

Schneiderian First-Rank Symptoms in Schizophrenia and Methamphetamine Psychosis: A Comparative Study

James Bradly Shelly

University of Cape Town

SHLJAM001

Master of Medicine (MMed) in Psychiatry Dissertation

The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.

Declaration

I hereby declare that the research reported herein is based on independent work performed by the candidate and listed contributors, including the candidate's research supervisor, and that neither the whole work, nor any part of it has been, is being, or is to be submitted for another degree to any other university. Furthermore, this work has not been reported or published prior to registration for this degree.

Signed,

Signed by candidate

Dr James Bradly Shelly,

In Cape Town,

On 18 August 2015.

Contents

Part A: Abstract	Pg. 4-6
Part B: Research Protocol	Pg. 8-21
Part C: Structured Literature Review	Pg. 22-41
Part D: Manuscript in Publication Format	Pg. 42-65
Part E: Appendices	Pg. 66-90

Part A:
Abstract

Objective

To determine the occurrence and associations of Schneiderian first-rank symptoms in patients diagnosed with schizophrenia and methamphetamine psychosis using structured clinical interviews for DSM-IV (SCID-I).

Method

Data from SCID-I interviews collected on two samples of patients, diagnosed with schizophrenia and with methamphetamine psychosis, as part of two separate research projects, was retrieved from the respective databases and compared. The two groups were compared on the presence of any one first-rank symptom, those who had two first-rank symptoms, and those who had more than two first-rank symptoms. We calculated the prevalence of different first-rank symptoms in schizophrenia and methamphetamine psychosis. We further performed a logistic regression and calculated adjusted and unadjusted odds ratios for the association between first-rank symptoms and diagnosis.

Results

One hundred and two patients fulfilled inclusion criteria for the study, 33 from the methamphetamine psychosis sample, and 69 from the schizophrenia sample. Prevalence of one, two, and more than two first-rank symptoms in the methamphetamine psychosis and schizophrenia groups was calculated as 69.6% and 69.7%, 21.2% and 20.3%, and 27.3% and 27.5% respectively. After adjusting for covariates, thought broadcasting occurred significantly more often in patients with schizophrenia compared to those with

methamphetamine psychosis (Odds ratio=3.61; 95% CI: 1.26-10.33; $p<0.05$). In turn, the odds of having auditory hallucinations in the form of voices conversing was significantly lower in patients with schizophrenia compared to those with methamphetamine psychosis (Odds ratio=0.27; 95% CI: 0.1-0.75; $p<0.05$). We found no significant association between any other first-rank symptoms as measured by the SCID-I and a diagnosis of schizophrenia or methamphetamine psychosis.

Conclusion

The symptom of thought broadcasting was significantly more likely to occur in patients diagnosed with schizophrenia than in patients diagnosed with methamphetamine psychosis. Auditory hallucinations of voices heard conversing was significantly less likely to occur in patients with schizophrenia than in those with methamphetamine psychosis. Overall, there was a significant overlap of first-rank symptoms and a diagnosis of either schizophrenia or methamphetamine psychosis, but this study did not show that patients with a diagnosis of schizophrenia are more likely to have first-rank symptoms when compared to those with methamphetamine psychosis.

Part B:
Research Protocol

Schneiderian First-Rank Symptoms in Schizophrenia and Methamphetamine Psychosis: A Comparative Study

Research Protocol

James Shelly

SHLJAM001

**Supervisor (Principle investigator psychosis
research project)**

Henk Temmingh

Preface

The following research protocol was submitted and presented to, as well as approved by, the University of Cape Town Department of Psychiatry in April 2012.

The protocol was approved by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee in July 2013. A copy of the approval letter is included in the appendices.

Introduction

Problem

Methamphetamine (MA)-related disorders pose a significant problem for mental health care providers, general health care providers and the community as a whole. They add to the already overwhelming burden of disease posed by mental illness in general. Percentages of patients presenting to 27 specialist substance abuse treatment programs in Cape Town with MA as their primary substance of abuse increased from 0.3% in 2002 to 42.3% in 2006 (Plüddemann, Plüddemann, Myers, & Parry, 2008). A significant proportion of patients admitted to psychiatric hospitals have methamphetamine use, and methamphetamine-related psychiatric problems, particularly methamphetamine-induced psychosis, place a significant burden on psychiatric services (Plüddemann, 2013).

Likewise, schizophrenia poses a significant problem for health care providers. From a burden of disease perspective, it poses a significant economic and service use impact. It ranks in the top 20 diseases in South Africa regarding estimated years lived with disability (Norman, Bradshaw, Schneider, Pieterse, & Groenewald, 2006), and in the top 30 leading causes of worldwide disability-adjusted life years (Murray & Lopez, 1997).

Methamphetamine psychosis is commonly described as closely simulating paranoid schizophrenia (Bell, 1965)(Davis & Schlemmer, 1980)(A. Baker & Dawe, 2005), and sometimes even as indistinguishable from paranoid schizophrenia (Connell, 1958). The positive symptoms of methamphetamine psychosis, in particular, are similar to those seen in schizophrenia, consisting mainly of delusions (particularly persecutory, but also delusions of reference) and hallucinations. Persecutory delusions are frequently reported to be characteristic of methamphetamine psychosis (Connell, 1958)(Griffith, Cavanaugh, & Oates, 1970)(Wada & Fukui, 1990)(Winger, Woods, & Hofmann, 2004). Few studies have been carried out which investigate specific symptomatological and phenomenological differences between the two.

Justification

MA-induced psychosis is an increasing problem, from both a diagnostic and management perspective.

Clinicians in psychiatric emergency departments have a tendency to attribute psychotic symptoms to primary psychotic disorders rather than to concurrent substance use (Schanzer, First, Dominguez, Hasin, & Caton, 2006). Given that the diagnosis has significant implications for future management, it is important to improve diagnostic approaches.

Consensus guidelines recommend antipsychotic treatment for patients diagnosed with first episode schizophrenia for at least 18- 24 months (Barnes & Schizophrenia Consensus Group of British Association for Psychopharmacology, 2011), and while no evidence-based guidelines regarding duration of treatment of methamphetamine psychosis have been published, it often only requires brief (ie. < 3 months) interventions (American Psychiatric Publishing, 2008). As exposure to antipsychotic medication increases ones risk of developing unwanted, and often serious, side-effects (eg. Extra-pyramidal side-effects, tardive dyskinesia, weight

gain, metabolic syndrome)(Leucht et al., 2013), accurate diagnosis has important implications for treatment planning (Glasner-Edwards, 2014).

Symptom studies may be a priority area because these results are basic knowledge for further studies of methamphetamine-induced psychosis. The phenomenological differentiation between schizophrenia and methamphetamine psychosis has implications on diagnosis, treatment planning, and prognosis.

Literature Review

Schneiderian first-rank symptoms include audible thoughts, voices heard arguing, voices heard commentating on one's actions or giving a running commentary, somatic and thought passivity experiences (delusions of control), thought insertion, thought withdrawal, thought broadcasting, and delusional perception (Oyeboode, 2008).

In 1959, Schneider attempted to operationalize the diagnosis of schizophrenia by describing the above symptoms, which he considered of first rank importance in differentiating schizophrenia from other similar illnesses (Wright, Stern, & Phelan, 2004). According to Schneider, the presence of one or more first-rank symptoms in the absence of organic disease can be used as positive evidence for schizophrenia, though he did not consider any of these symptoms necessary for the diagnosis (Crichton, 1996).

The ICD-10 puts a large emphasis on all Schneiderian first-rank symptoms in its diagnostic criteria for schizophrenia (World Health Organization, 1992). The DSM-IV diagnostic criteria put an emphasis on voices giving a running commentary or two or more voices conversing, and bizarre delusions, such as delusions of control, thought withdrawal and insertion (American Psychiatric Association, 2000).

Studies have been performed investigating the diagnostic significance of

Schneiderian first-rank symptoms in schizophrenia (Carpenter, Strauss, & Muleh, 1973)(Salleh, 1992)(Peralta & Cuesta, 1999)(Nordgaard, Arnfred, Handest, & Parnas, 2008)(Tandon & Greden, 1987). Some studies have found that the presence of Schneiderian first-rank symptoms should be regarded as strongly suggestive of schizophrenia in the absence of organic etiology (Salleh, 1992)(Tandon & Greden, 1987). However, although first rank symptoms, when examined individually, have been found to occur more frequently in schizophrenia, this co-occurrence is not sufficient to warrant diagnostic specificity to first-rank symptoms (Carpenter et al., 1973)(Salleh, 1992)(Peralta & Cuesta, 1999)(Nordgaard et al., 2008). Due to this diagnostic non-specificity, DSM 5 has placed less of an emphasis on Schneiderian first-rank symptoms as part of the schizophrenia diagnosis (the presence of only one first-rank symptom is no longer sufficient to fulfill criterion A). The ICD-11 will also de-emphasize first-rank symptoms in their schizophrenia diagnostic criteria (ICOSR, 2013). However, although the DSM and ICD are among the most commonly used psychiatric diagnostic systems in western countries, there are at least 23 other diagnostic systems operationalizing the diagnosis of schizophrenia, most of which feature first-rank symptoms (Peralta & Cuesta, 2005). There are no studies looking at first-rank symptoms in methamphetamine psychosis versus schizophrenia.

Young and Scoville, in 1938, first reported the occurrence of psychosis arising from the use of amphetamine-type stimulants (Alil et al., 2006). Many other case histories and small studies were subsequently published in this area and several literature reviews have also been published (BELL, 1965)(Davis & Schlemmer, 1980)(A. Baker & Dawe, 2005)(Connell, 1958)(Srisurapanont et al., 2011)(A. Baker, Bucci, Lewin, Richmond, & Carr, 2005)(Sato, Chen, Akiyama, & Otsuki, 1983). Many studies investigated general symptomatology and phenomenology in methamphetamine psychosis (Nelson & Sass, 2008)(Curran, Byrappa, & McBride, 2004)(Dore & Sweeting, 2006)(B. M. Angrist & Gershon, 1970)(B. Angrist, Sathananthan, Wilk, & Gershon, 1974), but did not compare these to those seen in schizophrenia.

