting positive life experiences of frequent ketamine users being rated as significantly less positive than those of the controls ($P = 0.002$). There was a statistically significant difference identified in the number of negative life experiences encountered by participants in the year prior to testing ($\chi 2 = 20.42$, $P < 0.001$), due to the frequent ketamine users experiencing more negative events than both infrequent ketamine users and controls (both $P < 0.001$). Group differences were found for the degree of negativity of the negative life experiences encountered ($F(2, 57) = 5.5$, $P = 0.007$), reflecting higher negativity ratings by frequent ketamine users compared with controls ($P = 0.005$).

Table 1. Group means (sd) for demographics.

	Controls	Infrequent Ketamine users	Frequent Ketamine users
Age (yrs)	28.05 (7.39)	25.05 (4.35)	24.80 (7.49)
Spot the word test score (no. correct)	48.95 (5.53)	48.50 (3.46)	44.48 (6.30)
BDI total	**5.50 (8.09)**	**7.20 (4.80)** [b]	**19.14 (10.65)** [a]
BDI Somatic	**3.70 (5.03)**	**4.85 (3.25)** [b]	**12.67 (6.44)** [a]
BDI Cognitive	**1.80 (3.50)**	**2.35 (1.84)** [b]	**6.48 (4.75)** [a]
Number of positive life events (LES)	4.50 (2.72)	4.35 (2.70)	3.90 (2.61)
Number of negative life events (LES)	**1.65 (2.18)**	**2.35 (2.48)** [b]	**7.00 (4.47)** [a]
Mean rating of positive life event (LES)	**2.37 (0.70)**	**1.86 (0.65)**	**1.52 (0.88)** [c]
Mean rating of negative life event (LES)	**0.97 (1.08)**	**1.34 (0.96)**	**1.93 (0.71)** [a]

a = F > C, b = F > InF, c = F < C (using Bonferroni corrected p values)

There were no differences in the number of years of regular ketamine use but, as expected, frequent ketamine users were found to ingest ketamine significantly more often than infrequent ketamine users, used significantly higher amounts in a typical session and rated themselves as significantly more concerned about their ketamine use on the Severity of Dependence scale (Table 2).

Table 2. Mean (sd) of ketamine use variables in the infrequent (n = 20) and frequent ketamine users (n = 21).

	Infrequent ketamine users	Frequent ketamine users	t_{39}	p
Years of regular ketamine use	5.33 (3.36)	5.62 (3.39)	-0.28	0.78
Number of days used ketamine in typical month	5.60 (2.41)	30.00 (0)***	-45.19	<0.001
Amount ketamine used in a typical session (g)	1.44 (1.54)	3.30 (2.07)**	-3.24	0.002
Severity of ketamine dependence score	1.60 (1.79)	7.86 (3.8)***	-6.80	<0.001

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

In terms of frequency of mixing ketamine with other recreational drugs, in the infrequent / frequent ketamine user groups, respective numbers of 'Sometimes mixed' were 7/7, 'Often mixed' were 4/5, 'Always mixed' were 6/4.

Table 3. Mean (sd) of other drug use in the infrequent (n = 20) and frequent ketamine users (n = 21).

	% regular drug use		Years of drug use		No. of days used per month	
	Infrequent K	Frequent K	Infrequent K	Frequent K	Infrequent K	Frequent K
Alcohol	75%	66.7%	9.23 (4.04)	8.96 (4.73)	13.53 (8.67)	19.07 (9.68)
Tobacco	90%	76.2%	10.58 (5.34)	10.81 (7.43)	26.61 (8.02)	29.25 (1.73)
Cannabis	60%	47.6%	8.54 (6.07)	10.25 (8.26)	8.67 (7.71)	18.33 (12.11)
MDMA	35%	14.3%	5.21 (3.81)	5.00 (1.73)	2.86 (2.27)	5.00 (4.58)
Amphetamine	10%	9.5%	11.50 (4.95)	4.50 (2.12)	4.00 (0)	10.00 (7.07)
LSD/Hallgn	15%	9.5%	4.83 (6.25)	9.00 (5.66)	2.67 (1.15)	5.50 (0.71)
Cocaine	35%	33.3%	7.00 (2.83)	7.29 (3.30)	4.71 (1.80)	10.00 (4.28)
Benzodiazepine:	5%	38.1%	2.00 (0)	1.78 (1.46)	6.00 (0)	13.13 (7.12)

There were no significant differences in the numbers in each ketamine user group who rated themselves as regular users or not of alcohol, tobacco, cannabis and cocaine. For these recreational drugs, there were no differences in years used, days per month or the amount taken.

The control group reported regular use of alcohol (75% of participants; 12.8 ± 6.38 days used in a typical month) and tobacco (25% of participants; 30 ± 0 days used in a typical month). Subjective reports of general drug use were verified with urinanalysis for 56 participants across the groups (urinanalysis unattained: 2 frequent and 3 infrequent ketamine users).

2. Subjective effects

SPI-A (Table 4)

There was a significant main effect of group on SPI-A total scores and all SPI-A subscale scores (A-F and O). These main effects reflected a dose-dependant effect, where frequent ketamine users scored higher than infrequent users, who in turn scored higher than controls for SPI-A total score and all subscale scores, apart from subscale D (Figure 1 and Table 5). For subscale D, the scores of the infrequent ketamine users did not differ from controls.

Table 4. Mean (sd) of SPI-A total and subscale scores (A-F & O) in the infrequent ketamine user (n = 20), frequent ketamine user (n = 21) and control (n = 20) groups.

	Group		
	Controls	Infrequent Ketamine	Frequent Ketamine
SPI-A Total & Subscales			
SPI-A Total Score	10.05 (12.28)	32.70 (17.10)	92.67 (27.86) [a]
SPI-A: A	1.70 (4.18)	4.00 (4.79)	17.48 (6.68) [a]
SPI-A: B	1.40 (1.96)	8.20 (7.14)	16.19 (5.76) [a]
SPI-A: C	2.35 (2.89)	7.85 (4.31)	18.67 (5.65) [a]
SPI-A: D	1.90 (2.63)	2.35 (2.76) [c]	9.52 (6.55) [b]
SPI-A: E	0.20 (0.89)	2.05 (2.80)	5.76 (4.57) [a]
SPI-A: F	1.15 (2.66)	4.30 (3.33)	12.19 (7.72) [a]
SPI-A: O	1.35 (1.87)	5.45 (4.15)	12.76 (4.61) [a]

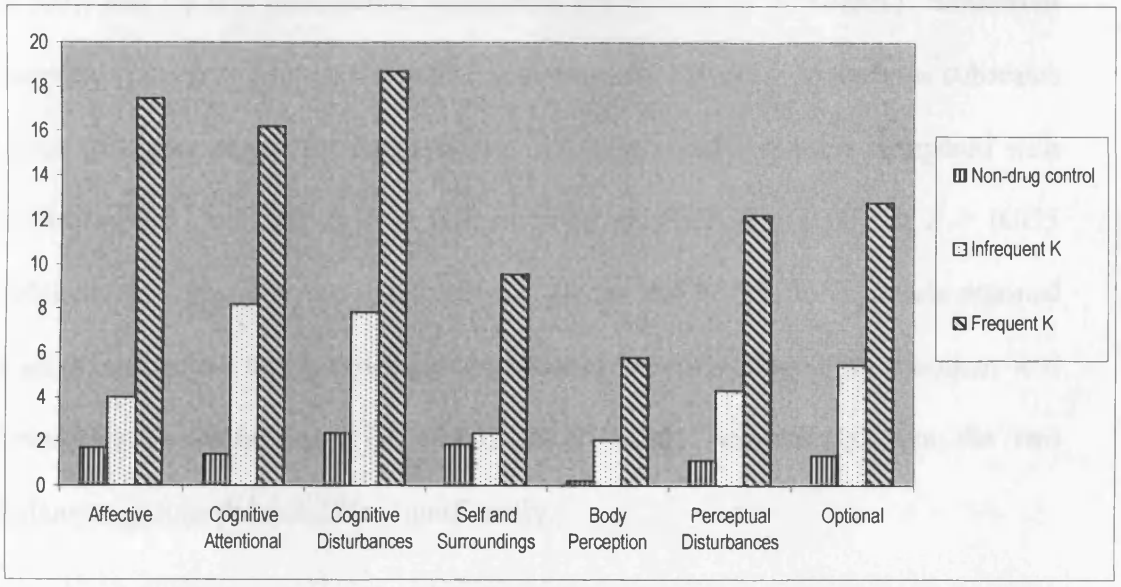
a = F > InF > C, b = F > C, c = F > InF (using Bonferroni corrected p values)

Table 5. Mean (sd) of SPI-A total and subscale scores (A-F & O) in the infrequent ketamine user (n = 20), frequent ketamine user (n = 21) and control (n = 20) groups.

	Statistical values			
SPI-A Total & Subscales	Group Main Effect	F > InF	F > C	InF > C
SPI-A Total Score	$\chi2$ = 45.99***	U = 11.5***	U = 1.0***	U = 50.0***
SPI-A: Affective (A)	$\chi2$ = 110.0***	U = 20.5***	U = 10.5***	U = 110.0*
SPI-A: Cognitive-Attentional (B)	$\chi2$ = 36.49***	U = 77.5**	U = 3.0***	U = 65.0***
SPI-A: Cognitive Disturbances (C)	$\chi2$ = 42.64***	U = 32.5***	U = 2.0***	U = 55.0***
SPI-A: Self and Surroundings (D)	$\chi2$ = 22.25***	U = 62.5***	U = 54.0***	
SPI-A: Body Perception (E)	$\chi2$ = 30.38***	U = 93.5**	U = 18.5***	U = 119.0**
SPI-A: Perceptual Disturbances (F)	$\chi2$ = 24.85***	U = 88.0**	U = 49.5***	U = 90.5**
SPI-A: Optional Extras (O)	$\chi2$ = 38.36***	U = 51.5***	U = 3.0***	U = 75.0***

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ (Bonferroni corrected p values)

Figure 1. SPI-A mean scores for all subscales, for the frequent ketamine, infrequent ketamine and control groups. (note: maximum scores for subscales A, D, O = 30 & for subscales B, C, E, F = 36).



O-LIFE (Table 6)

Table 6. Mean (sd) of O-LIFE total and subscale scores (A-F & O) in the infrequent ($n = 20$), frequent ketamine users ($n = 21$) and controls ($n = 20$).

	Group		
	Controls	Infrequent Ketamine	Frequent Ketamine
OLIFE Total & Subscales			
Total score	9.50 (7.18)	17.65 (6.51)	20.29 (9.30) [a]
Unusual Experiences	2.40 (2.33)	5.20 (2.89)	6.67 (3.51) [a]
Cognitive Distortions	3.70 (2.70)	6.40 (3.22)	6.86 (3.79) [a]
Introvertive Anhedonia	4.60 (1.60)	1.05 (1.10)	2.14 (1.77) [b]
Impulsive Nonconformity	4.50 (1.19)	5.05 (2.11)	4.52 (1.83)

a = F > C & InF > C, b = F < C & InF < C (using Bonferroni corrected p values)

There was a main effect of group ($F_{2,58} = 10.6$, $P < 0.001$) for OLIFE total score. This reflects higher OLIFE total scores in frequent ($P < 0.001$) and infrequent ketamine users ($P = 0.005$), compared with controls. However there were no significant differences between the two ketamine groups for OLIFE total score. There were main effects of group on three OLIFE subscale scores: Unusual Experiences ($F_{2,58} = 10.92$, $P<0.001$), Cognitive Disorganisation ($F_{2,58} = 5.5$, $P = 0.007$), and OLIFE Introvertive Anhedonia ($F_{2,58} = 28.59$, $P < 0.001$). Bonferroni corrected post hoc tests on Unusual Experiences & Cognitive Distortions subscales revealed higher scores for frequent and infrequent ketamine users compared with controls (UE: $P < 0.001$ & $P = 0.01$ respectively; CD: $P = 0.009$ & $P = 0.035$ respectively), however the two ketamine groups did not differ. Controls attained higher scores on the Introvertive Anhedonia subscale than both frequent and infrequent ketamine users ($P < 0.001$ & $P < 0.001$ respectively), but the two ketamine groups did not differ significantly.

Delusional ideation & Dissociation (Table 7)

Table 7. Group means (sd) for delusional ideation & dissociation.

	Controls	Infrequent Ketamine users	Frequent Ketamine users
PDI 'Yes' score	**3.28 (2.59)**	**7.35 (3.53) [c]**	**9.80 (5.50) [a]**
PDI 'Distress' score	2.54 (1.65)	1.85 (0.56)	2.36 (0.94)
PDI 'Preoccupation' score	2.01 (1.33)	2.24 (0.56)	2.55 (0.98)
PDI 'Conviction' score	3.09 (1.75)	3.06 (0.55)	3.00 (0.89)
DES score	**291.50 (225.98)**	**492.00 (357.91) [b]**	**1028.10 (491.87) [a]**

a = F > C, b = F > InF, c = F < C (using Bonferroni corrected p values)

Kruskal-Wallis tests indicated highly significant group differences in the number of 'Yes' items responded to on the PDI ($\chi 2 = 18.2$, $P < 0.001$). This was due to both frequent ketamine users and infrequent ketamine users responding 'Yes' to more PDI items than controls (Frequent: U = 54.5, $P < 0.001$; Infrequent: U = 61, $P < 0.001$). No differences emerged in the PDI Preoccupation, Distress and Conviction scores.

There were also group differences in DES score ($\chi 2 = 23.74$, $P < 0.001$), reflecting higher scores of frequent ketamine users than infrequent ketamine users (U = 84, $P = 0.001$) and controls (U = 36, $P < 0.001$).

3. Cognitive Assessments (Table 8)

Episodic memory

RMANOVA showed highly significant main effects of group ($F_{(2,58)} = 6.7$, $P = 0.002$), and delay on prose recall scores ($F_{(1,58)} = 50.12$, $P < 0.001$), but no interaction. As seen in Table 7, controls had higher recall scores than both frequent

(P = 0.008) and infrequent ketamine users (P = 0.007); overall immediate recall was better than delayed recall (Figure 2).

Table 8. Mean (sd) scores on cognitive tasks of infrequent ketamine users (n = 20), frequent ketamine users (n = 21) and controls (n = 20).

