Published in final edited form as:

J Psychiatr Res. 2015 February ; 61: 64–72. doi:10.1016/j.jpsychires.2014.12.012.

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

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

^aDepartment of Psychiatry, Yale School of Medicine, 300 George St, New Haven, CT, USA

^bGuangzhou Brain Hospital, The Affiliated Brain Hospital of Guangzhou Medical University, 36 Mingxin Road, Liwan District, Guangzhou, Guangdong Province 510370, China

^cUnited States Department of Veterans Affairs, VA Connecticut Healthcare System, West Haven, CT, USA

^dGuangzhou Baiyun Mental Health Hospital, China

^eDepartment of Biostatistics, Yale School of Public Health, New Haven, CT, USA

^fBiological Psychiatry Center, Beijing Hui-Long-Guan Hospital, Peking University, Beijing 100096, China

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 administrated ketamine or saline, 187 inpatients of ketamine abuse; 154 inpatients

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*Corresponding author. Guangzhou Brain Hospital, 36 Mingxin Rd, Liwan District, Guangzhou, Guangdong 510370, China. fanni2005@126.com (N. Fan).

Contributors

Ni Fan and Ke Xu designed the study and wrote the protocol. Ke Xu wrote the first draft of the manuscript and Ni Fan revised the manuscript. John H Krystal and Robert H Pietrzak contributed to data interpretation, discussion and the manuscript preparation. Xiaoyin K, YiDing and Chao Zhou recruited the chronic ketamine abusers. Yuping Ning and Hongbo He helped on subject recruiting. Xifan Zhang, Daping Wang and Yuping Liu helped enrolling ketamine abusers. John H Krystal, Diana Limoncelli and Ismene Petrakis contributed to data collection for the acute ketamine administration group. Da Dun Chen and Xiangyang Zhang collected data for the early course and chronic schizophrenia groups; Ralitza Gueorguieva and Zuoheng Wang involved data analysis and contributed to the manuscript preparation.

All authors contributed to and have approved the final manuscript.

Conflict of interest

Dr. Krystal has served as a scientific consultant to Novartis Pharma AG and Naurex, Inc. He holds stock in Biohaven Medical Sciences and stock options in Mnemosyne Pharmaceuticals, Inc. Dr. Krystal is a co-sponsor for three patents. Dr. Petrakis provides consultation for Alkermes Company and Recovery Centers of America.

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.

Keywords

Ketamine psychosis; Schizophrenia; Positive and Negative Syndrome Scale (PANSS); Factor analysis; Symptom severity

1. Introduction

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

2.2. Assessment of psychotic symptoms

Psychiatric symptomatology was assessed using the PANSS (Kay et al., 1987). The PANSS includes: positive symptom domain (P, 7 items), negative domain (N, 7 items) and general pathology domain (G, 16 items).

2.3. Statistical analysis

All data analyses were conducted using JMP Statistic Discovery from SAS, version 9.0 (<http://www.jmp.com/software/jmp/>).

To identify the factor structure of the PANSS, we conducted principal axis factor analysis with varimax rotation. The factor solutions for each group were determined by the Kaiser's criteria (eigenvalue greater than 1.0 or more) and inspections of screen plots. We used the cutoff 1.5 to determine the number of factors. Only items whose factor loading was greater than 0.4 were retained for establishing factor structure (Jiang et al., 2013). Items were allowed to be cross-loaded on different factors in different groups.

To compare the symptom severity in five groups including saline infusion in healthy subjects as a benchmark for comparison, acute ketamine infusion, chronic ketamine use, early-course of schizophrenia and chronic schizophrenia, we conducted Kruskal–Wallis test (the non-parametric equivalent to one-way ANOVA) on the total PANSS scores and the subscale scores for each of three classic clusters (Positive, Negative, and General pathology subscales). Post-hoc pairwise comparisons between the groups were performed using

Wilcoxon test. Individual symptom severity in ketamine psychosis and schizophrenia psychosis was compared using Kruskal–Wallis test for each item rating among four groups. The healthy control group was excluded for these comparisons due to low variability. Bonferroni corrections were applied to adjust for multiple comparisons.