Some studies have made comparisons between broader categories of symptoms seen in methamphetamine psychosis and schizophrenia, eg. positive vs. negative vs. cognitive symptoms (Bell, 1965)(Srisurapanont et al., 2011)(Yui, Ikemoto, Ishiguro, & Goto, 2000)(Tomiyama, 1990). Most have found little distinguishable difference between the two groups, with the positive symptoms of methamphetamine psychosis consisting mainly of delusions (particularly persecutory delusions and delusions of reference) and hallucinations (Alil et al., 2006). However, these studies looked at broader categories of symptoms, eg. delusions, hallucinations and incoherent speech, rather than specific subsets.

One study found demographic, family and clinical differences between early-phase primary psychotic disorders with concurrent substance use and substance-induced psychoses (Caton et al., 2005). This study found higher PANSS (positive and negative syndrome scale) scores and lower insight into illness scores in primary psychosis, and more frequent visual hallucinations in substance-induced psychotic disorders, but used only the PANSS to investigate psychotic symptoms, and thus did not explore first-rank symptoms specifically.

One study, which compared phenomenology of schizophrenia with that of drug-induced cocaine and phencyclidine psychoses, found that certain first-rank symptoms, particularly thought broadcasting and thought withdrawal, occurred more frequently in patients with schizophrenia (Rosse et al., 1994).

No studies were found directly comparing specific first-rank symptoms in Schizophrenia and methamphetamine psychosis.

Aims

Firstly, we aim to determine whether there is any association between the presence of first-rank symptoms and psychotic disorder diagnosis

classified as either schizophrenia or methamphetamine psychosis.

Secondly, we aim to determine the ability of first-rank symptoms to correctly classify psychotic disorder diagnoses.

Objective

To determine the frequency and occurrence of first-rank symptoms in schizophrenia and methamphetamine psychosis as measured by structured clinical interviews using the SCID-I-RV.

Hypothesis

We aim to explore the hypothesis that Scheiderian first-rank symptoms are more likely to occur in patients with schizophrenia compared to patients with methamphetamine psychosis.

Methods

Study Design

This will be a secondary analysis of data from two separate cross-sectional studies.

Sample and participants

Information on clinical and demographic patient variables from a database that forms part of a larger research project investigating the phenomenology and neurobiology of psychotic disorders will be extracted and entered into a new database. In particular, data on patients with a diagnosis of schizophrenia admitted to a large psychiatric hospital and taking part in the mentioned psychosis research project will be extracted.

Data on methamphetamine psychosis was collected from participants with various methamphetamine related presentations, admitted to the same large psychiatric inpatients unit, as well as related psychiatric units, or who were living in the community and attending drug treatment centers and outpatient clinics. This data was contained in a separate database that formed part of a study on methamphetamine psychosis. Relevant symptom data will be extracted from this database and entered into the new database mentioned above.

We estimate a sample size of 90 patients (30 MA-induced psychosis and 60 Schizophrenia) to be adequate to detect a small to moderate effect size of 0.30 for a relative difference with approximately 80% power at a 5% significance level, assuming a first-rank symptoms event rate of approximately 25% in methamphetamine psychosis cases, and 55% in schizophrenia controls.

Measurement

The SCID-I-RV for DSM-IV-TR (structured clinical interview for DSM-IV, Research Version) was used to determine the principal Axis I diagnosis. The SCID-I-RV is a semi-structured clinical interview tool for determining the major DSM IV Axis I diagnoses. The SCID-I-RV is organized into diagnostic modules that include interview questions, diagnostic criteria and ratings. Module A assesses mood episodes; Module B assesses psychotic symptoms, including first rank symptoms; Module C diagnoses psychotic disorders; Module D diagnoses mood disorders; and Module E diagnoses substance use disorders.

Data from SCID module B collected on each group (schizophrenia and methamphetamine psychosis) will be retrieved from the database and compared. Module B records the following Schneiderian first-rank symptoms: delusions of control, thought insertion, thought withdrawal, thought broadcasting, voices keeping running commentary/ two or more

voices conversing.

Variables will be extracted from the above databases and entered into a new database according to the symptom definitions defined above.

Diagnostic interviews were conducted by qualified psychiatrists, and one research nurse. All have received training and have experience in the conducting of SCID's. Regular meetings were held to improve reliability and a senior psychiatrist checked the reliability of the SCID data.

Analysis

Firstly, we will compare participants with methamphetamine psychosis and schizophrenia on the presence of any first-rank symptom. We will then classify participants into three groups: those who have only one first-rank symptom, a second group who have two first-rank symptoms, and a third group who have more than two first-rank symptoms.

We will conduct bivariate comparisons between the schizophrenia and methamphetamine groups to determine whether there is any association between the number of first-rank symptoms and diagnosis.

In addition, we will classify participants according to type of first-rank symptom and compare schizophrenia and methamphetamine groups.

Chi-square tests will be used to compare the presence or absence of any first-rank symptoms between the two groups, as well as the presence of each particular first-rank symptom. Where appropriate, Fisher's exact test will be used. We will use student's t-test to analyze continuous data. Where appropriate we will conduct logarithmic transformations for skewed data. We will construct a series of multivariate logistic regression models examining the association between the presence of one or more first-rank symptoms, as well as each individual first-rank symptom and diagnosis, coded as schizophrenia = 1, and methamphetamine psychosis = 0. Models

will be adjusted for age, gender, marital status, ethnicity, educational level, and employment status. Odds ratios and appropriate 95% CI's will be calculated. Two sided tests will be used throughout. We will set the alpha at the 5% level. Stata version 11 will be used for all statistical analyses.

Variables/ Confounders / Limitations

Selection bias - including inpatients only may not represent people suffering with schizophrenia and/or methamphetamine psychosis as a whole. As patients diagnosed with schizophrenia were recruited from an inpatient sample, and at least part of the methamphetamine group from an outpatient and community-based sample, these groups may contain differences in variables that may have a potential confounding role, such as illness severity and socio-economic background. Where possible, we will attempt to adjust for such potential covariates.

Sample size may limit the extent of analysis of the data for multivariate models.

The SCID was not specifically designed to measure first rank symptoms. It does not measure delusional perception (a true perception to which a person attributes false meaning). This could lead to an underestimation in the measurement of first-rank symptoms. Other tools, such as the Manual for the Assessment of Schizophrenia (Landmark, 1982), or the Scale for Assessment of Positive Symptoms (Andreasen, 1984) may be more appropriate.

Ethics and Communication

I will be added as a co-investigator to the previously mentioned psychosis study. The study was approved by the human research ethics committee of the University of Cape Town.

All participants signed a written informed consent document.

Logistics

Timetable

2011: Literature review and protocol development.

2012: Protocol presentation and data collection.

2013: Data analysis and report development.

2014: Report development, completion and submission.

References

- American Psychiatric Association Ed (2000). *Diagnostic and Statistical Manual of Mental Disorders*. Fourth Edition, Text Revision. Amer Psychiatric Pub.
- Alil, R., Baigent, M., Marsden, J., Montiero, M., Srisurapanont, M., Sunga, A., et al. *WHO multi-site project on methamphetamine-induced psychosis: A descriptive report of findings from participating countries*.
- Angrist, B., Sathananthan, G., Wilk, S., & Gershon, S. (1974). Amphetamine psychosis: Behavioral and biochemical aspects. *Journal of Psychiatric Research*, 11, 13-23.
- Angrist, B. M., & Gershon, S. (1970). The phenomenology of experimentally induced amphetamine psychosis--preliminary observations. *Biological Psychiatry*, 2(2), 95-107.
- Baker, A., & Dawe, S. (2005). Amphetamine use and co-occurring psychological problems: Review of the literature and implications for treatment. . [null] *Australian Psychologist*, 40(2), 88.
- Baker, A., Bucci, S., Lewin, T. J., Richmond, R., & Carr, V. J. (2005). Comparisons between psychosis samples with different patterns of substance use recruited for clinical and epidemiological studies. *Psychiatry Research*, 134(3), 241-250.
- Barnes, T. R., & Schizophrenia Consensus Group of British Association for Psychopharmacology. (2011). Evidence-based guidelines for the pharmacological treatment of schizophrenia: Recommendations from the british association for psychopharmacology. *Journal of Psychopharmacology (Oxford, England)*, 25(5), 567-620.
- Bell, D. S. (1965). Comparison of amphetamine psychosis and schizophrenia. *The British Journal of Psychiatry : The Journal of Mental Science*, 111, 701-707.

- Carpenter, W. T., Jr, Strauss, J. S., & Muleh, S. (1973). Are there pathognomonic symptoms in schizophrenia? an empiric investigation of schneider's first-rank symptoms. *Archives of General Psychiatry*, 28(6), 847-852.
- Caton, C. L., Drake, R. E., Hasin, D. S., Dominguez, B., Shrout, P. E., Samet, S., et al. (2005). Differences between early-phase primary psychotic disorders with concurrent substance use and substance-induced psychoses. *Archives of General Psychiatry*, 62(2), 137-145.
- Connell, P. (1958). *Amphetamine psychosis* Maudsley.
- Crichton, P. (1996). First-rank symptoms or rank-and-file symptoms? *The British Journal of Psychiatry : The Journal of Mental Science*, 169(5), 537-40; discussion 541-50.
- Curran, C., Byrappa, N., & McBride, A. (2004). Stimulant psychosis: Systematic review. *The British Journal of Psychiatry : The Journal of Mental Science*, 185, 196-204.
- Davis, & Schlemmer. (1980). *The amphetamine psychosis* [null]
- Dore, G., & Sweeting, M. (2006). Drug-induced psychosis associated with crystalline methamphetamine. *Australasian Psychiatry : Bulletin of Royal Australian and New Zealand College of Psychiatrists*, 14(1), 86-89.
- Glasner-Edwards, S., Mooney, L.J. (2014). Methamphetamine psychosis: Epidemiology and management. *CNS Drugs*, 28(12), 1115-1126.
- Griffith, J., Cavanaugh, J., & Oates, J. (Eds.). (1970). *Psychosis induced by administration of d-amphetamine in human volunteers. in: Psychotomimetic drugs* [null]. New York: Raven Press.
- Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Orey, D., Richter, F., Samara, M., Barbui, C., Engel, R., Geddes, J., Kissling, W., Stapf, M., Lassig, B., Salanti, G., Davis, J. (2013). Comparative Efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 2013 (0).
- Murray, C. J., & Lopez, A. D. (1997). Global mortality, disability, and the contribution of risk factors: Global burden of disease study. *Lancet*, 349(9063), 1436-1442.
- Nelson, B., & Sass, L. A. (2008). The phenomenology of the psychotic break and huxley's trip: Substance use and the onset of psychosis. *Psychopathology*, 41(6), 346-355.
- Nordgaard, J., Arnfred, S. M., Handest, P., & Parnas, J. (2008). The diagnostic status of first-rank symptoms. *Schizophrenia Bulletin*, 34(1), 137-154.
- Norman, R., Bradshaw, D., Schneider, M., Pieterse, D., & Groenewald, P. (2006). MRC burden of disease research unit. revised burden of disease estimates for the comparative risk factor assessment, south africa 2000; 2006. [null]
- Oyebode, F. (Ed.). *Sims' symptoms in the mind, an introduction to descriptive psychopathology* [null] (4th ed.) Saunders.
- Peralta, V., & Cuesta, M. J. (1999). Diagnostic significance of schneider's first-rank symptoms in schizophrenia. comparative study between schizophrenic and non-schizophrenic psychotic disorders. *The British Journal of Psychiatry : The Journal of Mental Science*, 174, 243-248.