	Group		
	Controls	Infrequent K users	Frequent K users
Prose recall immediate	**8.40 (3.06)**	**5.48 (2.99)** [b]	**5.71 (2.38)** [a]
Prose recall delayed	**7.35 (3.3)**	**4.68 (2.95)** [b]	**4.60 (2.1)** [a]
Digit span forwards	10.30 (2.34)	9.25 (2.61)	8.57 (2.44)
Digit span backwards	**7.45 (2.82)**	**5.15 (1.98)** [b]	**4.71 (2.08)** [a]
Verbal fluency total	19.10 (7.63)	14.65 (2.98)	13.14 (4.07)
Category fluency total	18.95 (7.01)	17.35 (3.03)	14.71 (4.56)

a = F < C, b = InF < C (using Bonferroni corrected p values)

Pre-morbid IQ (assessed by 'spot the word' test) was a significant covariate for prose recall scores (p = 0.004), however covarying prose recall for pre-morbid IQ did not affect the outcome of the analysis and group differences remained highly significant ($F_{(2,57)}$ = 5.67, p = 0.006). BDI total score was not a significant covariate for prose recall scores.

Working memory

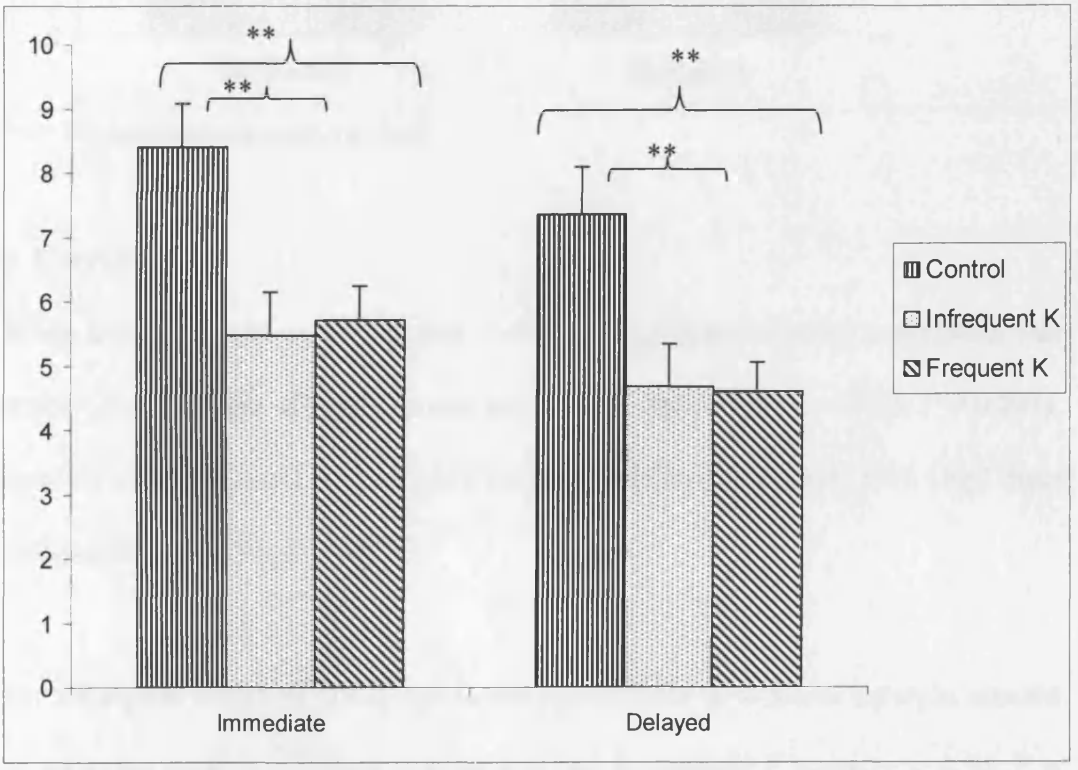
There were no group differences in digit span forwards. Significant group differences in digit span backwards ($F_{(2,58)}$ = 43.76, P = 0.001) reflected higher scores for controls, compared with both frequent (P = 0.001) and infrequent (P = 0.008) ketamine users. Frequent and infrequent ketamine users did not differ from one another (Figure 3).

Executive functioning

Verbal fluency: Group differences were found for verbal fluency total score ($\chi 2$ = 7.3, P = 0.026). No specific differences emerged between any 2 groups (Figure 4). Errors were at floor level.

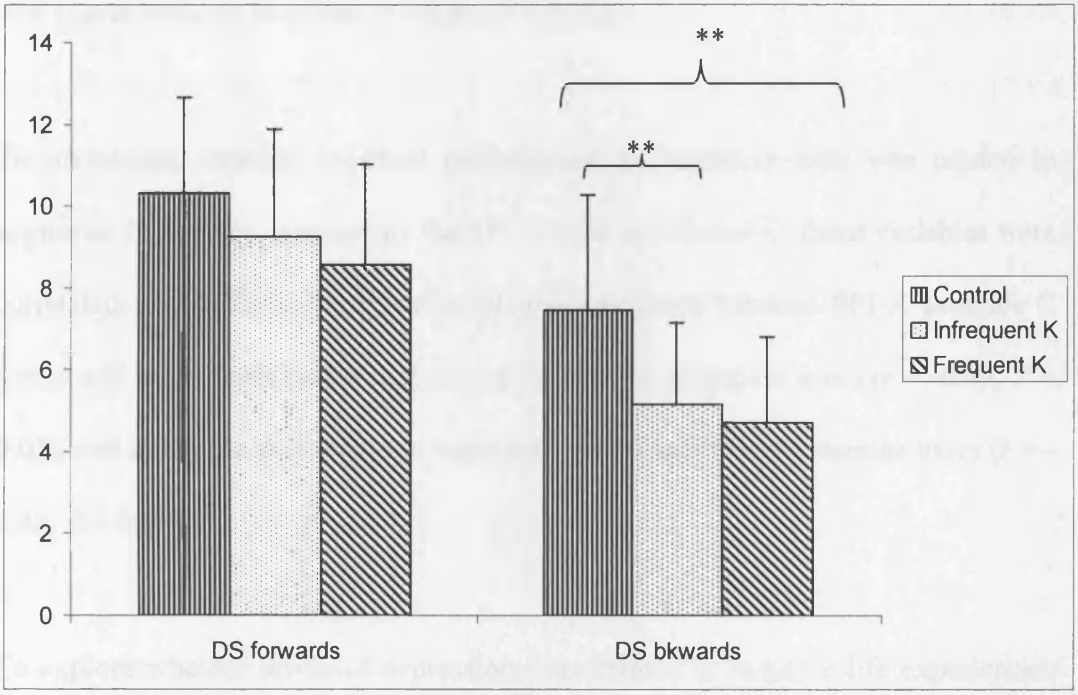
Category fluency: There was no group effect identified for category fluency total score (Figure 4) and errors were again at floor level.

Figure 2. Immediate and delayed prose recall mean scores for control, infrequent ketamine and frequent ketamine groups. Bars represent standard errors.



** $P < 0.01$ (Bonferroni corrected p values)

Figure 3. Digit span forwards and backwards mean scores for control, infrequent ketamine and frequent ketamine groups. Bars represent standard errors.



** $P < 0.01$ (using Bonferroni corrected p values)

4. Correlations

When ketamine users were grouped together a significant negative correlation was found between years of ketamine use and OLIFE total score (r = -0.38, P = 0.007). Amount of ketamine used in a typical session correlated negatively with Digit Span backwards (r = -0.37, P = 0.009).

For infrequent ketamine users significant correlations were found between amount of ketamine used in a typical session and SPI-A subscale C score (r = 0.50, P = 0.012).

For frequent ketamine users only, significant correlations were found between BDI totals and SPI-A total scores ($r = 0.66$, $P = 0.001$), subscale A scores ($r = 0.63$, $P = 0.001$) and subscale B scores ($r = 0.55$, $P = 0.005$).

To investigate whether impaired performance on cognitive tests was related to cognitive difficulties assessed by the SPI-A subscales B and C, these variables were correlated. A significant negative correlation was found between SPI-A subscale C scores and Digit Span backwards scores for frequent ketamine users ($r = -0.49$, $P = 0.01$), and a trend in this direction was observed for infrequent ketamine users ($r = -0.45$, $P = 0.023$).

To explore whether levels of depression were related to negative life experiences, BDI and number of negative life experiences were correlated. A positive correlation was found between BDI total and number of negative life events for infrequent ketamine users only ($r = 0.55$, $P = 0.006$).

No significant correlations emerged between cannabis use variables and specific subjective or cognitive measures.

DISCUSSION

To the best of our knowledge, this is the first study to investigate symptomatology deemed characteristic of the pre-psychotic state in recreational ketamine users. Furthermore, it is the first study of daily users of the drug. The three groups studied were well matched for demographics, and the two ketamine groups were well matched for other drug use.

Summary of main findings

There were five main findings of the study:

a) Frequent ketamine users demonstrated a higher level of pre-psychotic symptomatology than infrequent ketamine users, with both groups demonstrating higher levels than controls. Furthermore, both groups of ketamine users experienced a higher level of psychotic proneness and delusional ideation compared with controls, but did not differ from one another on these measures.

b) Contrary to prediction, frequent ketamine users experienced higher levels of dissociation compared with infrequent ketamine users and controls.

c) In line with hypotheses, both groups of ketamine users demonstrated marked deficits on prose recall immediate and delayed tasks.

d) No specific differences emerged between any 2 groups on the verbal and category fluency tasks.

e) Both groups of ketamine users showed selective impairment in the manipulation but not maintenance of information in working memory.

Who were the ketamine participants?

The two ketamine groups had both used the drug for 5-6 years, but clearly differed in their level of use, with frequent users ingesting ketamine daily and infrequent users once or twice a week. On average, frequent users consumed 3.3g per session, a significantly higher amount than infrequent users, who consumed an average of 1.4g per session ('sessions' were reported to last between 12-72 hours). Although infrequent users reported consuming less than half the amount of ketamine reported by frequent users, both average amounts consumed are sufficient to induce marked psychotic-like symptomatology in healthy, drug-naïve volunteers (Krystal et al.,

1994; Malhotra et al., 1996; Morgan et al., 2004a; Newcomer et al., 1999a). The anaesthesia literature reports that an intravenous dose of 2mg/kg of body weight usually produces surgical anesthesia within 30 seconds after injection, with the anesthetic effect usually lasting five to ten minutes. Although the bioavailability of intra-nasally consumed ketamine is only 50%, it is apparent that both frequent and infrequent ketamine users had developed a tolerance for the drug as they were not experiencing periods of unconsciousness. In addition, although it is not known whether people may become dependant upon ketamine, the few single case reports of ketamine addiction in the literature (Hurt & Ritchie, 1994; Moore & Bostwick, 1999), and a recent larger scale study (Muetzelfeldt et al., 2008), indicate that ketamine dependency is a distinct possibility within the cohort of ketamine users. Indeed, this study found that frequent ketamine users rated themselves as significantly more concerned about their ketamine use on the Severity of Dependence scale (SDS), suggesting evidence of a higher level of dependence amongst frequent users. SDS norms for ketamine users are not available.

Subjective effects

Symptomatology characteristic of the pre-psychotic state

A 'frequency' effect was observed in the SPI-A data; frequent ketamine users reported higher overall levels of pre-psychotic symptomatology compared with infrequent users, who in turn reported higher overall levels than controls. This pattern was observed for all subscales of the SPI-A, except D (self and surroundings), where infrequent ketamine users scored in line with controls. In discussing these findings, I shall use some quotes from participants as illustrations.

Chronic ketamine use therefore appears to induce affective-dynamic disturbances (SPI-A subscale A). This category of pre-psychotic symptomatology is associated with changes in mood and emotional responsiveness, and in one's ability to tolerate stress. Most ketamine users reported more variable and extreme moods since starting ketamine, often stating they became annoyed or irritated much more easily, although some noted their mood had generally improved. For example, ketamine users said:

"My mood is more erratic. I have more ups and more downs. The frequency of highs and lows are more." (infrequent user 2)
"I'm more moody and more intolerant. I get more snappy, frowning a lot, and more annoyed easily." (frequent user 2)

Ketamine users also reported being more ambivalent towards people and pursuits, often stating they were more withdrawn and could not be bothered with things as much as before they used ketamine. For example, ketamine users said:
"I'm much more happy to sit back and watch life pass me by." (frequent user 3)
"I'm more withdrawn, I just can't be bothered anymore." (frequent user 16)
"You lose a lot of motivation and goal-direction in your life. You're satisfied with what you're doing – which is absolutely nothing." (frequent user 9)

These findings suggest chronic ketamine use mimics the attenuated negative symptomatology characteristic of the pre-psychotic state (e.g. Häfner et al., 1999; Klosterkötter et al., 1997; Tsuang et al., 2000), which very often develops months and years before fully-manifest positive symptomatology is observed. Interestingly,

it appears that chronic ketamine users were still able to derive pleasure from experiences (a loss of this ability would indicate an attenuated negative symptom), as both groups of ketamine users had lower scores on the Introvertive Anhedonia factor of the OLIFE than controls.

Related to the reported changes in mood and motivation, *frequent* users differed significantly in their levels of depression (BDI-II total scores), compared with infrequent users and controls. Indeed, of these frequent users fourteen (67%) had clinically significant levels of depression. BDI total score and SPI-A total score were significantly correlated, sharing 44% of the variance. This finding can be interpreted in two ways. Firstly, pre-psychotic symptoms may have been picked up by the BDI (e.g. problems concentrating, emotional withdrawal). Secondly, depressive symptoms may have been picked up by the SPI-A (e.g. affective changes) and may thus be responsible for group differences in levels of pre-psychotic symptomatology. The former interpretation is more probable for three reasons. Primarily, although it was not possible to covary for BDI total scores due to the non-parametric distribution of the SPI-A data, the variance shared between the variables was below 45%, indicating the SPI-A total scores were representing something other than just depressive symptomatology. In addition, a level of depressive-like symptomatology is in line with predictions that chronic ketamine use induces psychotic-like experiences, as this would include attenuated negative symptomatology. Finally, ketamine users were asked to provide accounts of *changes* since starting the drug, which would suggest the depressive-like symptomatology reported was not previously present or had significantly worsened. Although a higher number of negative life events in the year prior to testing could

account for this change, a lack of correlation for frequent ketamine users between BDI and number of negative life events (LES) does not appear to support this.