3. Results

3.1. Participant characteristics of ketamine psychosis and schizophrenia psychosis

3.1.1. Subjects with ketamine psychosis—There was no significant group difference in age between the acute ketamine and chronic ketamine groups ($p = 0.22$). There were significantly more men in the chronic ketamine group than in the acute ketamine group ($p < 0.05$). Subjects in the acute ketamine group were significantly more educated than subjects in the chronic ketamine group ($p < 0.05$). All subjects in the chronic ketamine group were Han Chinese, while there were mixed ethnicities in the acute ketamine group (Table 1).

The patients in the chronic ketamine group were particularly severe ketamine abusers. Age of onset was 19.97 years old. Ketamine use was heavy with average daily dose of 3.37 ± 2.72 g (range of 0.1–15 g) and maximal dose was 6.9 ± 6.0 g (range of 0.7–28 g). Average duration of use was 6.3 ± 3.1 years and 75.4% of them were daily users. The average number of hospitalizations for the treatment was 3.19 ± 2.57 . Eighty-six percent of ketamine abusers were polydrug users. The most common drugs co-used with ketamine were 3,4-methylenedioxy-N-methylamphetamine MDMA (44%), amphetamine (11%), codeine (11%).

3.1.2. Subjects with schizophrenia psychosis—There was no significant difference in gender and years of education between two schizophrenia groups. The average age of the chronic schizophrenia group was significant older than the average age of inpatients in early schizophrenia group ($p < 0.001$). The age of first hospitalization did not significantly differ between two schizophrenia groups ($p > 0.05$). All patients in the chronic schizophrenia group were treated with antipsychotics. The average dose of chlorpromazine equivalents (mg) was 493.08 ± 533.62 . The detailed medication and dose of chlorpromazine equivalents is presented in Supplemental Table 2. No subject in either chronic schizophrenia or early schizophrenia group abused substances except cigarette smoking.

3.2. Factor structure of PANSS in the acute ketamine, chronic ketamine, early schizophrenia and chronic schizophrenia groups

Principal component factor analysis identified five factors for each group: negative, positive, cognitive, depressed, and excitement (for chronic ketamine and two schizophrenia groups) or dissociation (for acute ketamine). The fifth factor was interpreted to represent excitement and had similar structure in the chronic ketamine and two schizophrenia groups, but appeared to represent disassociation domain in the acute ketamine group. Factor structures and loadings for each group are presented in Table 2A–D.

To evaluate the degree of the similarity of factor structure among the four groups, we described items in each factor as common symptoms and uncommon symptoms. The common symptom presented across at least 3 out of 4 groups. The uncommon symptoms

were loaded in one or two groups only. Among the 30 PANSS items, 19 items were common, suggesting highly consistent symptoms between ketamine-psychosis and schizophrenia-psychosis (Table 3). Among 19 common items, 15 items were the same as the previously established five factor model for schizophrenia (Wallwork et al., 2012) (Table 3: items are highlighted as red).

The detailed factor structures were described below.

Negative factor: The items in this factor were most consistent across the four groups. Six common symptoms were: blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive/apathetic social withdrawal (N4), lack of spontaneity & flow of conversation (N6), and motor retardation (G7). These six symptoms were completely identical of Negative factor in Wallwork's five factor model. The uncommon symptom of difficulty of abstract thinking (N5) was in the chronic ketamine and chronic schizophrenia groups. Conceptual disorganization (P2) and poor attention (G11) were seen in the chronic schizophrenia group only.

Positive factor: Four common symptoms were delusion (P1), hallucination (P3), Excitement (G9) and lack of insight (G12). Uncommon symptoms of suspiciousness/persecution (P6) showed in the early schizophrenia and chronic schizophrenia, while grandiosity (P5) showed only in the chronic schizophrenia group.

Depressed factor: Three out of five symptoms were common across four groups: anxiety (G2), guilty feelings (G3), and depression (G6). Uncommon symptoms, somatic concern (G1) and tension (G4), were loaded on this factor in the chronic schizophrenia only.