- Peralta, V., Cuesta, M.J. (2005). The underlying structure of diagnostic systems in schizophrenia: A comprehensive polydiagnostic approach. *Schizophrenia research* 79(2-3), 217-229.
- Plüddemann, A., Plüddemann, A., Myers, B. J., & Parry, C. D. (2008). Surge in treatment admissions related to methamphetamine use in cape town, south africa: Implications for public health. *Drug and Alcohol Review*, 27(2), 185-189.
- Plüddemann, A., Dada, S., Parry, CDH., Kader, R., Parker, JS., Temmingh, H., van Heerden, S., de Clercq, C., Lewis, I. (2013). Monitoring the prevalence of methamphetamine-related presentations at psychiatric hospitals in Cape Town, South Africa. *African Journal of Psychiatry* 16:45-49.
- Rosse, R. B., Collins, J. P., Jr, Fay-McCarthy, M., Alim, T. N., Wyatt, R. J., & Deutsch, S. I. (1994). Phenomenologic comparison of the idiopathic psychosis of schizophrenia and drug-induced cocaine and phencyclidine psychoses: A retrospective study. *Clinical Neuropharmacology*, 17(4), 359-369.
- Salleh, M. R. (1992). Specificity of schneider's first rank symptoms for schizophrenia in malay patients. *Psychopathology*, 25(4), 199-203.
- Sato, M., Chen, C. C., Akiyama, K., & Otsuki, S. (1983). Acute exacerbation of paranoid psychotic state after long-term abstinence in patients with previous methamphetamine psychosis. *Biological Psychiatry*, 18(4), 429-440.
- Schanzer, B. M., First, M. B., Dominguez, B., Hasin, D. S., & Caton, C. L. (2006). Diagnosing psychotic disorders in the emergency department in the context of substance use. *Psychiatric Services (Washington, D.C.)*, 57(10), 1468-1473.
- Srisurapanont, M., Arunpongpaisal, S., Wada, K., Marsden, J., Ali, R., & Kongsakon, R. (2011). Comparisons of methamphetamine psychotic and schizophrenic symptoms: A differential item functioning analysis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 35(4), 959-964.
- Tandon, R., & Greden, J. F. (1987). Schneiderian first rank symptoms: Reconfirmation of high specificity for schizophrenia. *Acta Psychiatrica Scandinavica*, 75(4), 392-396.
- Tomiyaama, G. (1990). Chronic schizophrenia-like states in methamphetamine psychosis. *The Japanese Journal of Psychiatry and Neurology*, 44(3), 531-539.
- Wada, K., & Fukui, S. (1990). Relationship between years of methamphetamine use and symptoms of methamphetamine psychosis. *Arukoru Kenkyu to Yakubutsu Izon = Japanese Journal of Alcohol Studies & Drug Dependence*, 25(3), 143-158.
- Winger, Woods, & Hofmann (Eds.). (2004). *A handbook on drug and alcohol abuse: The biomedical aspects* [null] (4th ed.) Oxford University Press.
- World Health Organization Ed. 1992. *The ICD-10 Classification of Mental and Behavioral Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization.
- Wright, Stern, & Phelan (Eds.). (2004). *Core psychiatry* [null] (2nd ed.) Saunders.

Yui, K., Ikemoto, S., Ishiguro, T., & Goto, K. (2000). Studies of amphetamine or methamphetamine psychosis in japan: Relation of methamphetamine psychosis to schizophrenia. *Annals of the New York Academy of Sciences*, 914, 1-12.

Acknowledgements

Henk Temmingh participated in the conception and design of the study, and edited the protocol draft manuscript.

Sean Baumann participated in the conception of the study.

Part C:
Structured Literature Review

Background

Schizophrenia is a heterogeneous clinical syndrome characterized by a range of cognitive, behavioral and emotional dysfunctions (American Psychiatric Association, 2013). A diagnosis of Schizophrenia, according to the DSM-IV, requires at least one month of active phase psychotic symptoms (delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and/or negative symptoms), in the context of at least six months of functional decline, and in the absence of other psychotic and affective disorders, substance-induced disorders, or psychiatric disorders related to a general medical condition (American Psychiatric Association, 2000).

Schneiderian first-rank symptoms include audible thoughts, voices heard arguing, voices heard commentating on one's actions or giving a running commentary, somatic and thought passivity experiences (delusions of control), thought insertion, thought withdrawal, thought broadcasting, and delusional perception (Oyebode, 2008).

In 1959, Schneider attempted to operationalize the diagnosis of Schizophrenia by describing the above symptoms, which he considered of first rank importance in differentiating schizophrenia from other similar illnesses (Wright, Stern & Phelan, 2004). According to Schneider, the presence of one or more first-rank symptoms in the absence of organic disease can be used as positive evidence for schizophrenia, though he did not consider any of these symptoms necessary for the diagnosis (Crichton, 1996).

Table 1 contains the ICD-10 research diagnostic criteria for a diagnosis of schizophrenia. First-rank symptoms are listed, and form a central aspect of these operationalized criteria.

Table 1

SCHIZOPHRENIA – ICD-10 Diagnostic criteria

This overall category includes the common varieties of schizophrenia, together with some less common varieties and closely related disorders.

F20.0 - F20.3

General criteria for Paranoid, Hebephrenic, Catatonic and Undifferentiated type of Schizophrenia:

G1. Either at least one of the syndromes, symptoms and signs listed below under (1), or at least two of the symptoms and signs listed under (2), should be present for most of the time during an episode of psychotic illness lasting for at least one month (or at some time during most of the days).

(1) At least one of the following:

- a) Thought echo, thought insertion or withdrawal, or thought broadcasting.
- b) Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception.
- c) Hallucinatory voices giving a running commentary on the patient's behaviour, or discussing him between themselves, or other types of hallucinatory voices coming from some part of the body.
- d) Persistent delusions of other kinds that are culturally inappropriate and completely impossible (e.g. being able to control the weather, or being in communication with aliens from another world).

(2) or at least two of the following:

e) Persistent hallucinations in any modality, when occurring every day for at least one month, when accompanied by delusions (which may be fleeting or half-formed) without clear affective content, or when accompanied by persistent over-valued ideas.

f) Neologisms, breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech.

g) Catatonic behaviour, such as excitement, posturing or waxy flexibility, negativism, mutism and stupor.

h) "Negative" symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses (it must be clear that these are not due to depression or to neuroleptic medication).

G2. Most commonly used exclusion criteria: If the patient also meets criteria for manic episode (F30) or depressive episode (F32), the criteria listed under G1.1 and G1.2 above must have been met before the disturbance of mood developed.

G3. The disorder is not attributable to organic brain disease (in the sense of F0), or to alcohol- or drug-related intoxication, dependence or withdrawal.

(World Health Organization, 1992)

The DSM IV-TR diagnostic criteria attempted to capture the concept of first-rank symptoms by including symptoms such as voices giving a running commentary on the patient's thoughts or behavior, or two or more voices conversing with each other, and bizarre delusions, such as delusions of control, thought withdrawal and insertion and thought broadcasting. In this

edition, Criterion A can be fulfilled if only one symptom of bizarre delusions, hallucinations consisting of a voice keeping a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other is present, highlighting the importance of first-rank symptoms in diagnosis (American Psychiatric Association, 2000).

Studies have been performed investigating the diagnostic significance of Schneiderian first-rank symptoms (FRS's) in schizophrenia:

Carpenter et al found that, individually, each FRS occurred with greater frequency in schizophrenia, but, taken together, they also occurred in a quarter of their cohort of patients with Bipolar Mood Disorder. They conclude thus that Schneider's system for identifying schizophrenia, while highly discriminating, can lead to diagnostic errors if FRS's are considered pathognomic (Carpenter, Strauss & Muleh, 1973).

Salleh studied the frequency of FRS's in 221 Malay patients with "functional psychosis". The prevalence of FRS's in schizophrenia was found to be 26.7%. The specificity of FRS for schizophrenia was calculated to be 87.8%, and their positive predictive value was 90.6%. The authors concluded that, based on these results, although FRS's cannot be regarded as pathognomic of schizophrenia, their presence should be regarded as highly suggestive of schizophrenia (Salleh, 1992).

Peralta and Cuesta examined the diagnostic accuracy of FRS's for schizophrenia in 660 in-patients with a range of psychotic disorders, finding FRS's to be highly prevalent in both schizophrenia and non-schizophrenic psychoses. They found that FRS do not significantly increase the likelihood of having schizophrenia, and thus are not useful in differentiating schizophrenia from other psychotic disorders (Peralta & Cuesta, 1999).

Tandon and Greden evaluated the prevalence of FRS's in 294 consecutive admissions to a research unit, with reference to their diagnostic distribution. They found the specificity of FRS's for schizophrenia to be 95%, and their

positive predictive value to be 90%. They concluded that FRS's should be considered strongly suggestive of schizophrenia in the absence of an organic syndrome (Tandon & Greden, 1987).

Nordgaard et al performed a critical review of FRS studies published in English between 1970 and 2005, and discussed theoretical implications of the epistemological issues of FRS's. They concluded that both ICD-10 and DSM-IV, in their diagnostic criteria for schizophrenia, emphasize FRS's to a degree that is not supported by the empirical evidence. They suggest that FRS's should be de-emphasized in the next reviews of our diagnostic systems, and that further research be performed aimed at validating FRS's as diagnostic tools (Nordgaard et al., 2008).