Chronic ketamine use also seemed associated with cognitive-attentional impediments and general cognitive disturbances (SPI-A subscales B & C respectively). Both groups of ketamine users experienced thought disorder-like experiences and attentional difficulties as assessed by the Cognitive Disorganisation factor of the OLIFE. Cognitive-attentional impediments refer to pre-psychotic symptomatology associated with reduced concentration and attention, and increased distraction (e.g. Cornblatt et al., 2002; Schultze-Lutter et al., 2007a), and 'slowed-down' thinking. Ketamine users often cited 'random thoughts' or 'random (external) stimuli' (e.g. patterns, colours) as the cause of the attentional changes, which mimics the pre-psychotic state where attention is drawn to what appears to the observer 'non-salient, irrelevant' environmental stimuli (Freedman & Chapman, 1973; Freedman, 1974; Hemsley, 1994; McGhie & Chapman, 1961, all cited in Corlett et al., 2006).

The cognitive disturbances seemingly induced by chronic ketamine were associated with formal thought disorder and indecisiveness. Formal thought disorder is characterised by unusual thought processes (including difficulties organising or connecting thoughts logically moment-to-moment) and the manifestation of this, termed schizophasia (includes impaired access to the lexicon, word approximation, and moving away from the intended conversational topic). Indeed, both frequent and infrequent ketamine users provided accounts of losing one's trail of thought,

either gradually or through sudden thought blockages, and an increased frequency of 'out of the blue' intrusive thoughts. For example:

"Intrusive thoughts occur – death, how the world is going. For example, I imagine how I will feel when my parents die. And then I think, where did that come from – out of the blue, but its 'full on'." (infrequent user 2)

"My thoughts tend to fade away as I go off on tangents, unless they are going at a rapid pace, then they will suddenly disappear. I try to think about what I was saying, but this stresses me out, so I'll start new thoughts." (infrequent user 3)

"I get a (thought) block, then other mad, crazy thoughts come." (frequent user 3)

These difficulties resemble thought disturbances experienced by individuals in a pre-psychotic state (Schultze-Lutter et al., 2007a). Many ketamine users also reported subsequent difficulties with expressive speech, with infrequent users tending toward milder impairments. One frequent user noted her speech could sometimes approximate 'jibberish', indicating a loss of voluntary control over speech generation, which Chaika (1990) argues is the fundamental impairment underpinning language difficulties observed in the psychoses. Although the language difficulties reported by ketamine users appear to reflect attenuated positive psychotic symptomatology, the unusual thought processes reported were not appraised negatively. Indeed, some ketamine users stated they actively enjoyed and encouraged losing their train of thought or 'going blank'.

"My mind goes blank, but in a comfortable way. I'm not bothered about thinking in that space of time. It becomes a relaxed state when it happens. Sometimes it's good to go with it, and just let go." (frequent user 11)

Only frequent users of ketamine showed disturbances in experiencing self and surroundings (SPI-A subscale D). Frequent users reported making connections between environmental stimuli or events and themselves, believing in some way they were the focus of the stimulus or event. *Some* frequent users stated they were aware the connections were not really present but enjoyed forming them. This is reminiscent of the concept of the 'happy schizotype' (McCreery & Claridge, 1995), which refers to particular groups of individuals in the general population (e.g. individuals who believe in the paranormal, members of specific new religious movements) who show similar positive psychotic-like symptomatology to that found in an exaggerated form in the idiopathic psychoses, but who are not distressed by these experiences. Other frequent users stated the formed highly improbable connections, but seemed less certain about dismissing them. For example:

"This happens all the time. I was on the tube, deciding whether to get off at Leicester Square or Holborn, and someone on the tube said Leicester Square, and I thought that was meant for me." (infrequent user 7)

"I try to connect things in my mind and somehow they do connect. I always think that something that happens has a hidden purpose that may not be showing at the time." (infrequent user 18)

"It feels like everything revolves around you – it's a bit egotistical. I could be doing something minor, like kick a can across the floor and think someone might make a face or something unrelated, but I think they're related. (frequent user 1)

"When I hear sirens, I can think they're coming to get me." (frequent user 18)

These higher subscale D scores appear similar to the unstable ideas of reference observed in the pre-psychotic state, which involves a heightened ability to form associations (between perceptions, thoughts, stimuli and events), so much so that associations are often formed where none exist (Corlett, Honey & Fletcher, 2007; Schneider, 1930).

Body perception disturbances and more general perceptual disturbances (SPI-A subscale E & F respectively) also seem to emerge as a result of chronic ketamine use. Ketamine users consistently reported medically-unexplainable brief feelings of itching, twitching and 'pins and needles' in their bodies. In the pre-psychotic literature such unusual body sensations are reliably observed (Klosterkötter et al., 1997, 2001). Furthermore, ketamine users reported increased sensitivity to light and / or noise, visual distortions (e.g. flashes, stars, flames), and changes in perceived acoustic stimuli, such as brief periods of muffled hearing or sounds seeming louder. Periods of muffled hearing have been linked with subsequent derealisation within the psychoses (Schultze-Lutter et al., unpublished). Bodily depersonalisation (a marked anomalous experience during the pre-psychotic state; Klosterkötter et al., 1997, 2001) was very occasionally noted by ketamine users (e.g. an arm or foot feeling separated from the rest of one's body), with only two frequent ketamine users describing brief 'out-of-body' experiences when 'sober'.

Such perceptual alterations are repeatedly observed in individuals deemed within the pre-psychotic state (Freedman & Chapman, 1973; Freedman, 1974; Hemsley, 1994). Indeed, it is proposed that attempts to account for alterations in visual and auditory perception coupled with attentional changes (noted in SPI-A subscale B) and a heightened ability to form associations (noted for frequent ketamine users only in SPI-A subscale D) result in the invention of bizarre, causal structures to explain them, which manifest clinically as delusions (Kapur, 2003; Kapur, Mizrahi & Li, 2005). The finding that ketamine users scored higher than controls on delusional ideation (assessed by the PDI) and the Unusual Experiences factor of the OLIFE (which assesses hallucinatory and delusional experiences) supports this.

Finally, chronic ketamine use was found to induce basic symptoms grouped within the SPI-A 'Optional' subscale. These included feelings that the world around them was unreal, distant and 'somehow weird' (derealisation) and uncontrollable perseverative focus on thoughts and images. The latter fits with the main theme of the Schneiderian first-rank symptoms of the psychoses (Mellor, 1970; Schneider, 1959); loss of control over one's train of thought. Interestingly, the 'Optional symptoms' were all appraised as fun and enjoyable (with the exception of motor blockages), and in some cases were 'encouraged'. A possible explanation of this is offered below.

Another interpretation of the SPI-A findings is that they reflect pre-existing differences between ketamine users and controls. However, this seems unlikely for three reasons. Firstly, participants were instructed to only rate themselves on variables where they had noticed changes since they started taking ketamine, which

is suggestive of ketamine-induced change. Secondly, previous studies support the existence of chronic ketamine-induced psychotic-like symptomatology in users (Curran & Monaghan, 2001; Morgan et al., 2004b). Finally, if pre-existing differences were responsible for our findings it would be hypothesised that no difference would be observed between ketamine user groups, however this was not the case. Although ketamine groups experienced similar levels of psychosis proneness on the OLIFE (despite both groups scoring higher than controls), this measure is not a clinical index of symptomatology and was not specific for basic symptoms. Therefore the OLIFE could not differentiate subtle ketamine-induced differences in clinical symptomatology. Furthermore, the *negative* correlation of years of ketamine use with OLIFE total scores may reflect a tolerance to ketamine's psychoactive effects rather than providing evidence for pre-existing differences between ketamine users and controls.

It is also highly improbable that group differences in pre-psychotic symptomatology were the reflection of other recreational drugs, as the ketamine groups did not differ in general drug use, apart from ketamine. The finding that cannabis use did not correlate with SPI-A or OLIFE scores in either ketamine group further strengthens this proposition.

Schultze-Lutter, Klosterkotter, Picker, Steinmeyer and Ruhrmann (2007b) investigated the ability of the SPI-A to predict the pre-psychotic state. They noted 2 partially overlapping basic symptom 'risk criteria' for defining the 'prodrome', based on data of the prospective Cologne Early Recognition (CER) study (Klosterkötter et al., 2001; Schultze-Lutter et al., 2006). The first risk criteria

specified an SPI-A score of 3 or above, and one of ten specific cognitive-perceptive basic symptoms (See Schultze-Lutter et al., 2007b). If these criteria are applied to ketamine users who took part in this study, 95% of infrequent users and 100% of frequent users would be deemed to be experiencing symptomatology at a level similar to individuals deemed within the pre-psychotic state.

Dissociation

Contrary to our hypothesis, frequent ketamine users reported more dissociative experiences in comparison to infrequent ketamine users and controls (who did not differ from one another). This finding is unlikely to be due to pre-existing differences between groups because only frequent ketamine users experienced higher levels of dissociation compared with controls. Rather, this finding is probably due to the daily use of ketamine in the frequent user group, a far higher frequency of ketamine use than previous studies have explored. Nevertheless, even at lower frequencies of ketamine use one study has shown *chronic* effects of ketamine on dissociative symptomatology (Curran & Morgan, 2000), and most acute ketamine challenge studies demonstrate significant dissociation (Anand et al., 2000; Krystal et al., 1994; Malhotra et al., 1996; Pomarol-Clotet et al., 2006).

Cognitive effects

Episodic memory

Both groups of ketamine users recalled less of a passage of prose than controls immediately and after a delay. Although no single memory task taps a single memory system, prose recall loads significantly upon episodic memory, and no deficits were identified in digit span forwards (working memory). In addition,

neither levels of depression nor pre-morbid IQ affected the differences identified. This pattern of prose recall impairment fits with impairment in verbal episodic memory observed in participants in the pre-psychotic state (Eastvold et al., 2007; Niendam et al., 2006). Interestingly, a significant impairment in verbal episodic memory has been found to be predictive of an imminent transition from a pre-psychotic state to fully-manifest psychotic symptomatology (Brewer et al., 2005; Lencz et al., 2006, both cited in Eastvold et al., 2007).

The prose recall task has been found to be the best laboratory test predictor of everyday memory performance (Sunderland, Watts, Baddeley & Harris, 1986) and therefore the findings of this study indicate that both frequent and infrequent ketamine users would experience memory problems in everyday life. This fits with SPI-A data which indicated ketamine users experienced disturbances in immediate recall and difficulties holding things in memory for less than half an hour (SPI-A subscales B & C). These findings also support the observation of episodic memory impairments as a result of both acute and chronic ketamine use in previous studies (e.g. Curran & Morgan, 2000; Curran & Monaghan, 2001), and Morgan et al.'s (2006) conclusion that chronically, ketamine appears to have more marked effects on episodic memory than other cognitive domains.

It is suggested these findings may have implications for the reliability of the data gathered through the SPI-A and the questionnaires. If all ketamine users were experiencing memory problems in everyday life, it is indeed probable that reports of subjective effects were influenced by these memory difficulties. It is argued that any impairment in episodic memory would have resulted in ketamine users under-

reporting symptomatology, as they had not initially encoded or had lost the storage of a memory trace. Therefore, if findings have been affected by everyday memory problems, the true picture of symptomatology may indeed be greater than that reported.

Working memory (WM)

The pattern of effects found on the digit span backwards task paralleled that on prose recall, with both groups of ketamine users performing significantly worse than controls, but similarly to one another. However there were no group differences identified in the digit span forwards task. It is not possible to compare digit span performance in this cohort of ketamine users with previous cohorts as the task has not been previously been used with this population. The findings suggest a specific deficit in the manipulation of information in WM, rather than maintenance. The finding of a *negative* correlation between digit span backwards scores and SPI-A subscale C scores (cognitive disturbances) for frequent ketamine users, and a trend in this direction for infrequent users may indicate that the more thought disordered users have the most difficulty with the manipulation of information in WM.

A selective impairment in manipulation of information in working memory is in line with deficits revealed following acute ketamine administration in healthy volunteers (Honey et al., 2003). This study is the first to show that chronic ketamine also impairs the manipulation but not the maintenance of information in working memory. This mimics the cognitive profile observed in the psychoses (Kim et al., 2004; Perry et al., 2001), including within the pre-psychotic state (Pukrop et al.,

2007; Simon et al., 2007), thus providing support for the ketamine model of the psychoses.

Executive functioning

Although group differences were found for the verbal fluency task, it was not clear where these lay. Contrary to prediction, there were no group differences in the category fluency task. Although the limited literature has provided mixed findings for the impairment of verbal fluency in ketamine users, an absence of impairment in category fluency is unusual (Curran & Morgan, 2000; Curran & Monaghan, 2001; Morgan et al., 2004b). It is therefore necessary to consider the context of the category fluency task. A factor which could not have been foreseen prior to testing was 'expert' knowledge ketamine users often reported regarding the category chosen: musical instruments. Whilst only anecdotal evidence, ketamine users frequently commented that the category fluency task was 'easy' as they had studied for music qualifications, or worked in the music industry or were involved in music in some other way. Therefore, the use of this specific category may have masked impairment of executive functioning. Alternatively, chronic ketamine use may not impair executive functioning, as was evidenced by Morgan et al. (2004b), who found performance on verbal fluency and category fluency was the same in ketamine users as in controls.

What other factors may account for the cognitive findings besides regular use of ketamine?

Another interpretation of the cognitive findings is that there were baseline differences between groups. Although it is not possible to rule out this

interpretation, there are three reasons why such differences are unlikely. Firstly, the groups were well matched for demographic variables and general drug use, which could impact upon cognitive scores. Secondly, although groups differed in premorbid IQ (with no specific differences between any 2 groups), no correlations were found between pre-morbid IQ and cognitive task scores. Finally, the high densities of NMDA receptors in the cerebral cortex and the hippocampus, areas important for higher executive functions and memory weakens this interpretation further.

Methodological considerations

The present study has methodological limitations endemic to most research with recreational drug users (Curran, 2000). For example, although the groups were well matched for demographic variables, they may have been a heterogeneous sample and differed in other ways, e.g. familial history of drug dependence. Recreational drug research is also complicated by difficulties recruiting participants (e.g. because of the illegal status of the drug), which may impact upon the representativeness of study samples.