Cognition factor: The common symptoms in this factor were stereotyped thinking (N7), poor attention (G11) and disturbance of volition (G13). Uncommon symptom, tension, (G4) was seen in the acute ketamine group only and conceptual disorganization (P2)/difficulty in abstract thinking (N5) were identified in the early schizophrenia group only.

Excitement or Disassociation factor: Three common symptoms were excitement (P4), hostility (P7), poor impulse control (G14) and were present in the chronic ketamine, early schizophrenia and chronic schizophrenia groups. However, none of these items were loaded on this factor in the acute ketamine group. In the acute ketamine group, this factor was constructed by conceptual disorganization (P2), somatic concern (G1), difficulty in abstract thinking (N5), uncooperativeness (G8) and lack of judgment and insight (G12) and was interpreted as disassociation factor.

3.3. Symptom severity comparisons

3.3.1. Comparison of total PANSS score and three subscale scores in five groups—PANSS scores obtained from the saline infusion among healthy controls were used as reference. Because symptom dimensions in the four psychosis groups were not completely identical, we were unable to directly compare the severity of symptom cluster across groups based on the five-factor model. Instead, we compared the severity of symptom

cluster in the classic three-factor model of PANSS with positive, negative, and general pathology subscales. Total PANSS score and each subscale score were compared among the five groups (Fig. 1A–D, left). Furthermore, we performed pairwise post hoc comparison of each symptom cluster (Fig. 1A–D, right).

Total PANSS scores among five groups were significantly different (Kruskal–Wallis test $\chi^2(4) = 540.6$, $df = 4$, $p < 0.0001$) (Fig. 1A, left). Each pairwise comparison was also significant after Bonferroni correction (p values < 0.0005) (Fig. 1A, right). Total scores of the PANSS in the two schizophrenia groups were significantly greater than in the scores of the two ketamine groups ($\chi^2(1) = 379.2$, p value < 0.0001 , Cohen's $d = 1.7$). The total PANSS in the chronic ketamine group was significantly greater than the score in the acute ketamine group ($\chi^2(1) = 84.7$, $p < 0.0001$, Cohen's $d = 1.4$). In the two schizophrenia groups, early-course of schizophrenia was associated with more severe symptoms than chronic schizophrenia ($\chi^2(1) = 379.2$, $p < 0.0001$, Cohen's $d = 1.3$).

The scores of symptom clusters in positive, negative and general pathology subscales were significantly different in the five groups (Fig. 1B–D) (p values < 0.0001). Post hoc comparisons showed that the ratings of negative and general pathology subscales in the chronic ketamine group were greater than the ratings in the acute ketamine group (p values < 0.0001), suggesting that chronic ketamine abuse produces more severe symptoms than acute ketamine administration. For the two schizophrenia groups, the ratings in positive and general pathology domains were greater in the early schizophrenia group than in the chronic schizophrenia group (p values < 0.0001).

3.3.2. Comparisons of each item rating in four groups—We further compared the rating of each item among the four psychosis groups and performed post-hoc pairwise comparisons. As showed in Fig. 2, although the symptom dimensions were similar between ketamine psychosis and schizophrenia, symptom severity across groups differed significantly. The p values of post hoc pairwise comparisons are listed in Supplemental Table 3. Of note, the ratings on emotional items (anxiety G2, feeling of guilty G3, and depression G6) and somatic concerns were greatest in the chronic ketamine group.

4. Discussion

This study provided the evidence for homology in the symptom dimensions between ketamine-associated psychosis and schizophrenia psychosis. The factor structure was similar for the positive, negative, cognitive and depressed domains measured by the PANSS. In contrast, the excitement domain, which included items associated with the sedative and dissociative effects of ketamine, differentiated the acute effects of ketamine from the persisting symptoms in the other groups. These symptoms are expected consequences of acute ketamine infusion in humans (Krystal et al., 1994).