Methamphetamine psychosis is a substance-induced psychosis, the essential features of which are prominent delusions and/or hallucinations that are deemed to be a direct physiological effect of the substance used. Substance-induced psychotic disorders are distinguished from primary psychotic disorders (eg. schizophrenia) by considering the onset, course, and other factors, ie. for substance-induced disorders, the onset of psychotic symptoms develop during or within a month of substance intoxication or withdrawal; the symptoms persist for less than one month following last use of the substance; the symptoms are not in excess of what might be expected, given the amount or duration of substance use (American Psychiatric Association, 2000).

People with primary psychotic disorders often present with symptoms and signs similar to those induced by the use of substances alone, presenting a diagnostic challenge (Caton, 2005). Methamphetamine (MA)-induced psychosis is commonly described as closely simulating, and sometimes even as indistinguishable from, paranoid schizophrenia (BELL, 1965)(Davis & Schlemmer, 1980)(Baker & Dawe, 2005)(Connell, 1958). The positive symptoms occurring in methamphetamine psychosis are similar to those of paranoid schizophrenia, consisting mostly of delusions (particularly persecutory, but also referential) and hallucinations. Persecutory delusions are frequently reported to be characteristic of methamphetamine psychosis

(Connell, 1958)(Griffith, Cavanaugh & Oates, 1970)(Wada & Fukui, 1990)(Winger, Woods & Hofmann, 2004).

Young and Scoville, in 1938, first reported the occurrence of psychosis arising from the use of amphetamine-type stimulants. They reported on individuals who had developed paranoid psychoses following treatment with Benzedrine, for narcolepsy (Alil, 2006).

Many other case histories and small studies were subsequently published in this area and several literature reviews have also been published:

Connell's monograph, published in 1958, describes 42 cases of amphetamine psychosis. He describes the clinical picture as one of paranoid psychosis with persecutory delusions, delusions of reference and auditory and visual hallucinations in a state of clear consciousness. He asserts that the clinical features of amphetamine psychosis might be such as to make it indistinguishable from Schizophrenia (Connell, 1958).

Baker et al compared the characteristics of five groups of patients with psychosis and varying patterns of substance use disorders. Regarding differences in illness and symptom profiles, they found substance users to have higher depression and reality distortion scores, but did not report in detail on specific symptomatological differences, predominantly reporting on socio-demographic and disability details (Baker et al., 2005).

Angrist et al studied behavioral and biochemical aspects of experimentally-induced amphetamine psychosis, documenting symptomatology and phenomenology, but not directly comparing it to Schizophrenia (Angrist & Gershon, 1970)(Angrist et al., 1974). Likewise, Dore and Sweeting described a case of methamphetamine-induced psychosis, highlighting phenomenology and relevant treatment. They comment on its resemblance to paranoid schizophrenia, but make no direct comparison (Dore & Sweeting, 2006).

Baker and Dawe published a review of the literature describing the prevalence

and course of the most common co-occurring psychological problems among methamphetamine users. They raise important concerns regarding the difficulty in distinguishing methamphetamine psychosis from a pre-existing psychosis exacerbated by methamphetamine use, but make only brief mention of phenomenology and symptomatology (Baker & Dawe, 2005).

Curran et al performed a systematic review of studies that have investigated stimulant use and psychosis, with primary outcome measures the increases in psychosis with stimulant use, and differences between stimulant users and non-users. Its results and discussion focus primarily on issues of sensitization and preventative mechanism of psychotic relapse, rather than comparison of phenomenology (Curran, Byrappa & McBride, 2004).

Grant et al reviewed the literature on methamphetamine psychosis in 2012. Citing multiple studies in Japanese, Taiwanese, Australian and Thai populations, they reported a high frequency of persecutory delusions and auditory hallucinations in patients with methamphetamine psychosis. They also cited some studies reporting delusions of reference, visual hallucinations and thought broadcasting as common symptoms of MA-psychosis (Grant et al., 2012).

Aims of this literature review

Firstly, we aimed to determine whether there exists any evidence in the literature of an association between the presence of Schneiderian first-rank symptoms and psychotic disorder diagnosis classified as either schizophrenia or methamphetamine induced psychosis.

Secondly, we aim to search the literature for any studies comparing methamphetamine psychosis with schizophrenia on other aspects of phenomenology, such as the presence of positive, negative, and other general psychopathology.

Studies included

We included the following types of study design:

- 1- Cross-sectional studies
- 2- Case control studies
- 3- Cohort studies
- 4- Randomised controlled trials, containing data on presence of first-rank symptoms
- 5- Systematic or narrative reviews

Case series, case reports and qualitative studies were excluded.

Population

Adults, aged 18 – 65, with a psychotic disorder, where psychotic disorder is defined to include the following disorders as diagnosed by any means:

- 1- Schizophrenia
- 2- Substance-induced psychotic disorder
- 3- Schizophreniform Disorder

Psychotic disorders to exclude are the following:

- 1- Schizoaffective disorder
- 2- Psychosis due to general medical condition
- 3- Moderate to severe intellectual disability associated with psychotic disorders
- 4- Personality disorders with psychotic symptoms
- 5- Dementia with psychotic symptoms

Phenomenological symptom of interest

The primary exposure of interest is Schneiderian first-rank symptoms,

diagnosed by means of DSM-IV, III-R, or any structured diagnostic tool.

Included as first-rank symptoms are:

- Audible thoughts
- Voices heard arguing
- Voices heard commentating on one's actions or giving a running commentary
- Somatic and thought passivity experiences (delusions of control)
- Thought insertion
- Thought withdrawal
- Thought broadcasting
- Delusional perception

The secondary exposure of interest is any other positive and negative symptoms of psychosis.

Comparison groups

We included studies that compared schizophrenia with methamphetamine induced psychosis.

Where a study contained only a subgroup comparing patients with schizophrenia and methamphetamine psychosis on the frequency of first rank symptoms, we indicated that the primary aim of the study was not an a priori comparison between schizophrenia and methamphetamine psychosis.

Assessment of study quality

Included studies will be structured and presented according to author's title, year of publication, populations studied, and type of instruments used to make diagnosis and measure symptoms. Summaries of the main study findings, major strengths and weaknesses of each study, in terms of design, rigour of diagnosis and assessment, and control for bias and confounding, will be

presented and commented on.

Literature Search Strategy

We searched Pubmed under the following search terms: “Schneiderian first rank symptoms”, “first-rank symptoms and schizophrenia”, “first-rank symptoms and methamphetamine psychosis”, “phenomenology in methamphetamine psychosis”, “specificity of first rank symptoms in schizophrenia”, “schizophrenia and methamphetamine psychosis”. We used the Boolean operators AND and OR. We hand searched references of articles for additional relevant studies.

Study selection

After the search was finalized, all citations were screened for eligibility according to the inclusion and exclusion criteria set out. Where there was uncertainty from the abstract as to whether the study qualified for inclusion, the full article was reviewed for possible inclusion. In case we found no studies fulfilling our inclusion criteria, we would aim to broaden our inclusion criteria to any studies comparing schizophrenia on the broader phenomenology of psychotic symptoms, first-rank symptoms included, with 1) any substance-induced psychosis (other than methamphetamine psychosis, and 2) other affective and non-affective psychotic disorders.

Results

Our Pubmed searches under the terms “Schneiderian first-rank symptoms”, “First-rank symptoms and schizophrenia”, “First-rank symptoms and methamphetamine psychosis”, “Phenomenology in methamphetamine psychosis”, “Specificity of first-rank symptoms in schizophrenia”, and “Schizophrenia and methamphetamine psychosis” yielded 88, 247, 0, 2, 18 and 137 results respectively. 498 study abstracts and/or titles (including 6 hand-searched references) were screened for relevance. Of these, 481

studies were excluded, as the study title or abstract did not match our review question, and a further 5 excluded as they did not meet our inclusion criteria in terms of population studied, diagnoses included or phenomenology of interest compared.

Figure 1 depicts the flow of search results and studies excluded and included.

Figure 1

Pubmed	
"Schneiderian first-rank symptoms"	88
"First-rank symptoms and schizophrenia"	247
"First-rank symptoms and methamphetamine psychosis"	0
"Phenomenology in methamphetamine psychosis"	2
"Specificity of first-rank symptoms in schizophrenia"	18
"Schizophrenia and methamphetamine psychosis"	137
Hand-searched references	7
498 Abstracts/Titles screened for relevance	
481 Studies excluded as abstracts/titles did not match study question	
5 Studies excluded as did not meet inclusion criteria in terms of population studied, diagnoses included or phenomenology of interest compared	
13 Studies included	

Table 2 summarizes the literature reviewed on first-rank symptoms and psychotic disorder diagnosis. 7 Studies were included, 5 cross-sectional in design, 1 systematic review, and 1 diagnostic test accuracy review, covering the time period from 1981 to 2015.

Table 3 summarizes the literature reviewed on studies comparing general phenomenology in methamphetamine psychosis and schizophrenia. 6 Studies were included, 5 cross sectional in design, and one systematic review, covering the time period from 1979 to 2013.

Discussion

In this review, we found that the literature does not support a high specificity and predictive value of first-rank symptoms for a diagnosis of schizophrenia when compared to other psychiatric disorders.

While all of the studies reviewed found that Schneiderian first-rank symptoms occurred more frequently in patients diagnosed with schizophrenia when compared to patients with other psychiatric disorders (both psychotic and non-psychotic), and that their presence should be regarded as suggestive of schizophrenia, only one study found a high specificity and predictive value of first-rank symptoms for a diagnosis of schizophrenia. However, this study, by Tandon and Greden, in 1987, included patients in whom schizophrenia was diagnosed using criteria strongly reliant upon their very presence, thus potentially biasing results in the direction of a high specificity of first-rank symptoms for schizophrenia. This was, in fact, a weakness of many of the studies reviewed here, with the exception of the study by Peralta and Cuesta, in 1999, in which diagnostic systems not heavily reliant on first-rank symptoms were used, in an attempt to reduce this potential bias. In their diagnostic test accuracy review in 2015, Soares-Weiser *et al* also conclude that first-rank symptoms alone should not be used to diagnose schizophrenia, as they are not specific enough to be considered pathognomic, although they comment on their potential use as a screening tool for formal psychiatric evaluation in emergency units. Another weakness of some of the studies reviewed here was the use of non-psychotic disorders in their comparison groups. Determining diagnostic relevance of first-rank symptoms requires differentiating between schizophrenia and other psychotic disorders.

Of the studies performed investigating the diagnostic significance of Schneiderian first-rank symptoms in schizophrenia, none were found including methamphetamine-induced psychosis in their comparisons with schizophrenia.