In addition, it could be argued that the high levels of depressive symptomatology observed in frequent ketamine users may have confounded findings. Although it could be argued that exclusion criteria for participants should have included 'BDI score of over 13', it is suggested this would have resulted in an unrepresentative sample. It is well known that drug misuse is associated with comorbid depression (Sanderson et al., 1990, cited in Abraham & Fava, 1999), with drug use cited either as a cause of depression or a form of self-medication for pre-existing depressive

symptomatology (Abraham & Fava, 1999). The association between the two is complex and beyond the scope of this discussion. Nevertheless, it may be useful to complete a future study which attempts to exclude individuals with significant levels of depressive symptomatology.

Although urinanalysis was completed, this was undertaken to verify general drug use, rather than ketamine use. Nevertheless, the subjective effects reported by participants painted an unique 'ketamine profile' (derealisation, 'out of body' experiences, bodily numbness, confusion and perceptual distortions), which strongly supports the assumption that ketamine was actually taken. Doses of ketamine used were based solely upon self-report data which may have introduced bias into the results as retrospective reporting can be inaccurate.

It was also noted that participants could at times forget instructions to rate *only* subjective day-to-day experiences (i.e. chronic effects of ketamine), and could sometimes get carried away describing the acute effects of ketamine. This was a particular difficulty with frequent ketamine users, and understandably so, as some of these individuals were ingesting ketamine several times daily and noted they rarely deemed themselves to be 'sober'. The rating of acute effects of ketamine on the SPI-A was of most concern. However as this measure is a semi-structured interview it was possible for interviewers to repeatedly check out whether participants were recalling chronic or acute effects, to limit the impact of this reporting bias. Nevertheless, it is recognised that this issue will have impacted upon the results of the study, as retrospective reporting is never completely accurate.

Finally, it is impossible to rule out pre-existing differences between ketamine users and controls without a prospective study. For the reasons explained above it is argued that this interpretation of the findings is unlikely.

This study also had several strengths. Firstly, all groups were well matched for demographic variables, thus minimising the chance that significant differences were the result of pre-existing differences between groups. Secondly, both ketamine groups were well matched for other drug use and years of ketamine use, thus minimising the likelihood that significant differences were the result of other drugs used, or the duration of ketamine use. Thirdly, the self-reported use of other drugs was objectively corroborated using urine samples. Finally, using the SPI-A (a semi-structured interview approach) enabled the chronic effects of ketamine use to be teased apart from acute effects. This would have been impossible had a self-report questionnaire been utilised.

Scientific and Clinical Implications

The results of this study indicate that ketamine use is associated with attenuated positive and negative psychotic-like symptomatology, with frequent users experiencing a higher level than infrequent users. In addition, they suggest that chronic ketamine use has selective detrimental effects on episodic and working memory. These findings have wide reaching clinical and scientific implications.

Firstly, the ketamine using population should be informed of the risks associated with long-term use of this drug. Longer-term ketamine users are likely to experience chronic effects of ketamine, which appear to be attenuated forms of experiences

sought out through acute use of the drug, and mimic symptomatology deemed characteristic of the pre-psychotic state. This is indeed a concerning observation given the rapidly increasing population of ketamine abusers in the UK and worldwide. Currently, there is a paucity of research into the effects of chronic ketamine use, and it is vital this omission be addressed. Although only anecdotal evidence, one frequent ketamine user interviewed reported experiencing what he described as a 'drug-induced' psychosis (not psychiatrically diagnosed or treated), which lasted several days and was extremely distressing. This raises the issue of ketamine's possible role in transition from attenuated psychotic-like symptomatology to fully manifest psychoses. It will thus be important to conduct longitudinal studies in which the potential progression of symptomatology is investigated and, following the cessation of ketamine use, the possibility of symptom remittance.

The second finding of clinical importance is the high levels of depression revealed amongst frequent ketamine users. This finding is interesting as acute ketamine has been reported to have prolonged antidepressant qualities in individuals with treatment resistant depression (e.g. Berman et al., 2000; Zarate et al., 2006). An explanation of this disparity may be that whereas *acute* ketamine appears to have anti-depressant qualities, *chronic* ketamine (at higher doses) may have depressant qualities. The latter hypothesis is speculative as the causal relationship between high levels of depressive symptomatology and chronic ketamine use is currently unclear. Indeed, it may be that chronic ketamine users experience higher levels of depression because of previous negative life events (although negative life events assessed in this study were not found to be associated with level of depression), the

chronic physical health difficulties induced by ketamine, or lifestyle, amongst other factors. Further studies are required to explore the relationship between depressive symptomatology, past life events, lifestyle and chronic ketamine use. However, if chronic ketamine use is shown to reliably induce depression, then this will have clinical implications for the ketamine using population.

Drug models of the psychoses have long been utilised to investigate psychotic symptomatology, and subsequently in the development of antipsychotic medications. *Acute* ketamine has been utilised widely to develop a ketamine model of the psychoses, which proposes glutamatergic dysfunction for symptomatology, and therefore as a target for antipsychotic treatment. However, the investigation of *chronic* ketamine as a model of the psychoses has been limited. The current study reinforces Honey et al.'s (2006) argument that as ketamine appears to induce subtler symptomatology than that experienced by individuals with fully-manifest psychotic symptomology, it may best model the pre-psychotic state. Specifically, this study indicates that *chronic* ketamine use provides a very useful model of pre-psychotic symptomatology, with good clinical and contextual validity (Fletcher & Honey, 2006). The clinical specificity of the model is questionable as frequent ketamine users experienced significant dissociation, which is not specific to the psychoses.

The findings of this study require replication, although currently they appear to provide evidence for a *chronic* ketamine model of the pre-psychotic state, indicating that *chronic* ketamine use may prove useful in the exploration of this state of idiopathic psychoses. This model argues that chronic NMDA antagonism and thus glutamate dysfunction appear to be an aspect of the pre-psychotic state. Exploration

of this state utilising chronic ketamine as a model may improve the reliability of early recognition. Furthermore, new drugs using the glutamate pathway may prove useful in the prevention of fully-manifest psychotic symptomatology (Patil et al., 2007).

Conclusion

The current study investigated levels of pre-psychotic symptomatology in *chronic* ketamine users employing a measure of basic symptoms, a novel area of investigation. It found a frequency effect of ketamine for symptomatology deemed characteristic of the pre-psychotic state, and a general effect of ketamine (both frequent and infrequent use) on a measure of psychosis proneness. For infrequent users only, amount of ketamine use was *positively* correlated with SPI-A subscale C scores, suggesting ketamine may most notably be related to cognitive disturbances. In support of this, both frequent and infrequent ketamine users were found to be similarly impaired in tasks tapping episodic and working memory. The findings lend support to the NMDA receptor hypofunction model of the psychoses, and suggest that glutamatergic disturbances may contribute to symptomatology deemed characteristic of the pre-psychotic state.

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Part 3: Critical Appraisal

Overview

This critique presents an opportunity to reflect upon the process of completing my DClinPsy thesis. I have focused on the following areas: the benefits of working as part of a research group, matters to consider when conducting research with the ketamine using population, clinically relevant observations, and the issue of socially constructed concepts in the field of research into the functional psychoses.

Reflections on working as part of a research group

Although it had not been my intent to undertake a joint thesis, by the end of the first year I found myself planning the design of my study as part of a comprehensive research group, consisting of 3 UCL supervisors (Professor Val Curran, Dr Oliver Mason and Dr Celia Morgan), and 2 other trainee clinical psychologists (Suzanna Hunt, UCL and Lisa Monaghan, Royal Holloway). This arrangement was of benefit from the outset.

My experience of research prior to doctoral training had been an isolating one. Previous research supervision had taken a didactic form, where I had muddled through the various stages of the research (i.e. design, data collection, analysis, etc), feeding back my plans to supervisors, yet never quite knowing whether my methods were 'correct'. Suddenly I found myself in a collaborative research context, which I very much valued. For example, there were many discussions at the outset of the research process regarding the design of the 3 studies to be completed by each trainee. These discussions involved agreeing on how each trainee would share participants, which developed my ability to *in practice* think about a number of study designs which would control for confounding factors, and select the most

appropriate. Through these discussions we were able to learn from one other, and bounce ideas and hypotheses off one another, a novel and enjoyable experience for me. I learnt how multiple perspectives and backgrounds are as valuable in the research process as they can be in clinical practice, as they introduce difference to your thinking. Furthermore, I began to realise that not only was I undertaking an extremely interesting piece of work, but I was also (finally) going to learn, *in practice*, how research 'should' be done.

The group context provided me with the containment I had never had during previous research I had undertaken. As an individual who enjoys and values joint working, I began to enjoy the research process and even have fun – something I never thought possible! For example, the otherwise daunting and potentially dull task of creating a semi-structured interview for the SPI-A (to improve inter-rater reliability across trainees) became a lively debate about the best way to structure questions, rate responses and record information. The task itself was divided between the 3 trainees, thus lightening the load, and providing opportunity for different interpretations of the SPI-A manual to be identified and then resolved. From keeping each other going during data collection, which at times could be very tiring and take much time out of our evenings and weekends, to thrashing out ideas for the interpretation of our individual data sets, and how best to write these up, I have not been able to fault working in a group context, and would highly recommend it. My thanks to you all for making it such an enjoyable experience, which has moved me from a position of recognising the importance of, but reluctantly undertaking research to seeking out research opportunities in my future career.

Reflections on conducting research with the ketamine using population

Research with chronic ketamine users is constrained by the common limitations of naturalistic drug studies, including poly-drug use, restricted study design and recruitment difficulties. I will reflect upon each in turn, and then consider further issues which are more specific to completing research with ketamine users.

Poly-drug use in the ketamine using population

Given that ketamine is illicit and has potential neurotoxicity, ethical approval will understandably not be granted to repeatedly administer ketamine to drug-naïve participants, as in acute challenge studies. Therefore, the only feasible way of studying the effects of chronic ketamine is to work alongside the naturalistic population of ketamine users. It has been argued that studies should only recruit people who use just ketamine (Narendran et al., 2005). However it would be extremely difficult to recruit such users, and even if a sample of sufficient size was collected, findings would not be generalisable to the general ketamine using population who are predominantly poly-drug users. A potential constraint with using this cohort of participants is therefore that their individual poly-drug profiles are unique, with unknown interactions and subsequent effects. A strength of my study design was that I attempted to control for this confounding factor by matching frequent and infrequent ketamine users for current poly-drug use. However this does not take into account historical drug use and interactions. Drug histories themselves can be problematic, as they are limited by several biases, such as social desirability and memory inaccuracies (especially as verbal episodic memory was found to be impaired in all ketamine users).

Furthermore, as ketamine and the majority of substances in the poly-drug history are illegal, it is not possible to be accurate about what drug was actually taken, or the real dose (Curran, 2000). Dosages of illicit substances differ widely. Another strength of my study was the verification of current drug use using urinanalysis. However this only provided information regarding drug use in the last few hours or days. Due to ketamine's short half-life, urinanalysis was not conducted to verify ketamine use. Although hair analysis could have been completed to overcome these limitations, it was too costly.

Hence, it is evident that although I attempted to control for both current and historical poly-drug use through my study design, this limitations was still problematic and could have impacted upon the findings I gathered.

Study design

Ketamine users and researchers were not blind to the participants' drug histories and current ketamine use, and therefore knew their group allocation. Although it has been suggested that this is straightforward to overcome by having one person obtain drug histories and another administer the tests (Curran, 2000), it is argued that even if such a design had been employed, it would have been evident from the answers given in the SPI-A which group participants were allocated to. Therefore, it was decided not to utilise a more sophisticated study design than between-subjects (e.g. single-blind). Nevertheless, this common limitation of naturalistic drug studies may have had a real impact upon the results gathered in the study, as the rater who was facilitating completion of the SPI-A may have been influenced by their expectations of the experiences different drug using groups would have (SD for

frequent and infrequent ketamine users, LM and SH for controls). It is suggested that future studies with chronic ketamine users could attempt to control for this limitation more appropriately by having a single-blind design (double-blind would not be possible as participants will obviously know which group they have been allocated to).

Recruitment issues

Recruitment of ketamine users was also a difficulty, partly due to the illicit status of the drug, and partly I believe due to higher levels of suspicion amongst (especially frequent) ketamine users. I was in email contact with a number of participants who understandably questioned my motivation for completing a study into ketamine. Following reassurance and more detailed explanation of rationale and aims some ketamine users became even more suspicious and at times accusatory (e.g. suggesting I was associated with an undercover police operation). It is therefore interesting to speculate whether the individuals who participated in the study were ketamine users who experienced less psychotic-like symptomatology, and were therefore less suspicious and willing to participate than those who did not participate. Alternatively, those who participated may have experienced similar or higher levels of psychotic-like experiences to those who did not participate, but the former may have appraised their experiences differently (i.e. *recognising* delusional ideation / paranoia and wanting to talk about it to further knowledge about chronic effects of ketamine). Non-participants may have simply been more aware or fearful of the consequences of 'being caught' (as ketamine is an illegal substance), perhaps due to previous experiences with the police. It is impossible to determine which of these explanations is more or less accurate without further investigation. In

addition, it is hypothesised that there may be a cohort of ketamine users who believe chronic ketamine use has no negative effects, and therefore may not be motivated to contribute to research studies. Interestingly, only one infrequent ketamine users in my study noted ketamine had no negative effects for them (despite reporting bodily sensations of numbness and stiffness).

Unsuprisingly, it was more difficult to recruit frequent than infrequent ketamine users. It is hypothesised that this may in part be the result of a higher level of attenuated negative psychotic-like symptomatology (e.g. social withdrawal and lack of motivation). Although frequent users volunteered at similar rates to infrequent users, there was a high DNA rate for appointments. Furthermore, when frequent ketamine users did attend, it was not always possible to undertake testing, as traces of white powder were noticed under their noses, or behaviour was indicative of a recent acute dose of ketamine. Furthermore, 2 potential research participants (frequent users) were excluded from the study during testing as they had asked to go to the toilet and returned clearly under the influence of acute ketamine (i.e. slurred expressive speech, impaired receptive speech, glazed eyes).