Similarly, the factor structure of symptoms in the chronic ketamine group showed greater similarity than the acute ketamine group to the symptom factor structure of the two schizophrenia groups. This difference might be interpreted to suggest that chronic ketamine effects provide a better overall model of schizophrenia than acute ketamine effects.

However, the severe psychiatric responses to repeated ketamine administration observed in the chronic ketamine are highly atypical among community-based chronic ketamine users (Morgan et al., 2010). Thus, it would seem that the chronic ketamine group in this study either represents an extreme neuroadaptation to repeated ketamine exposure or the expression of an underlying propensity for developing a psychotic disorder revealed in the response to chronic ketamine administration.

In this study, the acute ketamine group generally manifested milder symptoms than the other groups. Ketamine has a very steep dose response curve in healthy humans such that differences of a few tenths of a mg/kg may determine whether or not psychotic symptoms are observed (Honey et al., 2008; Krystal et al., 1994). Although there was not a correlation between ketamine dose and the level of psychosis observed across studies, the between study dose differences constitute a very narrow range of ketamine dosing. Thus it is possible that higher subanesthetic ketamine doses would produce symptom levels more similar in intensity to the other groups.

The factor structures of PANSS identified in the schizophrenia groups are consistent with the previously well-established five factor model for schizophrenia (Wallwork et al., 2012). Among 20 items in Wallwork's five factor model, 18 items are loaded on the same factors in the early course of schizophrenia group and 17 symptoms are loaded on the same factors in the chronic schizophrenia group, which validates the factor structure findings in this study. Between the two groups of schizophrenia, individuals in the early course of schizophrenia had more severe overall symptoms, positive and general pathology symptoms than those in chronic schizophrenia. The differences between early course and chronic studies are consistent with a lifelong neurodevelopmental model for this disorder (Frost et al., 2004; McGlashan and Hoffman, 2000).

Of note, the configuration of the depressed domain was consistent across four groups (G2, G3, G6). However, the scores of three symptoms in the depressed domain were significantly different among four groups with the lowest score in the acute ketamine group. The score of G6 in the acute ketamine group was no difference with the saline control ($p > 0.05$). In the chronic ketamine group, the depressive symptom (G6) was as severe as in the early stage of schizophrenia group. These findings were consistent with other previous studies with ketamine infusion in healthy subjects and frequent ketamine abusers (Morgan et al., 2010; Scheidegger et al., 2012; Zhang et al., 2014), suggesting acutely ketamine administration in healthy subjects has little effect on depressive symptoms. However, repeated, long-term ketamine use for the treatment of depression may increase risk of depression.

This study has a number of limitations. First, this study was unable to control for the racial, ethnic, cultural, and contextual differences across the groups. For example, the acute ketamine group is a U.S. young adult sample of mixed ethnicity selected as a "super healthy" group devoid of risk factors for psychosis. In contrast, the chronic ketamine, early schizophrenia and chronic schizophrenia groups were Han Chinese individuals that were recruited from Chinese provinces that speak different Chinese dialects (chronic ketamine versus early schizophrenia and chronic schizophrenia). We previously reported that measurement of the PANSS in the U.S. and Chinese groups can be influenced by ethnicity

and culture (Aggarwal et al., 2011). Symptom severity measured by the PANSS in our acute ketamine U.S. group from the U.S. and three other groups from China might be influenced by such culture differences. However, the symptom clusters of measured by the PANSS are similar across different ethnicities. For example, a recent study reported the same five factors of the PANSS were shared in schizophrenia patients among Caucasian, Chinese and Brazilian groups (Stefanovics et al., 2014). In this study, four out of five symptom dimensions were shared among four groups from two ethnic groups, suggesting that common underlying neurobiological mechanisms of psychosis may share across different ethnic backgrounds. Additionally group differences also included different stage (chronic ketamine/early schizophrenia versus chronic schizophrenia) and gender (chronic ketamine versus early and chronic schizophrenia), presence of polydrug abuse (chronic ketamine versus early and chronic schizophrenia), chronicity of illness (early schizophrenia versus chronic ketamine and chronic schizophrenia), and uneven sample size between groups. These group differences may have introduced unappreciated confounds into the data.