In their review, in 1979, Janowsky and Risch conclude that Schneiderian first-rank symptoms do occur in patients with experimentally-induced amphetamine psychosis. However, given that there was no schizophrenia comparison group in any of the studies they reviewed, no conclusions can be made regarding diagnostic specificity of first-rank symptoms in amphetamine psychosis when compared to schizophrenia.

In the remaining 5 studies reviewed here, patients with schizophrenia and other primary psychotic disorders were compared to patients with methamphetamine and other substance-induced psychotic disorders on a number of demographic, family and clinical factors. Results were varied: Rosse *et al* found that two specific first-rank symptoms, thought broadcasting and thought withdrawal, occurred more frequently in their sample of patients with schizophrenia than in their sample of patients with cocaine-induced psychosis, and Caton *et al* found that patients with primary psychotic disorders scored higher on positive and negative symptom and general psychopathology subscales than patients with substance-induced psychosis. Seemingly in contrast to this, both Srisrapanont *et al* and Medhus *et al* found no significant difference in the severity or frequency respectively of positive symptoms experienced by patients with schizophrenia and methamphetamine psychosis, thus supporting the proposal of methamphetamine psychosis as a model for schizophrenia.

We found no studies directly comparing schizophrenia with methamphetamine-induced psychosis on the presence of Schneiderian first-rank symptoms. In addition, we found no studies exploring the diagnostic specificity of Schneiderian first-rank symptoms for schizophrenia compared to methamphetamine-induced psychosis.

Gaps or Needs for Further Research

Symptom studies are important, as the diagnostic differentiation between a substance-induced and a primary psychotic disorder informs different

treatment plans.

Methamphetamine-induced psychosis is an increasing problem, from both a diagnostic and management perspective, and as diagnosis has significant implications for future management and treatment planning, it is critically important to improve diagnostic approaches.

The ability to differentiate clinically between schizophrenia and methamphetamine psychosis has implications on diagnosis, treatment planning, and prognosis. The current study aims to investigate this apparent gap in the literature.

A consideration made during the planning of the literature review, was whether to search and review the literature on the presence or absence of first-rank symptoms in other substance-induced psychotic disorders. It was decided that this was beyond the scope of this study, but may be an area of interest for future work in this field.

Table 2: Schneiderian first-rank symptoms (FRS) and psychotic disorder diagnosis

Author	Year	Study design	Population studied	Diagnostic and measurement instruments used	Main findings	Strengths	Weaknesses
Silverstein, Harrow	1981	Cross-sectional	<ul style="list-style-type: none"> • 107 hospitalized schizophrenia patients • 76 hospitalized non-schizophrenia patients (specific diagnoses undefined) 	<ul style="list-style-type: none"> • DSM II; • Psychotic Symptom Inventory • Carpenter et al Psychiatric Assessment Interview 	FRS not more effective than non-Schneiderian psychotic symptoms in delineating central characteristics of the schizophrenic syndrome.	<ul style="list-style-type: none"> • Appropriate method • Direct comparison of groups • Appropriate tools used 	<ul style="list-style-type: none"> • Outdated diagnostic tools • Reliance on FRS for schizophrenia diagnosis • Non-schizophrenia patients' diagnoses not defined • Schizoaffective disorder included in schizophrenia group • Focus on mental state at follow-up, not during acute illness • Hospitalized patients may not be representative
Tandon, Greden	1987	Cross-sectional	<ul style="list-style-type: none"> • 58 hospitalized schizophrenia patients • 236 hospitalized non-schizophrenia psychiatric patients (including patients with mood disorders, "toxic psychosis", and schizoaffective disorder) 	<ul style="list-style-type: none"> • Research Diagnostic Criteria • Schedule for Affective Disorders and Schizophrenia 	High specificity and predictive value of FRS for schizophrenia	<ul style="list-style-type: none"> • Appropriate tools used 	<ul style="list-style-type: none"> • Comparison groups both psychotic and non-psychotic patients • Reliance on FRS for schizophrenia diagnosis • Hospitalized patients may not be representative • Retrospectively collected sample
O'Grady	1990	Cross-sectional	<ul style="list-style-type: none"> • 15 hospitalized schizophrenia patients • 84 hospitalized non-schizophrenia patients (including schizoaffective disorder, mood disorders and "other" diagnoses) 	<ul style="list-style-type: none"> • Schedule for Affective Disorders and Schizophrenia • First-rank Symptoms Questionnaire • Research Diagnostic Criteria • Carpenter's Flexible System • New Haven Index 	Did not support the hypothesis that FRS are specific to schizophrenia	<ul style="list-style-type: none"> • Rigorous use of diagnostic and measurement tools • Definition and differentiation of narrow and wide definitions of FRS 	<ul style="list-style-type: none"> • Reliance on FRS for schizophrenia diagnosis • Comparison group included non-psychotic patients • Hospitalized patients may not be representative • Small sample size • Poor concordance of FRS with three diagnostic tools used • Unclear distinction between schizoaffective disorder and affective disorders
Salleh	1992	Cross-sectional	<ul style="list-style-type: none"> • 180 hospitalized schizophrenia patients • 20 hospitalized "affective psychosis" patients • 7 hospitalized "paranoid state" patients • 14 hospitalized "other non-organic psychosis" patients 	<ul style="list-style-type: none"> • Present Status Examination 	Although FRS are not pathognomic of schizophrenia, their presence should be regarded as strongly suggestive.	<ul style="list-style-type: none"> • Semi-structured interview based on standardized questionnaire • Inter-rater reliability 	<ul style="list-style-type: none"> • Unclear whether sample is in- or out-patients • Study design not rigorous • Possible bias in sampling • ICD-9 relies on FRS for schizophrenia diagnosis
Peralta, Cuesta	1999	Cross-sectional	<ul style="list-style-type: none"> • 352 hospitalized schizophrenia patients • 88 hospitalized schizophreniform disorder patients • 37 schizoaffective disorder patients • 83 mood disorder patients • 25 delusional disorder patients • 25 brief reactive psychosis patients • 25 atypical psychosis patients 	<ul style="list-style-type: none"> • Manual for the Assessment of Schizophrenia • DSM III-R • Feighner criteria • Scale for the Assessment of Positive Symptoms 	FRS do not significantly increase the likelihood of having schizophrenia.	<ul style="list-style-type: none"> • Rigorous design • Largest study at single centre • Met recommended statistical quality criteria for a diagnostic feature • Use of diagnostic tools not based upon FRS 	<ul style="list-style-type: none"> • Low inter-rater reliability for some symptoms • Assessments of FRS and diagnosis not made blindly
Nordgaard, Arnfred, Handest, Parnas	2007	Systematic Review	<ul style="list-style-type: none"> • 40 studies reviewed and compared 		Both DSM-IV and ICD-10 emphasize first-rank symptoms to a degree that is not supported by the empirical evidence.	<ul style="list-style-type: none"> • Extensive review of wide range of studies • Methodological flaws and errors identified and reported. 	<ul style="list-style-type: none"> • Methods not clearly defined or outlined.
Soares-Weiser <i>et al</i>	2015	Diagnostic test accuracy review	<ul style="list-style-type: none"> • 21 Studies reviewed, including 5515 patients in analysis 		It is not recommended that FRS alone be used to diagnose Schizophrenia	<ul style="list-style-type: none"> • Extensive review • Rigorous design • Methods, flaws and errors well reported 	<ul style="list-style-type: none"> • Did not include studies with substance-induced psychosis • Many studies included not designed for purpose • Wide variety of reference standard used for diagnosis • Diagnostic accuracies may be over-estimated

Table 3: Studies comparing phenomenology in methamphetamine psychosis and schizophrenia

Author	Year	Study design	Population Studied	Diagnostic and measurement instruments used	Main findings	Strengths	Weaknesses
Janowsky, Risch	1979	Systematic review	<ul style="list-style-type: none"> 4 prospective studies reviewed, including 15 non-schizophrenic patients with experimentally-produced amphetamine psychosis 	<ul style="list-style-type: none"> Present state exam 	FRS do occur in patients with experimentally-produced amphetamine psychosis	<ul style="list-style-type: none"> First literature review of experimentally produced amphetamine psychosis in non-schizophrenic patients Appropriate method Exposure clearly defined and measured 	<ul style="list-style-type: none"> Incomplete case report descriptions Studies reviewed not designed for purpose Small sample size No schizophrenia comparison groups
Tomiyama	1990	Cross-sectional	<ul style="list-style-type: none"> 8 hospitalized methamphetamine psychosis patients 3 methamphetamine psychosis outpatients 11 hospitalized schizophrenia patients 	<ul style="list-style-type: none"> Medical chart review Behavioral observation in wards Present state exam Scale for the Assessment of Negative Symptoms 	Chronic methamphetamine psychosis and schizophrenia share phenomenologic similarities, but should be considered separate entities.	<ul style="list-style-type: none"> Appropriate method Confounding controlled for by age and sex matching 	<ul style="list-style-type: none"> No rigorous use of measurement instruments for positive symptoms Reliance on ward observations Possible selection bias in schizophrenia sample due to non-random sampling Small sample size Possible differences in in- and out-patient sample
Rosse <i>et al</i>	1994	Cross-sectional	<ul style="list-style-type: none"> Study 1: 34 hospitalized cocaine-dependent patients; 16 hospitalized schizophrenia patients Study 2: 16 hospitalized cocaine-dependent patients having previously used PCP 	<ul style="list-style-type: none"> DSM-III-R SCID Cocaine Experience Questionnaire Schedule for the Assessment of Positive Symptoms 	<ul style="list-style-type: none"> Thought broadcasting and thought withdrawal occurred more frequently in the schizophrenia sample than the cocaine-induced-psychosis sample No significant difference in first-rank symptoms between cocaine- and PCP-induced psychosis 	<ul style="list-style-type: none"> Appropriate method Selection bias controlled for by careful screening of substance abusers for endogenous psychiatric disorders. 	<ul style="list-style-type: none"> Possibility of recall bias introduced by post-hoc review of PCP-induced psychosis No schizophrenia comparison group in study 2
Caton <i>et al</i>	2005	Cross-sectional	<ul style="list-style-type: none"> 217 hospitalized primary psychotic disorder patients 169 hospitalized substance-induced psychosis patients Sample collected across 5 psychiatric emergency departments 	<ul style="list-style-type: none"> Psychiatric Research Interview for Substance and Mental Disorders (PRISM) Positive and Negative Syndrome Scale (PANSS) 	Primary psychotic disorder patients scored higher on positive symptom subscale, negative symptom subscale, and general psychopathology subscale.	<ul style="list-style-type: none"> Appropriate method and reporting Diagnostic reliability 	<ul style="list-style-type: none"> Possible confounders in the form of poly-substance use First-rank symptoms not specifically compared Schizophrenia not specifically differentiated from other primary psychotic disorders
Srisrapanont <i>et al</i>	2011	Cross-sectional	<ul style="list-style-type: none"> 168 methamphetamine psychosis patients 169 schizophrenia patients Sample collected across 4 countries 	<ul style="list-style-type: none"> Manchester Scale 	The severity of psychotic symptoms seen in methamphetamine psychosis and schizophrenia patients are the same, given the same level of syndrome severity, supporting the proposal of methamphetamine psychosis as a model for schizophrenia.	<ul style="list-style-type: none"> Appropriate method First DIF analysis comparing methamphetamine psychosis and schizophrenia 	<ul style="list-style-type: none"> First-rank symptoms not directly compared Small sample size for DIF analysis Cannot exclude the effect of treatment Schizophrenia sample may not be representative due to treatment resistance or medication intolerance
Medhus <i>et al</i>	2013	Cross-sectional	<ul style="list-style-type: none"> 33 hospitalized schizophrenia patients 9 hospitalized methamphetamine psychosis patients 	<ul style="list-style-type: none"> Positive and Negative Syndrome Scale ICD-10 Mini-International Neuropsychiatric Interview 	No differences in positive symptoms found between methamphetamine-psychotic and schizophrenia patients	<ul style="list-style-type: none"> Appropriate method Exposure clearly defined and accurately measured 	<ul style="list-style-type: none"> Inclusion of poly-substance users possible confounder First-rank symptoms not directly compared Limited use of tools Diagnosis only confirmed on discharge

