



# Preliminary analysis of positive and negative syndrome scale in ketamine-associated psychosis in comparison with schizophrenia

Ke Xu <sup>a,c</sup>, John H. Krystal <sup>a,c</sup>, Yuping Ning <sup>b</sup>, Da Chun Chen <sup>f</sup>, Hongbo He <sup>b</sup>, Daping Wang <sup>b</sup>, Xiaoyin Ke <sup>b</sup>, Xifan Zhang <sup>d</sup>, Yi Ding <sup>b</sup>, Yuping Liu <sup>b</sup>, Ralitza Gueorguieva <sup>a,e</sup>, Zuoheng Wang <sup>e</sup>, Diana Limoncelli <sup>c</sup>, Robert H. Pietrzak <sup>a,c</sup>, Ismene L. Petrakis <sup>a,c</sup>, Xiangyang Zhang <sup>f</sup>, Ni Fan <sup>b,\*</sup>

<sup>a</sup> Department of Psychiatry, Yale School of Medicine, 300 George St, New Haven, CT, USA

<sup>b</sup> Guangzhou Brain Hospital, The Affiliated Brain Hospital of Guangzhou Medical University, 36 Mingxin Road, Liwan District, Guangzhou, Guangdong Province 510370, China

<sup>c</sup> United States Department of Veterans Affairs, VA Connecticut Healthcare System, West Haven, CT, USA

<sup>d</sup> Guangzhou Baiyun Mental Health Hospital, China

<sup>e</sup> Department of Biostatistics, Yale School of Public Health, New Haven, CT, USA

<sup>f</sup> Biological Psychiatry Center, Beijing Hui-Long-Guan Hospital, Peking University, Beijing 100096, China

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## ABSTRACT

**Objective:** Studies of the effects of the *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist, ketamine, have suggested similarities to the symptoms of schizophrenia. Our primary goal was to evaluate the dimensions of the Positive and Negative Syndrome Scale (PANSS) in ketamine users (acute and chronic) compared to schizophrenia patients (early and chronic stages).

**Method:** We conducted exploratory factor analysis for the PANSS from four groups: 135 healthy subject administered ketamine or saline, 187 inpatients of ketamine abuse; 154 inpatients of early course schizophrenia and 522 inpatients of chronic schizophrenia. Principal component factor analyses were conducted to identify the factor structure of the PANSS.

**Results:** Factor analysis yielded five factors for each group: positive, negative, cognitive, depressed, excitement or dissociation symptoms. The symptom dimensions in two schizophrenia groups were consistent with the established five-factor model (Wallwork et al., 2012). The factor structures across four groups were similar, with 19 of 30 symptoms loading on the same factor in at least 3 of 4 groups. The factors in the chronic ketamine group were more similar to the factors in the two schizophrenia groups rather than to the factors in the acute ketamine group. Symptom severities were significantly different across the groups (Kruskal–Wallis  $\chi^2(4) = 540.6$ ,  $p < 0.0001$ ). Symptoms in the two ketamine groups were milder than in the two schizophrenia groups (Cohen's  $d = 0.7$ ).

**Conclusion:** Our results provide the evidence of similarity in symptom dimensions between ketamine psychosis and schizophrenia psychosis. The interpretations should be cautious because of potential confounding factors.

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## 1. Introduction

Ketamine, an uncompetitive *N*-methyl-D-aspartate glutamate receptor (NMDAR) antagonist, has been used in behavioral studies

\* Corresponding author. Guangzhou Brain Hospital, 36 Mingxin Rd, Liwan District, Guangzhou, Guangdong 510370, China.

E-mail address: [fanni2005@126.com](mailto:fanni2005@126.com) (N. Fan).

in animals and humans as a pharmacologic model for symptoms and cognitive impairments associated with schizophrenia (Abi-Saab et al., 1998; Krystal et al., 2003; Lahti et al., 2001; Zugno et al., 2013). Ketamine acute administration in healthy subjects produces symptoms that experienced raters employing validated rating scales for assessing schizophrenia score as positive symptoms (psychosis), negative symptoms (withdrawal, amotivation, blunted affect), thought disorder (Adler et al., 1998; Adler et al., 1999), and cognitive impairment (Curran and Monaghan, 2001;

Krystal et al., 1999, 1994; Lahti et al., 1995; Malhotra et al., 1997). Ketamine also produces alterations in cortical circuit function in healthy subjects that resemble schizophrenia, including reductions in working memory-related prefrontal cortical activation (Anticevic et al., 2013; Driesen et al., 2013) and functional connectivity (Dawson et al., 2014). Recent data suggest that genes associated with NMDA receptor signaling, potentially mimicking some aspects of NMDA receptor antagonism, contribute in important ways to the heritable risk for schizophrenia (Tarabeux et al., 2011; Timms et al., 2013). For these reasons, the effects of NMDA receptor antagonists emerge as one of the central models for schizophrenia drug development (Coyle et al., 2002; Javitt, 2008; Nikiforuk et al., 2013; Vollenweider and Kometer, 2010).