In addition, a high proportion of infrequent ketamine users who volunteered were male. As I wanted to match the frequent and infrequent ketamine groups for gender, I stopped recruiting men, which may have introduced bias to the sample. It is unclear whether the infrequent population of ketamine users is predominantly male, and therefore whether the trends in volunteering reflected this, or whether female infrequent ketamine users were less motivated to volunteer, for reasons currently unknown. Although it could be argued that the amount of monetary compensation

provided to participants (£15) biased the sample towards participants on a low income and with time to spare, it was apparent that few participants were completing the research for the money. Rather, participants frequently noted their interest in finding out more about the long-term effects of ketamine, so as to inform their community. Indeed, the majority of participants were employed (12 infrequent, 10 frequent) in posts of varying income (e.g. administrator, recruitment consultant). Nevertheless the reliance on participant's altruism could have implications for the generalisability of findings to the wider ketamine using community.

The difficulties with recruitment detailed above will probably have impacted upon the results gained, as the ketamine users who participated may not have been representative of the whole ketamine using population.

The impact of memory on findings

The SPI-A and subjective rating scales utilised to gather data in this study relied heavily on intact episodic memory. However, findings indicated that both groups of ketamine users experienced impaired episodic memory in comparison to controls. This will no doubt have had an impact upon findings. It is argued that one of the strengths of the study was the use of the SPI-A, as this measure was a semi-structured interview, which enabled raters (SD, SH & LM) to use their clinical skills to probe participants for detailed answers and descriptions of their experiences, rather than accepting simple yes/no answers, or a rating on the SPI-A without an explanation or evidence to back up the participants claims. However, retrospective reporting is always inaccurate, as it is biased by beliefs, socially

desirable responses and acquiescence. Therefore, it is inevitable that biases in memory would have impacted upon results, perhaps even more so for ketamine users in comparison to healthy, drug-naïve controls due to their observed episodic memory impairment.

The SPI-A explicitly asked participants to rate *only* experiences that were new or had changed since they started using ketamine. Participants were *not* expected to comment on whether they believed these new or altered experiences to be the result of ketamine use, but simply to report if they had noticed anything new or anything that had significantly changed in the areas the SPI-A questions asked about. However, although participants were not asked to attribute perceived changes to ketamine use, asking them to think back to how they were when they first started taking ketamine, and comparing this to their years of ketamine use and their current state would have relied heavily on episodic memory.

Developing an understanding of ketamine use

Although this research project employed quantitative methods and analyses, there was much qualitative information gathered through meeting with ketamine users, especially when I visited participants at home. This is in line with ethnographic research: the task of systematically describing a culture or community from the perspective of the people for whom it is a way of life, where the researcher observes from within and is thus part of the culture / community. A caveat prior to this discussion: the following observations and hypotheses are based upon anecdotal evidence, rather than systematically collected data.

Although I did not explicitly ask ketamine users why they began taking ketamine, or the reasons for continuing to use, such information often came up during the SPI-A interview. It was evident that ketamine users (whether infrequent or frequent) began using ketamine after several years of other poly-drug use (supported by Muetzelfeldt et al., 2008). The trigger for ketamine use was not always clear, although some stated that it had been preceded by a significant negative life event (e.g. death of a sibling, relationship breakdown). This fits the reasons ketamine users provided for continued ketamine use: facilitating a shift of focus from negative thoughts about the past, present or future to either not thinking at all (via dissociation), or thinking about existential topics and / or minutiae (e.g. pattern of light the sun forms on the floor). This shift was associated with a change in affect, namely to a contented and happy mood. These findings fit with qualitative data gathered by Muetzelfeldt et al. (2008), who found some (but not all) ketamine users liked ketamine-induced dissociation and feelings of contentedness (which in cases replaced feelings of unhappiness). It is hypothesised that for some users, ketamine's function is as an agent of 'negative thought avoidance', which may be indicative of self-medication. This was more prominent for frequent users, which fits with the higher level of depression revealed in this group (discussed below). For example, ketamine users stated:

"I'm generally more happy than before I took K because I don't ruminate on bad things as much." (infrequent user 18).

"I used to be the moodiest, jumpiest teenager ever. I swear I got happier since I started taking ketamine. I get moody again if I haven't had K for a while and can't get hold of it." (frequent user 6).

"I've become more positive because you look into yourself - this has helped me to change. It also helps dull unpleasant feelings. Its made me more relaxed." (frequent user 8).

Although for some users acute ketamine appeared to aid the avoidance of unwanted and distressing negative automatic thinking, this study found that chronic ketamine use appears to lead to a loss of thought control (SPI-A subscales B & C). Interestingly, anecdotally it seems the content of more chaotic, out-of-control thinking experienced by ketamine users differs to ruminative thinking: i.e. thoughts are focused on unimportant previous events, and attention and thus thoughts are drawn to seemingly non-salient stimuli. Such experiences were often rated as enjoyable and sometimes encouraged.

Other ketamine users noted that the trigger for ketamine use had been becoming more involved in the 'dance' or 'squat' scene, and they perceived this as a positive shift. Therefore it is hypothesised that another potential reason for ketamine use is the need to feel part of a social group and the development of one's own identity within this. Indeed, some ketamine users noted that one reason for their continued use of ketamine was the context in which they lived. Many users commented that although sometimes they thought about stopping or cutting down on their ketamine use, their friendships and social activities revolved around the drug within the ketamine-using community. The severing of relationships and the loss of identity associated with a move away from ketamine use was deemed too high a price to pay for ceasing use. Indeed, another study has found that ex-ketamine users had to completely remove themselves from the environment of their using patterns in order

to give up, and they subsequently miss the feeling of being in a 'team' (Muetzelfeldt et al., 2008).

Ketamine users also reported that one of the primary reasons for continuing with ketamine use was their enjoyment of its acute effects. This fits with Muetzelfeldt et al.'s (2008) study, which found that "melting into the surroundings", "visual hallucinations" and "out-of-body experiences" were the most appealing aspects of ketamine for approximately 66% of users. The increasing recreational ketamine use warrants further study in this area, in order to inform interventions for ketamine addiction. Furthermore, it would be useful to understand the factors that differentiate those who use ketamine daily from those who maintain a recreational style of use.

Cultural considerations

Ketamine users (both frequent and infrequent) who reported a history of regular heroine or crack cocaine use perceived the change in their drug use as a positive step forwards. It is hypothesised that the beliefs of ketamine users were influenced by cultural and societal beliefs about drug use.

For the purposes of this critical review, cultural beliefs refer to the 'squat' and / or 'dance' cultures which ketamine users are very much a part of. Squatting refers to the act of occupying an abandoned or unoccupied space or building the squatter does not own, rent or otherwise have permission to use. The 'squat culture' refers to a counter-culture which calls into question the widely accepted goal of society, to own property, and attempts to promote ideas of sharing, hospitality and community

in societies where such ideas have been marginalised. Squats are often residences, but can also be used as social centres, pirate radio stations, cafés and venues for dance music events. The dance culture refers to a community who are united by their enjoyment of dance music and clubbing. The culture is also commonly associated with poly-drug use, hedonism and rave parties.

Anecdotally, it was observed that infrequent users tended to align themselves with the 'dance' culture, whereas frequent ketamine users aligned themselves more with the 'squat' culture. Ketamine users noted that within these cultures, the use of ketamine is generally appraised positively. It was widely believed that both cultures associate ketamine with being open to freeing up your thinking and questioning the world around you, as well as sometimes being an indication of an interest in philosophy and a sign of intelligence. This fits with findings that ketamine use is associated with a desire for experimentation and openness to new experiences (Muetzelfeldt et al., 2008). In my study, ketamine users said:

"I don't think ketamine causes these experiences, but rather it is a catalyst for these experiences, for spiritual activity. The spirits are breaking the boundary of this world and the other side. It (ketamine) helps you to tune in, like tuning a radio dial." (infrequent user 1).

"It (ketamine) makes you more aware, you see things (not literal reference to visual hallucinations) *you can't normally see."* (frequent user 19).

Therefore it appears that ketamine use may be positively appraised and thus reinforced by the beliefs of specific cultures, which associate ketamine with valued

traits. It is important to note this information was gained through discussions with ketamine users, whose accounts may be biased and thus not representative of the wider beliefs of the 'squat' and / or 'dance' cultures. Nevertheless, ketamine users clearly *perceive* a cultural acceptance and value of their drug use. Indeed, another limitation of naturalistic drug studies is that it is not possible to separate the neurochemical effects of the recreational drug of interest (in this case ketamine) from the culture drug users reside within.

Some ketamine users also noted that society in general does not appear to have any particular beliefs about ketamine use, as it is a relatively new drug in the vocabulary of the general population. In contrast, it was suggested that societal beliefs about crack cocaine and heroine use are extremely negative, and are propagated by the media. An interesting area of future research may be to qualitatively explore the attitudes of individuals within the above cultures, or within the general population towards ketamine use.

Clinically relevant observations

Why might ketamine users enjoy positive psychotic-like symptomatology?

The observation that some ketamine users noted enjoying and at times actively encouraging unusual thought processes (including uncontrollable perseverative focus on thoughts and images), a decreased ability to discriminate between fantasy and reality, unstable ideas of reference and derealisation is reminiscent of the concept of the 'happy schizotype', coined by McCreery and Claridge (1995). This term refers to particular groups of individuals in the general population who show similar positive psychotic-like symptomatology to that found in an exaggerated

form in the idiopathic psychoses, but who are not distressed by these experiences. Examples include individuals who believe in the paranormal (Thalbourne & Delin, 1994), those who have out-of-body experiences (McCreery & Claridge, 1995), members of specific new religious movements (Day & Peters, 1999), and those who have profound religious experiences (Jackson & Fulford, 1997). Studies (e.g. Peters, Day, McKenna & Orbach, 1999; Day & Peters, 1999) have shown that although such individuals do not show as florid delusions as individuals with psychoses, they experience similar levels of delusional ideation as the clinical cohort and have similar levels of conviction in those beliefs. However they are significantly less distressed and preoccupied by their experiences, suggesting that positive psychotic-like experiences are *not* always associated with distress, withdrawal or difficulties in adjustment. Indeed, it has been argued that a moderate degree of schizotypy (i.e. psychosis proneness) may even have adaptive value, being helpful and constructive for the individual and in some cases being associated with creativity (Claridge, 1985, as cited in Day & Peters, 1999).

It may be that *some* chronic ketamine users appraise the positive non-acute psychotic-like symptomatology they experience as non-aversive, and furthermore enjoyable and sought after because of the cultural contexts in which they live. Indeed, it is well known that drug users often take hallucinogenic or dissociative substances to open the gateways of perception and creativity, and thus positively appraise the consequences of acute drug consumption. For example, as the famous literary icon Aldous Huxley once stated:

"To be shaken out of the ruts of ordinary perception, to be shown for a few timeless hours the outer and inner world, not as they appear to an animal obsessed with survival or to a human being obsessed with words and notions, but as they are apprehended, directly and unconditionally, by Mind at Large - this is an experience of inestimable value to everyone and especially to the intellectual" (The doors of perception, 1954).

As a result of using ketamine in a social context which places value and positive meaning on unusual experiences, and where the aetiology of such experiences is explainable and controllable, *some* ketamine users may appraise their longer-term unusual experiences positively. This explanation is supported by my study's finding that although both groups of ketamine users had higher levels of delusional ideation on the PDI compared with controls, there was no evidence of increased distress or preoccupation associated with these delusional ideas. It is also supported by Claridge (1997) who noted that it is the way in which positive psychotic-like experiences are reacted to or appraised which causes them to become distressing or deemed an 'illness'.

It is important to note that I am not proposing chronic ketamine users fit the 'happy schizotype' model. Evidence suggests this is not the case as firstly, not all chronic ketamine users stated non-acute positive psychotic-like symptomatology was benign or enjoyable. Secondly, some positive psychotic-like experiences were consistently appraised in a negative way. Finally, all ketamine users also experienced negative psychotic-like symptomatology, which was always appraised negatively, and is absent in the 'happy schizotype' model. Rather, it is proposed

that the appraisal pathways of *some* chronic ketamine users and 'happy schizotypes' may be similar, as a direct result of cultural context. Further research is required to explore this matter because chronic ketamine is proposed to be a model of the pre-psychotic state. Using chronic ketamine as a way of exploring cultural influence upon appraisals of psychotic-like symptomatology may have clinical implications for those deemed to be in the pre-psychotic state.

Depressive symptomatology

Another main finding of my study was the high levels of depression in frequent ketamine users. This seems at odds with the concept of the 'happy schizotype'. Furthermore, the proposal that ketamine appears to induce depression seems at odds with current research which suggests ketamine has prolonged antidepressant qualities (e.g. Berman et al., 2000; Zarate et al., 2006). An explanation of this disparity may be that whereas *acute* ketamine appears to have anti-depressant qualities, *chronic* ketamine (at higher doses) may have depressant qualities. The latter hypothesis is speculative as the causal relationship between high levels of depressive symptomatology and chronic ketamine use is currently unclear. If chronic ketamine use is shown to reliably induce depression, then this has clinical implications for the ketamine using population.

Although it was found that negative life events in the year prior to testing were not associated with level of depression for frequent ketamine users, it is not known how lifestyle impacted (if at all) on levels of depression, and conversely, how levels of depressive symptomatology impacted upon lifestyle. Anecdotally, it appeared that frequent ketamine users had a tendency to neglect themselves. Through discussion I

learnt of the many physical ailments ketamine users experienced as a result of ketamine use, and the infrequency with which they consulted a medical professional about them or self-treated. Frequent ketamine users sometimes appeared to neglect their personal hygiene, and could wear stained clothing (the latter could be the result of not having access to a washing machine in squats). Furthermore, when I visited a squat to undertake research interviews and cognitive testing, a high level of neglect was evident. For example, rooms were littered and dirty, with mouldy food left out to rot. Further research is required to systematically investigate the relationship between depressive symptomatology, past life events, lifestyle and frequent ketamine use.

The construct of the 'prodrome'

"The tendency has always been strong to believe that whatever received a name must be an entity or being, having an independant existence of its own. And if no entity answering to the name could be found, men did not for that reason suppose that none existed, but imagined that it was something peculiarly abstruse and mysterious." (John Stuart Mill, quoted in Sarbin, 1991, p. 173).