Second, patients in the chronic schizophrenia group had long time treatment with a variety of antipsychotic medications, while three other groups had not. All patients in this group met the criteria of refractory schizophrenia and half of the patients were treated with clozapine. To address the effects of antipsychotics on the PANSS score, we tested the correlation between the PANSS score and dose for the latest antipsychotic medication (Chlorpromazine equivalents). We found that there was no significant correlation ($r^2 = 0.009$, $p = 0.06$). We further tested the correlation of antipsychotic dose and each subscale of the PANSS and found no significant correlations ($ps > 0.05$). Consistent with previous findings, correlation between course of illness and general pathology subscale was significant ($p = 0.02$) (Kay et al., 1987), however, there was no significant correlation after correcting for multiple testing. No significant correlation for the course of schizophrenia and total PANSS score was observed ($p > 0.5$). In the early stage of schizophrenia group, all patients had no prior history of antipsychotic exposure. They were recruited during the first admission to a psychiatric hospital and PANSS was assessed prior to administration of antipsychotics. These results suggest that it is reasonable to compare psychotic symptom clusters in two schizophrenia groups with psychosis in two ketamine groups.

Third, because of high-rate of polydrug use among ketamine users, we were unable to rule out the influences of other substances. We attempted to address this concern by recruiting the predominant individuals using ketamine as the drug of choice within the past six months prior to enrollment to the study. They were heavy ketamine users who required inpatient treatment for ketamine detoxification. Nevertheless, co-use of other drugs could be potential confounding factors for in the assessment of ketamine-associated psychosis. Three drugs, MDMA, amphetamine and codeine, commonly co-use drugs in this chronic ketamine group. Previously, several cases of persistent psychosis induced by MDMA use was reported, but no reports used the PANSS to assess psychotic symptoms (Patel et al., 2011; Potash et al., 2009). Our previous study found that amphetamine administration was associated with positive psychotic symptoms, while ketamine administration was associated with broader spectrum of psychotic symptoms including positive, negative symptoms and cognitive impairments (Krystal et al., 2005b). It is likely that ketamine associated psychosis in our chronic ketamine group is not fully influenced by amphetamine use.

Finally, because of the nature of the study, we are unable to conduct inter-rater reliabilities across groups although the agreement within each group was high ($\kappa > 0.8$). With these limitations in mind, we are cautious the interpretations of the findings.

In summary, this study explores the similarities in the dimensions of symptoms in ketamine psychosis and schizophrenia psychosis. These similarities support the ongoing exploration for the biological bases of the similarities observed across these groups in the effort to better understand the nature of glutamate synaptic dysfunction in schizophrenia. These data also support continued exploration of the hypothesis that drugs reverse the acute and chronic effects of ketamine in humans might play a role in the treatment of schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding source

This work is supported by grants from Chinese National Key Clinical Program in Psychiatry to Guangzhou Brain Hospital and from Health Bureau of Guangzhou (No: 20131A011091), China, the grant K12 DA000167 from National Institute on Drug Abuse, US, and APA/Merck Early Academic Career Award, US.

This work is supported by grants from Chinese National Key Clinical Program in Psychiatry to Guangzhou Brain Hospital and from Health Bureau of Guangzhou (No: 20131A011091), China, the grant K12 DA000167 from National Institute on Drug Abuse, US, and APA/Merck Early Academic Career Award, US. We thank the Alcohol Center at Veteran Affairs of Connecticut Healthcare and the Center of Translational neuroscience of Alcoholism supported by National Institute on Alcohol Abuse and Alcoholism.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jpsychires.2014.12.012>.

Fig. 1.

Comparisons of total PANSS score, positive, negative, and general pathology subscales in the five groups: in each panel, **left** figure represents comparisons in the five groups; **right** figure represents post hoc pairwise comparison. If circles overlap, it means no significant pairwise difference. If circles are far apart, it means there is significant pairwise difference. Significance level was set at 0.001 for Bonferroni correction (0.05/40). **A.** Total PANSS; **B.** Positive subscale; **C:** Negative subscale; **D.** General pathology subscale. AK: Acute ketamine; CK: Chronic ketamine; EC-SZ: Early course of schizophrenia; C-SZ: chronic schizophrenia.