References

- Alil R, Baigent M, Marsden J, Montiero M, Srisurapanont M, Sunga A, Vial R, Wada K: WHO Multi-Site Project on Methamphetamine-induced Psychosis: A descriptive report of findings from participating countries. In Edited by Anonymous 2006:[Anonymous]
- American Psychiatric Association Ed. 2000. *Diagnostic and Statistical Manual of Mental Disorders*. Text Revision ed.: Amer Psychiatric Pub.
- American Psychiatric Association. 2013. *Diagnostic and statistical manual of mental disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing.
- Angrist, B., Sathananthan, G., Wilk, S. & Gershon, S. 1974. Amphetamine psychosis: behavioral and biochemical aspects. *Journal of psychiatric research*. 11:13-23.
- Angrist, B.M. & Gershon, S. 1970. The phenomenology of experimentally induced amphetamine psychosis--preliminary observations. *Biological psychiatry*. 2(2):95-107.
- Baker, A. & Dawe, S. 2005. Amphetamine use and co-occurring psychological problems: Review of the literature and implications for treatment. . *Australian psychologist*. 40(2):88. DOI:10.1080/00050060500094654.
- Baker, A., Bucci, S., Lewin, T.J., Richmond, R. & Carr, V.J. 2005. Comparisons between psychosis samples with different patterns of substance use recruited for clinical and epidemiological studies. *Psychiatry research*. 134(3):241-250. DOI:10.1016/j.psychres.2005.02.006.
- BELL, D.S. 1965. Comparison of Amphetamine Psychosis and Schizophrenia. *The british journal of psychiatry : The journal of mental science*. 111:701-707.
- Carpenter, W.T.,Jr, Strauss, J.S. & Muleh, S. 1973. Are there pathognomonic symptoms in schizophrenia? An empiric investigation of Schneider's first-rank symptoms. *Archives of general psychiatry*. 28(6):847-852.
- Caton, C.L., Drake, R.E., Hasin, D.S., Dominguez, B., Shrout, P.E., Samet, S. & Schanzer, B. 2005. Differences between early-phase primary psychotic disorders with concurrent substance use and substance-induced psychoses. *Archives of general psychiatry*. 62(2):137-145. DOI:10.1001/archpsyc.62.2.137.
- Connell, P. (1958). *Amphetamine psychosis* Maudsley.
- Crichton, P. 1996. First-rank symptoms or rank-and-file symptoms? *The british journal of psychiatry : The journal of mental science*. 169(5):537-40; discussion 541-50.
- Curran, C., Byrappa, N. & McBride, A. 2004. Stimulant psychosis: systematic review. *The british journal of psychiatry : The journal of mental science*. 185:196-204. DOI:10.1192/bjp.185.3.196.
- Davis & Schlemmer. 1980. *The Amphetamine Psychosis*.
- Dore, G. & Sweeting, M. 2006. Drug-induced psychosis associated with crystalline methamphetamine. *Australasian psychiatry : Bulletin of royal australian and new zealand college of psychiatrists*. 14(1):86-89. DOI:10.1111/j.1440-1665.2006.02252.x.
- Grant, K.M., LeVan, T.D., Wells, S.M., Li, M., Stoltenberg, S.F., Gendelman, H.E., Carlo, G. & Bevins, R.A. 2012. Methamphetamine-associated

- psychosis. *Journal of neuroimmune pharmacology : The official journal of the society on NeuroImmune pharmacology*. 7(1):113-139.
DOI:10.1007/s11481-011-9288-1; 10.1007/s11481-011-9288-1.
- Griffith, J., Cavanaugh, J. & Oates, J. Eds. 1970. *Psychosis induced by administration of d-amphetamine in human volunteers. In: Psychotomimetic Drugs*. New York: Raven Press.
- Janowsky, D., Risch, C. 1979. Amphetamine Psychosis and Psychotic Symptoms. *Psychopharmacology*. 63:73-77.
- Medhus, S., Mordal, J., Holm, B., Mørland, J. & Bramness, J.G. 2013. A comparison of symptoms and drug use between patients with methamphetamine associated psychoses and patients diagnosed with schizophrenia in two acute psychiatric wards. *Psychiatry research*. 206(1):17-21.
DOI:http://dx.doi.org.ezproxy.uct.ac.za/10.1016/j.psychres.2012.09.023.
- Nordgaard, J., Arnfred, S.M., Handest, P. & Parnas, J. 2008. The diagnostic status of first-rank symptoms. *Schizophrenia bulletin*. 34(1):137-154.
DOI:10.1093/schbul/sbm044.
- O'Grady, J. 1990. The prevalence and diagnostic significance of Schneiderian first-rank symptoms in a random sample of acute psychiatric inpatients. *The British Journal of Psychiatry*. 156:496-500.
- Oyebode, F. Ed. 2008. *Sims' Symptoms in the Mind, An Introduction to Descriptive Psychopathology*. 4th ed.: Saunders.
- Peralta, V. & Cuesta, M.J. 1999. Diagnostic significance of Schneider's first-rank symptoms in schizophrenia. Comparative study between schizophrenic and non-schizophrenic psychotic disorders. *The british journal of psychiatry : The journal of mental science*. 174:243-248.
- Rosse, R.B., Collins, J.P., Jr, Fay-McCarthy, M., Alim, T.N., Wyatt, R.J. & Deutsch, S.I. 1994. Phenomenologic comparison of the idiopathic psychosis of schizophrenia and drug-induced cocaine and phencyclidine psychoses: a retrospective study. *Clinical neuropharmacology*. 17(4):359-369.
- Salleh, M.R. 1992. Specificity of Schneider's first rank symptoms for schizophrenia in Malay patients. *Psychopathology*. 25(4):199-203.
- Silverstein, M., Harrow, M. 1981. Schneiderian First-Rank Symptoms in Schizophrenia. *Arch Gen Psychiatry*. 38(3):288-93.
- Soares-Weiser, K., Maayan, N., Bergman, H., Devnport, C., Kirkham, A.J., Grabowski, S., Adams, CE. 2015. First rank symptoms for schizophrenia (Review). *Cochrane Database of Sytematic Reviews*. Issue 1. Art No.: CD010653. DOI: 10.1002/14651858.CD010653.pub2.
- Srisurapanont, M., Arunpongpaisal, S., Wada, K., Marsden, J., Ali, R. & Kongsakon, R. 2011. Comparisons of methamphetamine psychotic and schizophrenic symptoms: a differential item functioning analysis. *Progress in neuro-psychopharmacology & biological psychiatry*. 35(4):959-964. DOI:10.1016/j.pnpbp.2011.01.014; 10.1016/j.pnpbp.2011.01.014.
- Tandon, R. & Greden, J.F. 1987. Schneiderian first rank symptoms: reconfirmation of high specificity for schizophrenia. *Acta psychiatrica scandinavica*. 75(4):392-396.

- Tomiyaama, G. 1990. Chronic schizophrenia-like states in methamphetamine psychosis. *The japanese journal of psychiatry and neurology*. 44(3):531-539.
- Wada, K. & Fukui, S. 1990. Relationship between years of methamphetamine use and symptoms of methamphetamine psychosis. *Arukoru kenkyu to yakubutsu izon = japanese journal of alcohol studies & drug dependence*. 25(3):143-158.
- Winger, Woods & Hofmann Eds. 2004. *A Handbook on Drug and Alcohol Abuse: The Biomedical Aspects*. 4th ed.: Oxford University Press.
- World Health Organization Ed. 1992. *The ICD-10 Classification of Mental and Behavioral Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization.
- Wright, Stern & Phelan Eds. 2004. *Core Psychiatry*. 2nd ed.: Saunders.

Part D:
Manuscript in Publication Format

Preface

The following manuscript has been prepared and presented in accordance with the instructions for authors for submission of research articles to the BioMed Central Psychiatry Journal. These instructions are included in the appendices.

Schneiderian First-Rank Symptoms in Schizophrenia and Methamphetamine Psychosis: A Comparative Study

James Shelly^{1,2*}, Henk Temmingh^{1,2+}

¹University of Cape Town, Rondebosch, Cape Town, South Africa

²Valkenberg Hospital, Observatory, Cape Town, South Africa

*Primary author

+Co-author/ Research Supervisor

E-mail addresses:

JS: jamisjb@gmail.com

HT: henk.temmingh@gmail.com

Abstract

Background

Methamphetamine psychosis is commonly described as simulating, and often indistinguishable from, Schizophrenia. The authors aimed to determine and compare the occurrence and associations of Schneiderian first-rank symptoms in patients diagnosed with Schizophrenia and methamphetamine psychosis using structured clinical interviews for DSM-IV (SCID-I).