As part of my thesis, I read around the concept of 'schizophrenia' to develop my own knowledge of the various proposed states (i.e. prodrome, acute, chronic), and the associated signs and symptoms. An area of discussion within the literature that particularly took my interest was Mary Boyle's (2002; 2004) work on 'schizophrenia' as a social construct. This position opposes the medical view that 'schizophrenia' is a diagnosable disorder or 'illness', which has biological antecedents, the exact nature of which will be discovered in the future. Instead the

conceptual framework suggests 'schizophrenia' is a construct which encompasses an organised set of beliefs that has been propagated by the dominant systems in society, namely medicine and science (Sarbin, 1991).

Boyle (2002) argued that the 'schizophrenia' construct is not a scientific concept for several reasons. Firstly, the concept of 'schizophrenia' and its predecessor 'dementia praecox', were introduced in the absence of any supporting empirical evidence. Interestingly, Kraepelin's construct of 'dementia praecox', which formed the basis of the modern construct of 'schizophrenia', was in part based upon post-encephalitic parkinsonism and other organic conditions which were unknown to Kraepelin and Bleuer in the early 20th century. Secondly, Boyle (2002) noted that the development and use of 'schizophrenia' as a diagnosis bears no relationship to the development and use of concepts in medicine and science, and is instead based upon inference from a pattern of regularities which conform to a syndrome (i.e. a meaningful cluster of signs and symptoms). Finally, she stated that DSM criteria for 'schizophrenia' do not refer to a meaningful pattern of phenomena which would justify the use of a diagnostic concept. Boyle (2002) therefore concluded that there is no clear evidence to confirm 'schizophrenia' as a brain disease, despite evidence showing unknown genetics play a key role.

I therefore decided to focus both my literature review and empirical paper on whether chronic ketamine models patterns of symptomatology, rather than focusing on whether ketamine provides a model of a specific categorical diagnosis (e.g. schizophrenia, schizoaffective or bipolar disorders). I reviewed findings from studies which recruited participants from across the functional psychoses, and

focused rather on types of symptomatology: namely positive and negative psychotic symptomatology and cognitive dysfunction. This approach was in line with Abi-Saab, D'Souza, Moghaddam and Krystal (1998) who suggested drug models may prove better at offering insight into psychotic symptomatology in general, rather than specific DSM-IV or ICD-10 diagnoses.

Reading Mary Boyle's work shifted my thinking, and I found myself questioning the validity of the construct of the 'prodrome', a concept which is disputed by theorists working within the area of the functional psychoses. Boyle (2002) wrote about the role language plays in maintaining the 'schizophrenia' construct, in that it reflects a reality already discovered or about to be discovered, thus making the label 'schizophrenia' part of our reality (e.g. through conducting research into 'schizophrenia'). In recognition of this, I therefore used language which reflected my position. I used the term pre-psychotic state throughout my literature review and empirical paper to indicate that I was not aligned with a position that accepts the 'prodrome' as a 'reality'. Rather, the term I used reflected the position that some individuals might transition to develop fully-manifest psychotic symptomatology (and thus receive a diagnosis), but that is not necessarily the case.

In 2004, Boyle published a paper that focused on the prevention of 'schizophrenia'. In it she stated that trying to prevent 'schizophrenia' as one would attempt to prevent lung cancer or diabetes makes little theoretical sense. In addition, she noted the ethical dilemma of prevention, as some individuals will not transition to fully-manifest psychotic symptomatology, and those who do can report finding positive symptomatology helpful, comforting and constructive (i.e. the 'happy schizotype'

model). Although these points led me to think more about the complexities surrounding prevention of psychotic symptomatology, I would argue that exploring the ketamine model of the psychoses with a view to prevention is still a useful endeavour. Given ketamine's unique ability to model attenuated *negative* psychotic symptomatology and cognitive dysfunction associated with idiopathic psychoses, glutamate agonists may nevertheless prove attractive interventions for individuals with such symptomatology, despite their potential for attenuating desirable positive symptomatology. I believe that this would be an interesting area of future research, whereby opinions on this matter are explored in cohorts of individuals who have experienced psychotic symptomatology and possibly been given a diagnostic label.

Reading Boyle (2004) also increased my awareness of how the potential role of social and interpersonal factors (e.g. social and educational disadvantage, child abuse and neglect) has been de-emphasised and obscured in the presentation of 'schizophrenia' research, possibly to discourage discussion of theoretical mechanisms which might link them to psychotic experiences. I believe that although this imbalance needs to be addressed, it is possible to have a both / and approach to research in this area. I believe research into social and interpersonal factors with clinical implications for more universal preventive interventions (e.g. involving public education aimed at normalising psychotic experiences to reduce stigma and social isolation), can be conducted side-by-side with research into more specific biological mechanisms (e.g. glutamate pathways).

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APPENDICES

Appendix 1

Details of joint thesis

This thesis was completed as part of a joint project to investigate the chronic effects of ketamine, cocaine and cannabis on pre-psychotic symptomatology and cognitive dysfunction.

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

1) Do ketamine users show psychotic symptomatology and cognitive dysfunction associated with the pre-psychotic state of the psychoses?
(Suzanna Duffin, Trainee Clinical Psychologist, UCL)

2) Prodromal symptoms in daily skunk users.
(Suzanna Hunt, Trainee Clinical Psychologist, UCL)

3) Chronic cocaine use and prodromal symptoms of schizophrenia
(Lisa Monaghan, Trainee Clinical Psychologist, Royal Holloway)

All trainees designed their studies together, and some participants were shared.

Below is an outline of the contribution of each individual member to the joint project:

1) Suzanna Duffin: Completed the semi-structured interview protocol for the SPI-A alongside Suzanna Hunt, and created a scoring sheet for the SPI-A. Collected data as outlined in my methodology from 21 frequent and 20 infrequent ketamine users.

Data for 20 matched control participants was selected from control data gathered by Suzanna Hunt and Lisa Monaghan.

2) Suzanna Hunt: Completed the semi-structured interview protocol for the SPI-A alongside Suzanna Duffin. Piloted full assessment battery with 1 recreational drug user and 2 controls. Collected data as outlined in her methodology for 29 daily skunk users and 15 controls (reporting no illicit drug use).

3) Lisa Monaghan: Piloted the SPI-A with recreational drug users. Collected data as outlined in her methodology for 30 cocaine users.

Appendix 2

Approved ethics application form

Amendment Approval Request Form

1. ID Number: 0052/001	Name and Address of Principal Investigator: Prof H Valerie Curran, Clinical Health Psychology, UCL

2. Title of Project:
The determinants and psychological consequences of ketamine use

3. Information about the amendment:

(a) Is the amendment purely administrative? YES

(b) Has the Participant Information Sheet/Consent Form been changed as a result of the amendment? YES If yes, please enclose a copy - enclosed

4. Summarise the issues contained in the amendment. Mr Justin Grayer, a postgraduate student (on the UCL Doctorate in Clinical Psychology), will be using a different psychological test (indirect semantic priming) with three of the groups involved in the main project (ketamine users, polydrug users and drug naive controls). He will recruit new participants who are not involved in the main project. The test of semantic priming asks participants to determine whether each of a series of stimuli is a real English word or not. Priming is indexed by reaction times to words which follow semantically related words. It is a widely used 20 minute test which does not produce any distress or fatigue. Mr Grayer will also be administering some of the questionnaires used in study 0052/001.

5. Please give any other information you feel may be necessary:
As in the main study, participants will be paid £7.50 per hour to compensate for their time and inconvenience. They will also be asked to provide a urine sample to screen for recent drug use (this project does not have the funding of the main project to analyse saliva and hair). There will be 16 volunteers in each of the three groups.

Signature of Principal Investigator: **Date of Submission: 2nd December 2005**

FOR OFFICE USE ONLY:

Amendments to the proposed protocol have been Approved **by the Research Ethics Committee.**

Chair's Signature: **Date:** 7/12/05.

Please return completed form to:
Ms Helen Dougal, Secretary of the UCL Research Ethics Committee
Graduate School, North Cloisters, Wilkins Building
Gower Street, London WC1E 6BT

Appendix 3

Volunteer Information Sheet

SUB-DEPARTMENT OF CLINICAL HEALTH PSYCHOLOGY
UCL PSYCHOLOGY

UCL

INFORMATION LEAFLET FOR VOLUNTEERS

Version 2 February 2007

The determinants and psychological consequences of ketamine use

Investigators: Lisa Monaghan, Suzanna Duffin, Suzanna Hunt, , Leslie Muetzelfeldt, Dr. Celia Morgan, Dr O Mason, Prof. H.Valerie Curran

Purpose of the study:
To determine the long term effects of recreational cannabis use

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

WHAT IS THE PURPOSE OF THE STUDY?

To determine the effects of using different types of recreational drugs upon mental functioning and mood.

SOME BACKGROUND TO THE RESEARCH

Many drugs have long term effects; for instance people who drink lots of alcohol often find their memories are not as good as they were. This can often be affected by factors such as the length of time they have been drinking and the quantity that they drink. The present study aims to find out what the long-term effects of using recreational drugs may be on mental state and cognition.

WHAT WILL BE STUDIED?

We will be looking at memory, problem solving and concentration as well as mood and mental state in people who use cannabis, people who take other drugs but not cannabis (eg cocaine; ketamine) and people who do not take any recreational drugs.

HOW WOULD I BE INVOLVED IF I AGREED TO TAKE PART?

If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

If you agree to participate, on the testing day you will come to the Psychopharmacology Laboratories at UCL or if you do not live locally the experimenter will come to your home. The experimenter will then record some information about your current drug use and patterns of use, including giving a hair and urine sample, and then complete some computer-based cognitive tasks, which will last for approximately 1 hour and will be followed by a break. You will take part in an interview about your mood and mental state, and this may take up to an hour. You will then be paid for participation.

CONFIDENTIALITY

Any information collected about you will be held in accordance with the 1998 Data Protection Act. All the information that is collected about you during the course of the research will be kept strictly confidential. Your results will have your name and any other details about you removed first so that you cannot be recognized from them.

If you require further information please ask the investigator

Thank you for reading this leaflet and we hope that you will be able to take part in the study.

You do not have to take part in the study if you do not want to. If you decide to take part, you may withdraw at any time without having to give a reason.

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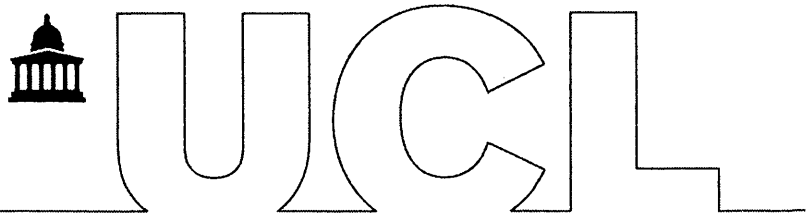
www.ucl.ac.uk/clinical-health-psychology

All proposals for research involving human subjects are reviewed by an ethics committee before they can proceed. This proposal was reviewed by the UCL Committee for the Ethics of non-NHS Human Research.

Appendix 4

Participant consent form

SUB-DEPARTMENT OF CLINICAL HEALTH PSYCHOLOGY
UCL PSYCHOLOGY



Consent Form

CONFIDENTIAL
The determinants and psychological consequences of ketamine use

Investigators: Dr. Celia Morgan, Suzanna Duffen, Suzanna Hunt, Lisa Monaghan, Leslie Muetzelfeldt, Prof. H.Valerie Curran

Please complete the following: *delete as neccessary*

1. Have you read the information sheet ? YES / NO

2. Have you had an opportunity to ask questions and discuss this study ? YES / NO

3. Have you received satisfactory answers to all your questions ? YES / NO

4. Have you received enough information about this study ? YES /NO

5. Which investigator have you spoken to about this study ? .....

6. Do you understand that you are free to withdraw from this study:
   * at any time YES / NO
   * without giving a reason for withdrawing YES / NO

7. Do you agree to take part in this study ? YES/ NO

Signed..... Date.....

Name (please print) .....

Investigator.....

Appendix 5

Semi-structured interview for the Schizophrenia Prediction Instrument – Adult Version (SPI-A)

SCHIZOPHRENIA PRONENESS INSTRUMENT – ADULT VERSION (SPI-A) INTERVIEW SCHEDULE

(30 MINS)

I would like to ask you a number of questions about some of your experiences since you started taking ketamine. I need to emphasise that I am not asking you about experiences you may have had WHILST you were on the drug or whilst you were coming down from the drug, BUT rather I'm interested in your everyday experiences.

A) Affective-dynamic disturbances

A1: Impaired tolerance to certain stressors

GENERAL QUESTION

- Do you think your ability to tolerate stress has decreased since you started taking ketamine? So specifically I am asking about stress that involves unusual or new things, social everyday situations (like having a chat or watching TV), and working under time pressure?

IF YES

OK – I'm going to ask you a few more specific questions about this now

GO TO A1.1

IF NO

move to A2

A1.1 Impaired tolerance for unusual, unexpected or specific novel demands

- Can you handle new, unusual or suddenly occurring tasks as well as before you started taking ketamine? Things like a specific demand at work or a visit to the local authorities, or moving or having a holiday?
- Do you feel like you can't handle it when something unusual or unplanned happens, so a situation like this would be too exhausting or too much?
- Do unusual or unplanned things happening cause feelings like being nervous, tense, restless, or dizzy, or problems with sleeping?

Rating: **Frequency I**

If needed: **Effects on performance behaviour (VI)**

A1.2 Impaired tolerance for certain social everyday situations (which are socially neutral)

- Can you still tolerate being around others or having conversations with others since you started taking ketamine?
- Can you still do things like go to the shops, go on public transport, or go to public events as comfortably as you did before you started taking ketamine?
- Do any of these situations cause feelings like nervousness, tenseness, restlessness, heart beating, sweating, pain or concentration difficulties?
- Do you sometimes feel like watching or hearing things like the radio or TV is just too much for your senses, like its exhausting or you can't handle it?

Rating: **Frequency I**

If needed: **Effects on performance behaviour (VI)**

A1.3 Reduced ability to work under pressure of time or rapidly changing different demands, therefore start to avoid such situations or be more rigid in their behaviour

(NOT B1 which is more to do with a cognitive deficit in not being able to divide attention)

- Are you as able to deal with having several different things to do at once and working under time pressure, as you were before you started taking ketamine?
- Does having multiple tasks to do, or being in time pressured situations make you more nervous and agitated now? Do you find you have problems with concentration during such situations, or you experience nervousness, heart racing, restlessness, sweating or pain?
- Do you have to avoid being rushed since starting to take ketamine?