Fig. 2. Comparison of each PANSS item in acute ketamine (AK), chronic ketamine (CK), early course of schizophrenia (EC-SZ), and chronic schizophrenia (C-SZ) groups. Significance level was set at 0.0003 (Bonferroni correction 0.05/180).

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) (Mean±)/(range)	–	20.0 ± 5.0 (11–24)	25.9 ± 9.5	24.4 ± 8.4
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).

Table 2A

Factor structure in the acute ketamine infusion group.

Item	Cognitive	Negative	Positive	Depressed	Disassociation
Disturbance of volition (G13)	0.727				
Preoccupation (G15)	0.726				
Stereotyped thinking (N7)	0.689				
Tension (G4)	0.625				
Mannerisms & posturing (G5)	0.587				
Poor attention (G11)	0.400				
Poor rapport (N3)		0.830			
Emotional withdrawal (N2)		0.815			
Blunted affect (N1)		0.788			
Lack of spontaneity& flow conversation (N6)		0.696			
Motor retardation (G7)		0.400			
Delusion (P1)			0.834		
Unusual thought content (G9)			0.825		
Hallucination (P3)			0.426		
Guilty feeling (G3)				0.817	
Depression (G6)				0.804	
Anxiety (G2)				0.546	
Active social withdrawal (G16)				0.532	
Somatic concern (G1)					0.629
Difficulty in abstract thinking (N5)					0.551
Conceptual disorganization (P2)					0.533
Uncooperativeness (G8)					0.475
Lack of judgment & insight (G12)					0.400
Eigenvalue	6.42	3.16	2.28	1.84	1.72
Variance (%)	15.1	14.1	10.4	7.96	7.48

Table 2B

Factor structure in the chronic ketamine abuse group.

Item	Negative	Cognitive	Positive	Excitement	Depressed
Blunted affect (N1)	0.816				
Emotional withdrawal (N2)	0.779				
Passive/apathetic social withdrawal (N4)	0.754				
Lack of spontaneity & flow of conversation (N6)	0.527				
Somatic concerns (G1)	0.540				
Motor retardation (G7)	0.445				
Difficulty in abstract thinking (N5)	0.409				
Unusual thought content (G9)		0.800			
Mannerisms & posturing (G5)		0.600			
Disorientation (G10)		0.600			
Preoccupation (G15)		0.564			
Poor attention (G11)		0.505			
Active social avoidance (G16)		0.445			
Delusion (P1)			0.658		
Hallucination (P3)			0.529		
Lack of judgment & insight (G12)			0.491		
Tension (P4)				0.800	
Grandiosity (P5)				0.792	
Hostility (P7)				0.651	
Guilty feelings (G3)					0.752
Depression (G6)					0.711
Anxiety (G2)					0.508
Eigenvalue	5.239	3.053	2.192	1.800	1.515
Variance	13.59	10.82	10.16	7.713	6.981

Table 2C

Factor structure in the early course of schizophrenia group.

	Negative	Cognitive	Positive	Depressed	Excitement
Blunted affect (N1)	0.825				
Emotional withdrawal (N2)	0.835				
Poor rapport (N3)	0.741				
Passive/apathetic social withdrawal (N4)	0.824				
Lack of spontaneity & flow of conversation (N6)	0.852				
Motor retardation (G7)	0.703				
Conceptual disorganization (P2)		0.743			
Difficulty in abstract thinking (N5)		0.569			
Stereotyped thinking (N7)		0.656			
Poor attention (G11)		0.654			
Disturbance of volition (G13)		0.536			
Delusion (P1)			0.883		
Hallucination (P3)			0.400		
Grandiosity (P5)			0.400		
Suspiciousness/persecution (P6)			0.785		
Unusual thought content (G9)			0.810		
Lack of judgment & insight (G12)			0.400		
Anxiety (G2)				0.713	
Guilty feelings (G3)				0.637	
Depression (G6)				0.586	
Excitement (P4)					0.575
Hostility (P7)					0.615
Mannerisms & posturing (G5)					0.500
Poor impulse control (G14)					0.680
Eigenvalue	5.852	4.028	2.544	2.006	1.516
Variance	16.17	10.91	9.55	9.47	7.05

Table 2D

Factor structure in the chronic schizophrenia group.