Methods

Data from SCID-I interviews collected on two samples of patients, diagnosed with schizophrenia and with methamphetamine psychosis, as part of two separate research projects, was retrieved from the respective databases and compared. The two groups were compared on the presence of any one first rank symptom, those who had two first rank symptoms, and those who had more than two first rank symptoms. We calculated the prevalence of different first rank symptoms in Schizophrenia and methamphetamine psychosis. We further performed a logistic regression and calculated adjusted and unadjusted odds ratios for the association between first rank symptoms and diagnosis.

Results

One hundred and two patients fulfilled inclusion criteria for the study, 33 from the methamphetamine psychosis sample, and 69 from the schizophrenia sample. Prevalence of one, two, and more than two first rank symptoms in the methamphetamine psychosis and schizophrenia groups was calculated as

69.6% and 69.7%, 21.2% and 20.3%, and 27.3% and 27.5% respectively. After adjusting for covariates, thought broadcasting occurred significantly more often in patients with schizophrenia compared to those with methamphetamine psychosis (Odds ratio=3.61; 95% CI: 1.26-10.33; p=0.017). In turn, the odds of having auditory hallucinations in the form of voices conversing was significantly lower in patients with schizophrenia compared to those with methamphetamine psychosis (Odds ratio=0.27; 95% CI: 0.1-0.75; p=0.012). We found no significant association between any other first rank symptoms as measured by the SCID-I and a diagnosis of schizophrenia or methamphetamine psychosis.

Conclusion

The symptom of thought broadcasting was significantly more likely to occur in patients diagnosed with schizophrenia than in patients diagnosed with methamphetamine psychosis. Auditory hallucinations of voices heard conversing was significantly less likely to occur in patients with schizophrenia than in those with methamphetamine psychosis. Overall, there was a significant overlap of first rank symptoms and a diagnosis of either schizophrenia or methamphetamine psychosis, but this study did not show that patients with a diagnosis of schizophrenia are more likely to have first rank symptoms when compared to those with methamphetamine psychosis.

Key Words

Schneiderian First-rank Symptoms; Methamphetamine Psychosis; Schizophrenia

Background

Methamphetamine-related disorders pose a significant problem for mental health care providers, general health care providers and the community as a whole, as a consequence of the health-related, legal and social impact of methamphetamine use.[1] They add to the already overwhelming burden of disease posed by mental illness in general.[1] Percentages of patients presenting to 27 specialist substance abuse treatment programs in Cape Town with methamphetamine as their primary substance of abuse increased from 0.3% in 2002 to 42.3% in 2006. [2]

Likewise, Schizophrenia poses a significant problem for health care providers. From a burden of disease perspective, it poses a significant economic and service use impact. It ranks in the top 20 diseases in South Africa regarding estimated years lived with disability and in the top 30 leading causes of worldwide disability-adjusted life years.[3][4]

Methamphetamine psychosis is commonly described as closely simulating, and sometimes even as indistinguishable from, Paranoid Schizophrenia.[5][6][7][8] The positive symptoms of methamphetamine psychosis are particularly similar to those of paranoid schizophrenia, consisting mainly of delusions (particularly of persecution, but also delusions of reference) and hallucinations. Delusions of persecution are frequently reported to be characteristic of methamphetamine psychosis.[8][9][10][11] Few studies have been carried out which investigate specific symptomatological and phenomenological differences

between schizophrenia and methamphetamine psychosis.

Schneiderian first-rank symptoms (FRS) include audible thoughts, voices heard arguing, voices heard commentating on one's actions or giving a running commentary, somatic and thought passivity experiences (delusions of control), thought insertion, thought withdrawal, thought broadcasting, and delusional perception.[12]

In 1959, Schneider attempted to operationalize the diagnosis of schizophrenia by describing the above symptoms, which he considered of first rank importance in differentiating Schizophrenia from other similar illnesses.[13] According to Schneider, the presence of one or more first-rank symptoms in the absence of organic disease can be used as positive evidence for schizophrenia, though he did not consider any of these symptoms necessary for the diagnosis.[14]

Clinicians in psychiatric emergency departments have a tendency to attribute psychotic symptoms to primary psychotic disorders, such as Schizophrenia, rather than to concurrent substance use.[15] Given that the diagnosis has significant implications for future management, with the recommended length of treatment with antipsychotics being significantly shorter for patients with substance induced psychosis compared to schizophrenia, it is important to improve diagnostic approaches.[17]

Consensus guidelines recommend antipsychotic treatment for patients diagnosed with first episode Schizophrenia for at least 18- 24 months, and while no evidence-based guidelines regarding duration of treatment of methamphetamine psychosis have been published, it often only requires brief (ie. < 3 months) interventions.[16] As exposure to antipsychotic medication increases ones risk of developing unwanted, and often debilitating and serious, side-effects (eg. EPSE's, TD, weight gain, metabolic syndrome), accurate diagnosis has important implications for treatment planning.[17]

Symptom studies may be a priority area because these results are basic knowledge for further studies of methamphetamine psychosis. The phenomenological differentiation between schizophrenia and methamphetamine psychosis has implications on diagnosis, treatment planning, and prognosis.

Recent literature has ascertained that Schneiderian first-rank symptoms, as a whole, are not specific to schizophrenia, and thus should not be considered pathognomic.[20] This is reflected in the DSM 5 diagnostic criteria for schizophrenia, with first-rank symptoms having been de-emphasized.[21] The ICD-11 is likely to follow suit in this regard.[23] However, certain first-rank symptoms (thought broadcasting and thought withdrawal) have indeed been found to occur significantly more frequently in patients with schizophrenia as compared to those with cocaine-induced and phencyclidine-induced psychoses.[18] This finding has not been

replicated in patients with methamphetamine psychosis, as no studies have been performed which directly compare the presence of Schneiderian first-rank symptoms in patients with schizophrenia and methamphetamine psychosis.

We aimed to explore the hypothesis that FRS occur more frequently in patients with a diagnosis of schizophrenia as compared to patients with methamphetamine induced psychosis.

Methods

Participants

This study is a secondary analysis of data collected from two cross-sectional studies, the first investigating the phenomenology and neurobiology of schizophrenia and related psychotic disorders, and the second investigating the neurobiology of methamphetamine psychosis. Information on clinical and demographic patient variables was obtained from two databases that form part of these two larger research projects.

Data was collected on patients with functional psychotic disorders admitted to Valkenberg Hospital, a large psychiatric hospital in Cape Town, South Africa (Risk factors and Psychobiology of Psychosis Study). Data was separately collected from participants with various methamphetamine related presentations, methamphetamine psychosis in particular, admitted to the same large psychiatric inpatients unit (Valkenberg Hospital), as well as related psychiatric units (Groote Schuur Hospital)(The

Methamphetamine Psychosis Study). In addition, participants who were living in the community and attending drug treatment centers and outpatient clinics were also recruited to take part in the methamphetamine psychosis study.

Subjects from the functional psychosis study database were included in the current study if they were age 18-59, fluent in English, and fulfilled diagnostic criteria for schizophrenia. They were excluded if they fulfilled criteria for any other Axis I disorder, had ever used any substance other than alcohol or nicotine, or if they fulfilled criteria for alcohol abuse or dependence.

Subjects from the methamphetamine study were included in the current study if they were age 18-59, fluent in English, and fulfilled criteria for substance-induced psychotic disorder, with methamphetamine as the attributable substance. They were excluded if they fulfilled dependence criteria for any substance other than methamphetamine.

Data collection

The SCID-I-RV for DSM-IV-TR (Structured Clinical Interview for DSM-IV, Research Version) was used to determine the principal Axis I diagnosis. The SCID-I-RV is a semi-structured clinical interview tool for determining the major DSM-IV Axis I diagnoses. The SCID-I-RV is organized into diagnostic modules that include interview questions, diagnostic criteria and ratings. Module A assesses mood episodes; Module B assesses psychotic

symptoms, including first-rank symptoms; Module C diagnoses psychotic disorders; Module D diagnoses mood disorders; and Module E diagnoses substance use disorders. Diagnostic assessment is conducted during Modules C (psychotic disorders) and D (mood disorders) and is dependent on operationalized criteria for schizophrenia. Diagnostic formulations are independent of the findings in Module B relating to psychotic symptom type or the presence of first-rank symptoms. Although the DSM-IV makes it possible to fulfill criterion A with only one positive symptom if it is a first-rank symptom, this does not necessitate a diagnosis of schizophrenia, but other psychotic disorders could also be diagnosed.

To fulfill DSM-IV diagnostic criteria for a substance-induced psychotic disorder, one must present with prominent delusions and/or hallucinations that develop during or within a month of use of a particular substance that is considered etiologically related to the disturbance. The symptoms do not precede the use of the substance, do not persist for longer than one month following cessation and/or withdrawal of the substance, and should not be substantially in excess of what might be expected, given the type, amount or duration of use of the particular substance.

For the functional psychosis study, diagnostic interviews were conducted by two psychiatrists, a psychiatry research fellow, and two research nurses. All had received extensive training and had experience in the conducting of SCID's. Regular meetings were held to improve reliability and a senior psychiatrist checked the reliability of the SCID data. A kappa

coefficient of 0.71 was obtained for the principle axis-I diagnosis, indicating substantial agreement between interviewers. Data used for the current study was collected between February 2009 and October 2012.

For the methamphetamine study, diagnostic interviews were conducted by a psychiatrist, a psychiatry research fellow within the department of psychiatry and mental health at the University of Cape Town, and one of the same research nurses as per the functional psychosis study, all of whom were trained on the administration of the SCID by the functional psychosis study's principle investigator. Data used for the current study was collected between November 2009 and February 2012.

The principal investigator in this study was not involved in the original data collection for either the functional psychosis study, or the methamphetamine study. He extracted data on Schneiderian first-rank symptoms, as measured by the SCID-I-RV (delusions of control, thought insertion, thought withdrawal, thought broadcasting, voices heard commenting on patient, voices heard conversing or arguing, and bizarre delusions), from the above databases and entered it into a new database, along with demographic data on patients' age, gender, ethnicity, marital status, employment status and level of education.

Both larger research projects mentioned above, as well as the current study, received ethical clearance by the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee. All participants in

the original studies gave written informed consent to participate in these studies.