Rating: **Frequency I**

If needed: **Effects on performance behaviour (VI)**

A2 Change in mood both positive and negative (usually low or emotionless mood – always unrelated to external events) AND emotional responsiveness

(NOT brief or transient change; NOT A3 which is to do with activities and interests losing their positive impact on client)

- Has your GENERAL mood changed overall since you started taking ketamine – for example has it become more negative and low?

- Can you be as happy, laugh and enjoy things as much as you used to?
- Do you think your feelings have become less intense since you started taking ketamine?
- Do you think you have become less emotionally involved in things since you started taking ketamine? Is this generally the case or just with certain things?

Rating: **Frequency I**

If needed: **Subjective burden (IV), Effects on quality of life (VI), Areas of life (VIII)**

A3 Decrease in positive emotional responsiveness towards others.

(decreased feelings of love, affection, sympathy, pity and/or interest towards other persons or previously important activities/hobbies. DO NOT score this item if decrease in responsiveness & hobbies, etc is a coping behaviour to a decreased stress tolerance with respect to everyday situations)

- Are you still as interested and emotionally involved in things you like to do - your hobbies etc. – as you were before you started taking ketamine?
- Do you still feel the same affection and/or interest for your relatives and friends as before you started taking ketamine?

Rating: **Frequency I**
If needed: **Subjective burden (IV), Effects on behaviour (VI)**

B) Cognitive-Attentional impediments

OK – I'm now going to ask you about your thinking and attention abilities since you started taking ketamine.

B1 Inability to divide attention

(difficulty splitting attention between stimuli which require different senses; problems *switching* attention not scored here)

- Can you do two things at the same time as easily as before you started taking ketamine? So for example, can you write notes *whilst* you talk to someone on the phone, or can you do the cooking AND talk to someone at the same time?
- Do you have to just do one thing at a time to make sure it gets done properly?

Rating: **Frequency II**

If needed: **Subjective burden (IV), Effects on B&P (VI)**

B2 Feeling overly distracted by stimuli

(one's attention is raised *randomly* by external stimuli you don't want to attend to); NOT difficulties intentionally splitting attention – this is scored in B1 or any sort of cognitive interference that occurs without the presence of an external stimulus (C2 &D3)

- Do you think that since you started taking ketamine, everything around you catches your attention, even if you don't want it to?
- Is your *thinking* interrupted, aimless or disturbed by being too aware of other things? For example, have you ever found that you can't focus on something because other things around you have *randomly* taken your attention away?

Rating: **Frequency II**

If needed: **Subjective burden (IV), Effects on B&P (VI)**

B3 Difficulties concentrating

(NOT because of any other cog disturbance such as intruding thoughts (C2) obsessive/ perseveration of thoughts (O1), thought pressure (D3), thought blocking (C3), disturbance of comprehension of visual or auditory material (C4), attn disturbances (B1, B2,O7) language problems; could be because of memory disturbances – score this in C.1.8./9 too)

- Concentration problems are when you find it difficult to keep your mind on a task for several minutes, like watching TV or reading, or making a cup of tea. Thinking

about that, do you think you have had more difficulties concentrating since you started taking ketamine?

- Do you know the reasons for your concentration problems – for example, are they because of your thoughts racing or are they triggered by work, or difficulties understating what others are saying to you?
- When you are concentrating on something, do thoughts about other things come into your mind? Are your thoughts suddenly gone or do you simply loose the train of thoughts? Is it always things like that which cause your difficulties concentrating?
- Can your concentration problems occur at any time or just when you feel quite stressed?

Rating: **Frequency I**

If needed: **Subjective burden (IV), Coping (V), Effects on B&P (VI)**

B4 Difficulties to hold things in mind for less than half an hour

- Have you noticed you have more difficulties keeping things in mind, even for half an hour, since you started taking ketamine? For example, after you have read something or watched something on TV, can you still remember the main content half an hour after?

Rating: **Frequency II**

If needed: **Subjective burden (IV), Coping (V), Effects on B&P (VI)**

Do not ask B5 if criteria B3 scored (NOTE: if C4 or C5 are scored, then score for B5 is invalid – see paper for explanation why)

B5 'Slowed-down' thinking

(general complaint that thinking has become slower and harder; which might occur AS A RESULT of other cognitive disturbances)

- Do you sometimes feel that your thinking has become slower, harder or more sluggish since you started to take ketamine?
- For example, is every answer in this interview a real effort?

Rating: **Frequency II**

If needed: **Subjective burden (IV), Coping (V), Effects on B&P (VI)**

B6 Lack of 'thought energy' or goal-directed thoughts

(NOT loss of performance of automatically performed skills - O11)

- Do you think you sometimes lack the strength or energy to think or speak, since you started taking ketamine?
- Do you sometimes have difficulties developing your own ideas or planning things, such as cooking?

Rating: **Frequency II**

If needed: **Subjective burden (IV), Coping (V), Effects on B&P (VI)**

C) *Cognitive disturbances*

OK - I'd now like to ask you some questions about your thinking and your decision making abilities since you started to take ketamine.

C1 Increased indecisiveness with regard to insignificant choices between equal alternatives

(different to loss of spontaneity and carefree responding - B3)

- Is it more difficult to make decisions since you started taking ketamine, even about the most unimportant things, such as which washing powder to go for?

Rating: **Frequency II**

If needed: **Subjective burden (IV), Effects on behaviour (VI), Areas of life (VIII)**

C2 Thought interference

(when *random* thoughts, unrelated to current thoughts or external events disturb the person's train of thought); NOT obsessive perseveration of thought (O1), thought blocking (C3), or distraction of attention by external stimuli (B2)

- Since you started taking ketamine, do you sometimes find it difficult to take part in a conversation or concentrate on a book or TV, because unimportant and unrelated thoughts enter your mind?
- Do you sometimes have difficulties participating in a conversation, because your thoughts drift away to other things that have nothing to do with what's being discussed since you started taking ketamine?

Rating: **Frequency II**

If needed: Subjective burden (IV), Effects on performance (VI)

C3 Thought blockages

(5 subtypes: sudden disappearance of old thought without replacement by new one / sudden disappearance of old thought *with* replacement by new one / slow and gradual disappearance of old thought without new thought afterwards / slow and gradual disappearance of old thought, as new intrude at same time / loss of thread, train of thoughts)

- Since you started taking ketamine, do you sometimes lose your train of thought, or do your thoughts suddenly disappear as if they were cut short?

- Do your thoughts suddenly stop sometimes, as if they are being blocked or as if the thought gradually fades?
- Does another thought take the place of the old one?

Rating: **Frequency II**

If needed: **Subjective burden (IV), Coping with it by increasing effort (V), Effects on performance (VI)**

C4 Disturbance of receptive speech

(When reading or listening to others, the person has difficulties or is unable to comprehend and recognise the meaning of words, word sequences or sentences, e.g. in conversations, movies, TV or radio) DO NOT score when due to concentration difficulties or when occurance is only during very high demand tasks such as a scientific lecture.

- Do you sometimes have difficulties *understanding* conversations, or when reading simple books or articles, since starting ketamine?
- Since you started to take ketamine, is it sometimes difficult to understand simple words or sentences – is it like you are reading or hearing something in a foreign, but well-known language: so you recognise the word but have to think about its meaning?

Rating: **Frequency II**

If needed: **Subjective burden (IV), Effects on performance, avoidance (VI)**

C5 Disturbance of expressive speech

(problems producing adequate words – word fluency and precision slowed down, difficulty finding correct words, sometimes words used which are associated but not correct); NOT a difficulty expressing feelings verbally and non-verbally.

- Do you speak as fluently and precisely as before you started taking ketamine? For example, is it sometimes difficult to find the right words or build the right sentences?
- Have you begun to use the same words and phrases again and again to avoid these difficulties?

Rating: **Frequency II**

If needed: **Subjective burden (IV), Effects on performance, speaking (VI)**

C6 Disturbance of immediate recall

(complaints about not being able to remember things for even a very short time - 5 to 40 sec)

- Do you sometimes have difficulties remembering things immediately since you started taking ketamine? For example, are the questions I'm asking hard to remember straight after I've asked them?
- Do you sometimes have difficulties to follow a conversation, because you quickly forget what was just said?

Rating: **Frequency II**

If needed: **Subjective burden (IV), Coping (V) , Effects on performance (VI)**

D) *Disturbances in experiencing self and surrounding*

I'm now going to ask you some questions about your emotions and your beliefs about yourself.

D1 Decreased capacity to discriminate between different kinds of emotions

(all feelings often experienced as monotone or tainted with a dysphoric quality, even positive ones). NOT change in mood and emotional responsiveness (A2) or a decrease of positive feeling toward others/ previously enjoyed activities (A3)

- Are you always able to tell the difference between unpleasant and pleasant, negative and positive feelings clearly and easily? How does this compare to before you started taking ketamine?
- Have all emotions become somehow unpleasant since you started ketamine?

Rating: **Frequency II**

If needed: **Subjective burden (IV)**

D2 Increased emotional reactivity in response to routine social interactions that affect the patient or his/her significant others

(emphasis on social interaction not everyday events like sad music, TV or books BUT on emotional reactivity to self and significant others which may have not been so strong previously AND the participant is aware they are over-reacting); NOT as the result of a specific trigger like thought perseveration (O1)

- Do the actions or comments of others, or discussions and arguments, get you more worked up now than before you started taking ketamine?
- Do you have the feeling that you are more sensitive now – that almost everything gets under your skin?

Rating: **Frequency I**

If needed: **Subjective burden (IV), Effects on B&P (VI)**

D3 Thought pressure

(great number of random, different thoughts/ images enter the mind and disappear again in quick sequences without the person being able to suppress or guide them) NOT thought interference (C1), nor though perseveration where many thoughts/ images come from shared theme (O1)

- Do you sometimes have the feeling that you are not able to control your thoughts, in comparison to the time before you started taking ketamine - Do your thoughts just run wild, impossible to control?
- Do you sometimes jump from one subject to another so much that your single thoughts feel unrelated to each other, since you started taking ketamine?

Rating: **Frequency II**

If needed: **Subjective burden (IV), Effects on B&P (VI)**

D4 Unstable ideas of reference, 'subject-centrism'

(individual feels they are the focus of attention but has no clear reason for this and overcomes this quickly NOT ideas of reference related to depressive, social anxiety or paranoid beliefs)

- Do you sometimes feel that things going on around you have a special meaning for you, even though you know at the same time that this is improbable or impossible? How does this compare to before you started taking ketamine?
- Do you sometimes feel as if random things were meant especially for you, e.g. comments on the radio or TV? What does it take for you to realise that this is just a sudden idea and not true? How long does this idea last?

Rating: **Frequency II**

If needed: **Severity (III), Subjective burden (IV), Areas of life (VIII)**

D5 Changed perception of the face or body of others

(face or body of others is seen as strange and peculiar, e.g. colour of skin, eyes or hair - may lead to impaired ability to recognise facial expressions)

- Do the faces or bodies of other people sometimes appear different or distorted since you started taking ketamine?

Rating: Frequency II

If needed: Severity (III), Subjective burden (IV), Effects on B&P (VI)

E) Body perception disturbances

E1 Unusual bodily sensations of numbness and stiffness

(resemble paraesthesias incl. numbness and stiffness, wandering sensations of stiffness, which can be transient or chronic. NOT real motor blockages (O10; where person can not move), NOR slowing down of movements UNLESS slowing down is accompanied by sensations of stiffness, NOR the feeling that the body, or parts of it do not belong to oneself (F6)

- Have you sometimes experienced unusual, numb or stiff feelings in your arms or legs or in another part of your body, since you started taking ketamine?
- When you experience this stiffness / numbness, do you feel as if you are paralysed and cant move, or are you actually moving slower? (qu to rule out O10 etc)

Rating: **Frequency II**

If needed: **Severity (III), Subjective Burden (IV), Effects on performance (VI), Consulting a doctor (VII)**

E2 Unusual bodily sensations of pain in a distinct area

(painful, often long-lasting sensations with a piercing, tearing or shooting quality, which cant be neurologically explained. Often occur at certain times of day, like sudden attack; often accompanied by affective disturbances; depth location is also often difficult. NOT Intense feelings of being electrified (E4)

- Do you sometimes have a peculiar pain, like a piercing, tearing or shooting feeling, since you started taking ketamine? Where is it located; how deep is it?
- Is this pain different from pains you had before you started taking ketamine?

Rating: **Frequency II**

If needed: **Severity (III), Subjective Burden (IV), Effects on performance (VI), Consulting a doctor (VII)**

E3 Migrating bodily sensations wandering through the body

(fluctuating, wandering sensations around body, which can increase to sometimes painful / attack-like severity); NOT a more static sensation (E5)

- Do you sometimes have irritating and uncomfortable body sensations that move through your body, and can even become painful since you started taking ketamine? If you do, what route do they take?

- Is this moving sensation different from sensations or pains you had before you started taking ketamine?

Rating: **Frequency II**

If needed: **Severity (III), Subjective Burden (IV), Effects on performance (VI), Consulting a doctor (VII)**

E4 Electric bodily sensations, feelings of being electrified

(feeling like being given an electric shock, which are not related to external influences. If described as painful, only score here NOT E2. If the electric sensations whirl, wander or circle around the body, score at E3 too)

- Since starting to take ketamine, do you sometimes experience a feeling that is like being given an electric shock?

Rating: **Frequency II**

If needed: **Severity (III), Quality of being new/different (IV), Subjective burden, (VI), Effects on performance (VI), Consulting a doctor, (VII)**

E5 Bodily sensations of movement, pulling or pressure inside the body or on its surface

(sensations perceived as if something is actually moving inside the body, organs or on the skin - itching, vibrating, shaking, knocking, trembling, quivering, twitching, crawling, digging, tearing, stroking); NOT just a sensations swirling, circling around body (E3)

- Since you started taking ketamine, do you sometimes have the feeling as if something is moving inside your body, or on your skin?
- How would you describe this feeling? Is it like a twitching, jumping, vibrating, knocking or trembling?

Rating: **Frequency II**

If needed: **Severity (III), Subjective Burden (IV), Effects on performance (VI), Consulting a doctor (VII)**

E6 **Sensations of the body or parts of it extending, diminishing, shrinking, enlarging, growing or constricting**

(can affect whole body or just parts, and generally 'attack-like'. Often accompanied by affective changes, which can escalate to panic depending on the 'reality' of the sensations); NOT sensations of body being heavy, light or empty, falling or sinking, NOR depersonalisation.