Item	Negative	Positive	Depressed	Excitement	Cognitive
Conceptual disorganization (P2)	0.644				
Blunted affect (N1)	0.843				
Emotional withdrawal (N2)	0.829				
Poor rapport (N3)	0.844				
Passive/apathetic thinking (N4)	0.826				
Difficulty in abstract thinking (N5)	0.711				
Lack of spontaneity & flow of conversation (N6)	0.765				
Motor retardation (G7)	0.617				
Delusion (P1)		0.918			
Hallucination (P3)		0.408			
Grandiosity (P5)		0.579			
Suspiciousness/persecution (P6)		0.713			
Unusual thought content (G9)		0.885			
Lack of judgment & insight (G12)		0.446			
Somatic concern (G1)			0.679		
Anxiety (G2)			0.751		
Guilty feelings (G3)			0.442		
Tension (G4)			0.716		
Depression (G6)			0.579		
Excitement (P4)				0.708	
Hostility (P7)				0.609	
Uncooperativeness (G8)				0.684	
Poor impulse control (G14)				0.570	
Stereotyped thinking (N7)					0.761
Disturbance of volition (G13)					0.844
Eigenvalue	6.150	3.950	2.426	1.999	1.545
Variance	19.39	10.11	8.91	7.83	7.32

Table 3

A summary of factor structure in the acute ketamine (AK), chronic ketamine (CK), early course of schizophrenia (EC-SZ) and chronic schizophrenia (C-SZ) groups (Highlighted red items are the same as previously established five factor model Wallwork et al., 2012).

		AK	CK	EC-SZ	C-SZ
Negative	N1 (Blunted affect)	+	+	+	+
	N2 (Emotional withdrawal)	+	+	+	+
	N3 (Poor rapport)	+	+	+	+
	N4 (Passive/apathetic withdrawal)	+	+	+	+
	N6 (Lack of spontaneity)	+	+	+	+
	G7 (Motor retardation)	+	+	+	+
	N5 (Difficulty in abstract thinking)		+		+
	P2 (Conceptual disorganization)				+
	G11 (Poor attention)				+
	G1 (Somatic concern)		+		
Positive	P1 (Delusion)	+	+	+	+
	P3 (Hallucination)	+	+	+	+
	G9 (Excitement)	+		+	+
	G12 (Lack of insight)		+	+	+
	P5 (Grandiosity)				+
	P6 (Suspiciousness)			+	+
Depressed	G2 (Anxiety)	+	+	+	+

	AK	CK	EC-SZ	C-SZ
	+	+	+	+
	+	+	+	+
G1 (Somatic concern)				+
G4 (Tension)				+
N7 (Stereotyped thinking)	+	+	+	+
G11 (Poor attention)	+	+	+	
G13 (Disturbance of volition)	+		+	+
G5 (Mannerisms & posturing)	+	+		
G15 (Preoccupation)	+	+		
G16 (Active social avoidance)		+		+
G4 (Tension)	+			
P2 (Conceptual disorganization)			+	
N5 (Difficulty in abstract thinking)			+	
G9 (Usual thought content)		+		
P4 (Excitement)		+	+	+
P7 (Hostility)		+	+	+
P5 (Grandiosity)		+		
G14 (Poor impulse control)		+	+	+
G5 (Mannerism & pasturing)			+	
G8 (Uncooperative)	+			+
P2 (Conceptual disorganization)	+			
G1 (Somatic concern)	+			

J Psychiatr Res. Author manuscript; available in PMC 2015 May 27.