In both animals and humans, the effects of chronic ketamine administration also have been used as a model for schizophrenia (Moghaddam and Krystal, 2012; Schobel et al., 2013; Stone et al., 2013). In contrast to studies of acute ketamine effects, the “chronic model” studies change in behavior and brain structure that persist after repeated ketamine administration (Chatterjee et al., 2012; Edward Roberts et al., 2014; Wiescholleck and Manahan-Vaughan, 2013). Typically, long-term ketamine abuse is associated with mild levels of persisting symptoms and cognitive impairments, below the severity levels associated with psychotic disorders, accompanied by reductions in cortical volumes and cortical activation (Morgan et al., 2009, 2010). However, a small minority of ketamine or phencyclidine abusers (another NMDA antagonist) develops a persisting psychiatric syndrome that has been suggested to resemble “endogenous” psychotic disorders, such as schizophrenia and bipolar disorder (Fauman and Fauman, 1980; Fine and Finestone, 1973; Javitt et al., 2012). These observations stimulate a generation of basic animal research on the chronic effects of NMDA receptor antagonists. Importantly, the chronic effects of NMDA receptor antagonists emerge as a distinct animal model from the acute effects of these drugs for medication development for schizophrenia (Cannon et al., 2013; Jentsch and Roth, 1999; Moghaddam and Jackson, 2003).

The purpose of the current study was to conduct a preliminary analysis of symptom dimensions in comparison of two forms of ketamine-associated psychosis (acute ketamine effects in healthy subjects, individuals hospitalized attributed to chronic ketamine abuse) and two phases of the illness (early course, chronic illness) in groups of schizophrenic inpatients. Because no theoretical model of symptom dimensions for ketamine psychosis is available, we conducted data driven, exploratory factor analyses for ketamine associated psychosis and schizophrenia psychosis. Two general strategies were employed to address this aim: 1) to characterize the degree of concordance of the factor structure of the principal symptom assessment tool for schizophrenia, PANSS (Kay et al., 1987); and 2) to compare the severity of the symptom clusters typically reported in studies of schizophrenia patients.

## 2. Methods

The study was approved by Yale Human Research Protection Program, and the Institutional Review Boards in Guangzhou Brain Hospital and Beijing Hui-Long-Guan Hospital. All participants in this study gave written informed consent prior to their participation.

### 2.1. Participants

Data for acute ketamine, early and chronic schizophrenia groups were extracted from our previously reported studies. For more information on these studies, please see references (Chen da et al., 2011; Dickerson et al., 2010; Krystal et al., 2005a, 2005b; Zhang

et al., 2012). Inclusion and exclusion criteria for each group are presented in the [Supplemental Material](#).

Acute ketamine administration: data were extracted from 135 healthy subjects using PANSS assessment. All participants in the studies were infused with ketamine or saline in randomized, single-blinded fashion. This study only reported on data from day in which subjects received ketamine or saline. Data from the day of saline was used as a reference for the purpose of group comparisons. The subject characteristics including demographics, methods including dose of ketamine administration are described in [Table 1](#) and [Supplemental Table 1](#).

Chronic ketamine use: 187 chronic ketamine abusers were recruited from substance abuse inpatient units in Guangzhou Brain Hospital and Guangzhou Baiyun Mental Health Institute, Guangdong, China. These individuals were heavy ketamine abusers and were voluntarily admitted to inpatient units for ketamine detoxification. Inclusion criteria were: 1) subjects voluntarily seeking inpatient treatment; 2) subjects with ketamine as a drug of choice for longer than 6 months prior to interview; and 3) documentation of the presence of ketamine in a urine sample. Patients with a prior history of psychiatric and neurological diseases were excluded. Patients who used other substances or who presented with current symptoms of depression were included because of high co-morbidity rates (Morgan et al., 2010; Tang et al., 2013). The patterns of the ketamine use are reported in [Table 1](#).

Early course of schizophrenia: A total of 154 patients with early course schizophrenia (operationalized as 1) symptom duration of less than five years, and 2) first psychiatric admission) who were not previously exposed to psychiatric medications were recruited from the inpatient unit of Beijing Hui-Long-Guan Psychiatric Hospital, Beijing, China. Demographics and clinical features are presented in [Table 1](#). A detailed description of these participants was reported elsewhere (Zhang et al., 2013).

Chronic schizophrenia: A total of 522 inpatients with schizophrenia were recruited from Beijing Hui-Long-Guan psychiatric hospital, Beijing, China (Chen da et al., 2011). The average dose of each antipsychotic with chlorpromazine equivalent is listed in [Supplemental Table 2](#).

**Table 1**

Demographic and clinical characteristics for acute ketamine (AK), chronic ketamine (CK), early course of schizophrenia (EC-SZ) and chronic schizophrenia (C-SZ).

	AK (N = 135)	CK (N = 187)	EC-SZ (N = 154)	C-SZ (N = 522)
Age (year)	24.8 ± 3.3	26.2 ± 5.0	26.2 ± 9.4	49.4 ± 11.1*
Sex (Male)	50%	90%*	60%	66%
Race				
Chinese	0	100%	100%	100%
Caucasian	76%	0	0	0
African American	12%	0	0	0
Other	12%	0	0	0
Education (year)	16.0 ± 2.1*	10.5 ± 2.7	7.6 ± 3.0	10.5 ± 8.3
Duration (month)	0	75.6 ± 37.2	25.6 ± 0.9	120.1 ± 114.1*
Number of hospitalizations	–	3.2 ± 2.3	1	3.4 ± 2.8
Age of onset (year)	–	20.0 ± 5.0	25.9 ± 9.5	24.4 ± 8.4
(Mean±)(range)	–	(11–24)		
Average daily ketamine use (gram) (Mean ± SD)/ (range)	–	3.4 ± 2.7 (0.1–15)	–	–
Maximum ketamine use (mean ± SD)/gram (range)	–	6.9 ± 6.0 (0.7–28)	–	–
Current smokers	0	73%	49%	76%**
Other substance abuse (Yes)	0	86%	0	0

\*p < 0.001 (Comparison in the four groups).

\*\*p < 0.05 (Comparison between the C-SZ group and the EC-SZ group).

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