- Do you sometimes feel as if your whole body or parts of it is going to shrink or grow or change in some way?

Rating: **Frequency II**
If needed: **Severity (III), Subjective Burden (IV), Effects on performance (VI), Consulting a doctor (VII)**

F) *Perception disturbances*

I'm going to ask you a few more questions about your vision and hearing now.

F1 Hypersensitivity to light or certain optic stimuli

(NOT scored if these experiences occur as a result of a migraine, epileptic aura or another known physical illness)

- Have you become much more sensitive to sunlight, or felt things were brighter than usual, since you started taking ketamine?
- Have you consulted a doctor about this? If so, what did they say?

Rating: **Frequency II**

If needed: **Subjective burden (IV), Coping (V), Effects on B&P (VI)**

F2 Photopsia

(are simple moving or fixed white, bright or coloured hallucinations in form of flashes, stars, flames, circles or very strong, blinding light. ONLY SCORE when it causes SUBJECTIVE complaints and is NOT related by the individual to the outside world but to themselves)

- Do you sometimes see flashes of light or other very bright figures like stars, dots or flames in your eyes? Have you always had this, or has it developed since you started taking ketamine?
- Have you consulted a doctor about this? If so, what did they say?

Rating: **Frequency II**

If needed: **Subjective burden (IV), Effects on B&P (VI)**

F3 Micropsia, Macropsia

- Do objects ever appear bigger or smaller than they really are, or distorted in any way?
- Have you always had this, or has this developed since you started taking ketamine?

Rating: **Frequency II**

If needed: **Severity (III), Subjective burden (IV), Effects on B&P (VI)**

F4 Hypersensitivity to sounds or noise

(sounds of unchanged intensity or quality are experienced as too loud, distracting or annoying; NOT changed intensity, quality of sound, F5)

- Are you much more sensitive to sounds and noise in comparison to before you started taking ketamine?
- Have you consulted a doctor about this? If so, what did they say?

Rating: Frequency II

If needed: Subjective burden (IV), Effects on B&P (VI)

F5 Changes in the perceived intensity or quality of acoustic stimuli

(Do not score a sole hypersensitivity to sounds without any qualitative changes in auditory perceptions (F4) or derealisation – which also requires visual perceptual distortions (O8) here)

- Do you sometimes have strange problems with hearing? Can you describe them?
- Do you sometimes have sudden and short-lived difficulties with your hearing such as sounds seeming muffled or less loud or short periods of deafness?
- Have you always had these experiences, or have they developed since you started taking ketamine?
- Have you consulted a doctor about this? If so, what did they say?

Rating: Frequency II

If needed: Severity (III), Subjective burden (IV), Effects on B&P (VI)

F6 Somatopsychic bodily depersonalisation

The body or parts of it are perceived as not belonging to oneself anymore, as isolated or separated from each other or not existing at all OR body is perceived as falling apart/ body parts seem no longer to be connected, although all parts still belong to the person affected. (NOT depersonalisation nor visual perceptions of changes in the person's face or expression which cause the individual to repeatedly check themselves in the mirror)

- Do you sometimes feel as if parts of your body have been separated from the rest of your body or do not exist anymore?
- Are you sometimes unable to feel your body or parts of it?
- Do you sometimes have a feeling as if your body could fall apart like a jigsaw?
- Have you always had this, or is it an experience that has developed since starting to take ketamine?

Rating: Frequency II

If needed: Severity (III), Subjective burden (IV), Effects on B&P (VI), Consulting a doctor (VII)

O) *Optional Extras:*

O1 Thought perseveration

(usually re: events, conversations, mundane things that have happened a few hours earlier, maybe even the day before; thoughts all following the same theme. NOT a depressive rumination about a negative future, NOR thought interference (C2) where unimportant thought/image interferes with funcitoning *without* being constantly repeated, NOR thought pressure (D3) where there is a succession of unrelated thoughts)

- Do you sometimes have to think about past unimportant conversations or events, when you want to think about something else?
- Does this ever take the form of images in your mind's eye?

Rating: **Frequency II**

If needed: **Subjective Burden (IV), Coping (V), Effects on B&P (VI)**

O2 Decreased ability to discriminate between ideas and perception, pure fantasy and true memories

- Are you sometimes unsure whether you actually see or hear something, or if you just imagined it?
- Do you sometimes become confused whether you have actually done certain things in the past or just imagined them? Do you ever ask others to make sure?
- Have you always had these experiences, or have they developed since you started taking ketamine?

Rating: **Frequency II**

If needed: **Subjective Burden (IV), Coping (V), Effects on B&P (VI)**

O7 Captivation of attention by details of the visual field

(NOT 'feeling overly distracted by stimuli' (B2) where attention is easily distracted by *all* kind of things going on in the environment, so that s/he has difficulties to focus on one thing, here, the attention is fixed on one thing and the rest of the environment is not paid any attention anymore)

- Since you starting taking ketamine, have you ever noticed that specific aspects of the environment you are looking at really stand out in a striking way, and seem somehow isolated from the rest?
- Do you ever have to stare at these details, without actually wanting to?

Rating: **Frequency II**

If needed: **Subjective Burden (IV), Coping (V), Effects on B&P (VI)**

O8 Derealisation

- Since starting ketamine, do you sometimes experience your surroundings as changed, unreal or strange? As if the world around you isn't quite real? (subtype 1)
- Have there been times when you have experienced a high, euphoric mood during which your surroundings, the landscape, animals or people seemed different, somehow great, impressive and moving? (subtype 2)

Rating: **Frequency II**

If needed: **Severity (III), Subjective Burden (IV)**

O10 Motor Blockages

(Impediment or complete blockage of intended motor actions that appear attack-like, all of a sudden, and vanish quickly)

- Are you sometimes, especially in the morning, suddenly unable to speak or move although you are fully awake?

Rating: **Frequency II**

If needed: **Subjective Burden (IV), Coping (V), Effects on B&P (VI)**

AND FINALLY....

Are there any other changes to how your mind works I may have missed? or any feelings or behaviours that you think have changed since you started taking ketamine?

How often has this affected you?
How much does it affect you?

Frequency
Looking at this scale and taking into account everything you have just told me, how frequently do you believe this ..... has occurred in the last week?

Severity (III)
Taking into account everything you have told me how severe has this been?

Subjective Burden (IV)
Taking into account everything you have just told me, how burdened do you feel by this?

Coping (V)

Taking into account everything you have just told me, do you believe you are currently able to cope with difficulties with this..... or do you think that the difficulties are not bad enough to have to "cope" with them?

Effects on Behaviour & Performance (VI)

Do you currently avoid certain places, situations, people or activities because of this.....?

Include information the participant has told you previously about their behaviour and functioning to judge this answer.

Effects on quality of life (VI)

Taking into account everything you have just told me, how has .....x..... affected your quality of life?

Consultation with a doctor (VII)

Have you considered consulting a doctor about these experiences? If so, how many appointments have you had, and how many doctors have you seen?

Areas of life (VIII)

Taking into account everything you have just told me, how many areas of your life do you believe .....x..... has affected in the last week?

Appendix 6

SPI-A item self-rating cards

FREQUENCY ONE PARTICIPANT
SCORING SHEET

	ABSENT (0)	RARE (I)	MILD (2)	MODERATE (3)	MODERATELY SEVERE (4)	SEVERE (5)	EXTREME (6)
(I) FREQUENCY	NEVER	LESS THAN ONCE A WEEK	ONCE IN A WEEK	SEVERAL TIMES A WEEK	RATHER DAILY, LONGER PERIODS OF IMPROVEMENT POSSIBLE (ONE TO SEVERAL DAYS)	DAILY SHORT PERIODS OF IMPROVEMENT POSSIBLE (up to 24 hours)	DAILY AND PERSISTENT

FREQUENCY TWO PARTICIPANT
SCORING SHEET

	ABSENT (0)	RARE (I)	MILD (2)	MODERATE (3)	MODERATELY SEVERE (4)	SEVERE (5)	EXTREME (6)
(II) FREQUENCY	NEVER	LESS THAN ONCE A MONTH	SHORT PERIODS ABOUT ONCE IN A MONTH	SEVERAL TIMES IN A MONTH OR WEEKLY	SEVERAL TIMES A WEEK	RATHER DAILY PERIODS OF IMPROVEMENT POSSIBLE	DAILY BUT NOT NECESSARILY CONTINUOUSLY

Use ONLY when frequency is in doubt

	ABSENT (0)	RARE (1)	MILD (2)	MODERATE (3)	MODERATELY SEVERE (4)	SEVERE (5)	EXTREME (6)
(3) SEVERITY		VERY LOW	LOW, SLIGHTLY IRRITATING	MODERATE, IRRITATING	MODERATELY SEVERE, IRRITATING	SEVERE, VERY IRRITATING	EXTREME, REALITY TESTING HARDLY POSSIBLE
(4) SUBJECTIVE BURDEN		NONE	MINIMAL	HARDLY ANY	LOW	MODERATE	HIGH
(5) COPING WITH IT BY INCREASING EFFORT		DOES NOT REQUIRE COPING	EASILY AND ALWAYS POSSIBLE	ALWAYS POSSIBLE	MOSTLY POSSIBLE	HARDLY / RARELY POSSIBLE	NOT POSSIBLE
(6) EFFECTS ON BEHAVIOUR, PERFORMANCE. LEVEL OF FUNCTIONING OR ENVIRONMENT		NONE	NONE	HARDLY ANY EFFECT	LITTLE AVIODANCE OF RESPECTIVE SITUATIONS, LIKITING ACTIVITIES. NO TO MILD DECREASE IN PERFORMACE	AVIODANCE OF RESPECTIVE SITUATIONS, OBVIOUS DECREASE IN PERFORMANCE, SOCIAL DIFFICULTIES	AVIODANCE. SIGNIFICANT DECREASE IN FUCNTIOING AND/OR CONFLICTS WITH ENVIRNMENT
(7) CONSULTING A DOCTOR FOR THE PROBLEM		NOT CONSIDERED	CONSIDERED	SERIOUSLY CONSDIERED	SINGLE CONTACT	ONE OT MORE APPOINTMENTS WITH SAME DOCTOR	CONSULTING VARIOUS DOCTORS
(8) AREAS OF LIFE		VERY CIRCUMSCRIPT WITHIN ONE AREA	ONE	FEW AND VERY CIRCUMSCRIPT	FEW	MOST	ALL

Appendix 7

SPI-A score sheets

SPIA SCORE SHEET **Participant ID:**.....

A = Affective-Dynamic Disturbances

		1	2	3	4	5	6	7	8	9
	A1.1: Impaired tolerance to unusual, unexpected or specific novel demands									
	A1.2: Impaired tolerance to certain social everyday situations									
B1	**A1.3**: Impaired tolerance to working under pressure of time or rapidly changing different demands									
A3	**A2**: Change in mood and emotional responsiveness									
	A3: Decrease in positive emotional responsiveness towards others									
	SUM SCORES 1-6 ONLY									

Extra information / verbatim quotes:

SPIA SCORE SHEET **Participant ID:**.....

B = Cognitive-Attentional Impediments

		1	2	3	4	5	6	7	8	9
	B1: Inability to divide attention									
B1, C2, D3	**B2**: Feeling overly distracted by stimuli									
B1, B2, B4 C2, O1, O7, D3, C3, C4, C6	**B3**: Difficulties concentrating									
	B4: Difficulties to hold things in mind for less than half an hour									
B3, C4, C5	**B5**: Slowed-down thinking									
O11	**B6**: Lack of 'thought energy', purposive thoughts									
	SUM SCORES 1-6 ONLY									

Extra information / verbatim quotes:

SPIA SCORE SHEET **Participant ID:**.....

C = Cognitive Disturbances

		1	2	3	4	5	6	7	8	9
B3	**C1**: Increased indecisiveness with regard to insignificant choices between equal alternatives									
B2, C3, O1	**C2**: Thought interference									
	C3: Thought blockages									
	C4: Disturbance of receptive speech									
	C5: Disturbance of expressive speech									
	C6: Disturbance in immediate recall									
	SUM SCORES 1-6 ONLY									

Extra information / verbatim quotes:

SPIA SCORE SHEET **Participant ID:.....**

D = Disturbances in Experiencing Self and Surrounding

		1	2	3	4	5	6	7	8	9
A2, A3	**D1**: Decreased capacity to discriminate between different kinds of emotions									
O1	**D2**: Increased emotional reactivity in response to routine social interactions									
C1, O1	**D3**: Thought pressure									
	D4: Unstable ideas of reference									
	D5: Changed perception of the face or body of others									
	SUM SCORES 1-6 ONLY									

Extra information / verbatim quotes:

SPIA SCORE SHEET **Participant ID:**.....

E = Body Perception Disturbances

		1	2	3	4	5	6	7	8	9
F6, O10	**E1**: Bodily sensations of numbness and stiffness									
E4	**E2**: Bodily sensations of pain in a distinct area									
E5	**E3**: Bodily sensations migrating through the body									
E2	**E4**: Bodily sensations of being electrified									
E3	**E5**: Bodily sensations of movement or pressure									
	E6: Bodily sensations of body / body parts changing size									
	SUM SCORES 1-6 ONLY									

Extra information / verbatim quotes:

SPIA SCORE SHEET

Participant ID:.....

F = Perception Disturbances

		1	2	3	4	5	6	7	8	9
	F1: Hypersensitivity to light / optic stimuli									
	F2: Photopsia									
	F3: Micropsia, macropsia									
F5	**F4**: Hypersensitivity to sounds / noise									
F4,O8	**F5**: Changed intensity / quality of acoustic stimuli									
	F6: Somatopsychic bodily depersonalisation									
	SUM SCORES 1-6 ONLY									

Extra information / verbatim quotes:

SPIA SCORE SHEET

Participant ID:.....

O = Optional Extras

		1	2	3	4	5	6	7	8	9
C2, D3	**O1**: Thought perseveration									
	O2: Less discrimination between ideas & perception, fantasy & true memories									
B2	**O7**: Captivation of attention by details of the visual field									
	O8: Derealisation									
	O10: Motor blockages									
	SUM SCORES 1-6 ONLY									