Analysis

We conducted bivariate analyses to compare the schizophrenia and methamphetamine groups on demographic variables. For bivariate analyses we used Chi-square tests with Fisher's exact test where appropriate. In addition, in order to adjust for age, gender, ethnicity, marital status, employment status and level of education, we constructed a series of logistic regression models with the dependent variable specified as diagnosis, coded as schizophrenia=1 and methamphetamine induced psychotic disorder=0. Odds ratios and appropriate 95% CI's were calculated. Two-sided tests were used and a 5% significance level was used throughout. We analyzed data using Stata version 11 for Windows.[19]

Results

Sample characteristics

The total sample included 102 participants, with diagnoses of methamphetamine psychosis (n=33) and schizophrenia (n=69). Table 1 describes the demographic characteristics of the sample. Compared to patients with Schizophrenia, patients with methamphetamine psychosis were significantly more likely to fall within the 18-34 age range.

Association between diagnosis and first rank symptoms

Prevalence of one, two, or more than two first-rank symptoms did not significantly differ between the two diagnostic groups. Figures 1 and 2 contain a breakdown of the prevalence of first-rank symptoms in the schizophrenia and methamphetamine psychosis groups.

We did not find any statistically significant association between the presence of at least one first-rank symptom and a diagnosis of schizophrenia or methamphetamine psychosis (OR: 1.15; 95% CI: 0.42-3.14; $p=0.788$).

The symptom of thought broadcasting was significantly more prevalent in the schizophrenia group: 42% compared to 24.2% in the methamphetamine psychosis group. This association remained significant after we adjusted for age, gender, ethnicity, marital status, employment status and level of education in the multivariable logistic regression model (OR: 3.61; 95% CI: 1.26-10.23; $p=0.017$).

The symptom of auditory hallucinations of voices heard conversing was significantly more prevalent in the methamphetamine group: 48.5% compared to 20.3% in the schizophrenia group. This association remained significant after we adjusted for age, gender, ethnicity, marital status, employment status and level of education, in the multivariable logistic regression model (OR: 0.27; 95% CI: 0.1-0.75; $p=0.012$).

All the other first-rank symptoms measured, with the exception of auditory

hallucinations of voices commenting on the patient's actions, showed greater prevalence in the schizophrenia group, though the values calculated were only of greater numerical value, and were not found to be statistically significant.

Table 2 describes adjusted and unadjusted odds ratios for the association between first-rank symptoms and diagnosis.

Discussion

We aimed to explore the hypothesis that Schneiderian first-rank symptoms would occur more frequently in patients with schizophrenia as compared to patients with methamphetamine psychosis. We found no studies in the literature making this direct comparison, so this was the first study of this type to our knowledge.

The main findings of this study were that the symptom of thought broadcasting occurred significantly more frequently and the symptom of voices heard conversing occurred significantly less frequently in patients with schizophrenia compared to patients with methamphetamine psychosis.

Rosse *et al's* study of cocaine- and phencyclidine-induced psychoses helped to inform our hypothesis. They found the symptom of thought broadcasting (as well as thought withdrawal) to occur significantly more frequently in their sample of patients with schizophrenia than in those with cocaine-induced psychosis.[18] Our finding of thought broadcasting being

present significantly more often in schizophrenia compared to methamphetamine psychosis is in keeping with this finding, perhaps speaking to some significance of this particular symptom in schizophrenia compared to substance-induced psychoses. The possible neuro-anatomical correlates of this and other symptoms in these conditions is perhaps an area worthy of investigation. While other previous studies failed to find the same result, none were specifically designed for this purpose. The finding that voices heard conversing occurred significantly less frequently in patients with schizophrenia than in those with methamphetamine psychosis was not in the hypothesized direction. However, given that both the ICD-10 and the DSM-IV have been concluded to give first-rank symptoms more emphasis in their diagnostic criteria for schizophrenia than is supported by the evidence, this finding should not be surprising.[20] The decreased emphasis placed on first-rank symptoms in the DSM 5 diagnostic criteria for schizophrenia, with the presence of just one first-rank symptom no longer being considered sufficient to fulfill criterion A, attests to this.[21]

It is possible that the finding of voices heard conversing occurring more frequently in the methamphetamine participants could be accounted for by the likelihood of a change in diagnosis over time from methamphetamine psychosis to schizophrenia. Indeed, a limitation of the study was that the cross-sectional design did not allow the authors to account for the possibility that patients diagnosed with methamphetamine psychosis might, later in life, receive a diagnosis of schizophrenia. This was further

emphasized by the finding of a significantly greater number of methamphetamine psychosis patients in the 18-34 age range. Although we adjusted for age in our analysis, results may have been skewed as a consequence of the cross-sectional nature of the study, as diagnostic change over time has been observed in longitudinal studies of psychotic disorders. Caton *et al* observed a change in diagnostic category from substance-induced psychosis to primary psychotic disorder at the one-year follow-up in 25% of their study sample diagnosed with substance-induced psychosis at baseline.[22] More recently, Niemi-Pynttärä found an 8 year cumulative risk to receive a schizophrenia spectrum disorder diagnosis of 30% (95% CI, 14-46%) in patients with methamphetamine psychosis, confirming that substance-induced psychoses predict schizophrenia to a greater extent than previously thought, and recommending that the clinical attention focused on substance-induced psychoses should be intensified.[24] The SCID was not specifically designed to measure first-rank symptoms. It does not measure delusional perception. This could potentially lead to an underestimation in the measurement of first-rank symptoms, and while this would have been true for both groups, and thus not a confounder, it could be argued that other tools, such as the Manual for the Assessment of Schizophrenia (Landmark, 1982), or the Scale for Assessment of Positive Symptoms (Andreasen, 1984) may be better suited to investigate the phenomenology of schizophrenia as pertaining to first-rank symptoms. As patients diagnosed with schizophrenia were recruited from an inpatient sample, and at least part of the methamphetamine group from an outpatient and community-based

sample, a selection bias may have been introduced, as these groups may contain differences in variables that may have an impact on symptom structure, such as illness severity, socio-economic background, geographical, language and cultural differences. We aimed to adjust for other factors, such as age, and proxies of socioeconomic status, such as employment and educational level. However, residual confounding factors such as chronicity of illness and medications received by the time of data collection, could still have influenced our findings.

Recommendations for further research on this subject might include a longitudinal study design, in order to attempt to account for the potential conversion over time from a diagnosis of methamphetamine psychosis to that of schizophrenia. Furthermore, given the similarities in findings between this study and that of Rosse et al, future research might focus more closely on the diagnostic significance of the symptom of thought broadcasting in schizophrenia when compared to substance-induced psychotic disorders in general, and methamphetamine psychosis in particular. Another area of interest might include the investigation of the neurological and/or anatomical correlates of these symptoms in these and other disorders.

Conclusions

The symptom of thought broadcasting was significantly more likely to occur in patients diagnosed with Schizophrenia than in patients diagnosed with methamphetamine psychosis, while the symptom of auditory

hallucinations, in the form of voices heard conversing, was significantly less likely to occur in patients with schizophrenia than in those with methamphetamine psychosis.

Overall, there was a significant overlap of first-rank symptoms and a diagnosis of either schizophrenia or methamphetamine psychosis, but this study did not show that patients with a diagnosis of schizophrenia are more likely to have first-rank symptoms when compared to those with methamphetamine psychosis.

Competing Interests

The authors declare that they have no financial or non-financial competing interests.

Authors' Contributions

JS conceived of the study, participated in its design and coordination, and drafted the manuscript.

HT participated in the design, recruitment and statistical analysis of the study and helped to edit the manuscript.

All authors read and approved the final draft of the manuscript.

Acknowledgements

The authors acknowledge the contributions of the following clinicians and researchers: Anne Uhlmann, Goodman Sibeko, Gameda Benefeld, Heidi Sinclair and Nastassja Koen.

References

1. Alil R, Baigent M, Marsden J, Montiero M, Srisurapanont M, Sunga A, Vial R, Wada K: **WHO Multi-Site Project on Methamphetamine-induced Psychosis: A descriptive report of findings from participating countries.** In Edited by Anonymous 2006:[Anonymous]
2. Plüddemann A, Plüddemann A, Myers BJ, Parry CD: **Surge in treatment admissions related to methamphetamine use in Cape Town, South Africa: implications for public health.** Drug Alcohol Rev 2008, **27**(2):185-189.
3. Norman R, Bradshaw D, Schneider M, Pieterse D, Groenewald P: **MRC Burden of Disease Research Unit. Revised Burden of Disease Estimates for the Comparative Risk Factor Assessment, South Africa 2000; 2006.** 2006, .
4. Murray CJ, Lopez AD: **Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study.** Lancet 1997, **349**(9063):1436-1442.
5. BELL DS: **Comparison of Amphetamine Psychosis and Schizophrenia.** Br J Psychiatry 1965, **111**:701-707.
6. Davis, Schlemmer: *The Amphetamine Psychosis*; 1980.
7. Baker A, Dawe S: **Amphetamine use and co-occurring psychological problems: Review of the literature and implications for treatment.** . Australian Psychologist 2005, **40**(2):88.
8. Connell P: **Amphetmaine Psychosis.** In Edited by Anonymous Maudsley; 1958:[Anonymous]
9. Griffith J, Cavanaugh J, Oates J: **Psychosis induced by administration of d-amphetamine in human volunteers.** In: **Psychotomimetic Drugs.** 1970, :.
10. Wada K, Fukui S: **Relationship between years of methamphetamine use and symptoms of methamphetamine psychosis.** Arukoru Kenkyuto Yakubutsu Ison 1990, **25**(3):143-158.
11. Winger, Woods, Hofmann: **A Handbook on Drug and Alcohol Abuse: The Biomedical Aspects.** 2004, :.
12. Oyebode F: **Sims' Symptoms in the Mind, An Introduction to Descriptive Psychopathology.** 2008, :.
13. Wright, Stern, Phelan: **Core Psychiatry.** 2004, :.
14. Crichton P: **First-rank symptoms or rank-and-file symptoms?** Br J Psychiatry 1996, **169**(5):537-40; discussion 541-50.
15. Schanzer BM, First MB, Dominguez B, Hasin DS, Caton CL: **Diagnosing psychotic disorders in the emergency department in the context of substance use.** Psychiatr Serv 2006, **57**(10):1468-1473.
16. Galanter M, Kleber H: **The American Psychiatric Publishing Textbook of Substance Abuse Treatment.** 2008, :.
17. Barnes TR, Schizophrenia Consensus Group of British Association for Psychopharmacology: **Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology.** J Psychopharmacol 2011, **25**(5):567-620.

18. Rosse RB, Collins JP, Jr, Fay-McCarthy M, Alim TN, Wyatt RJ, Deutsch SI: **Phenomenologic comparison of the idiopathic psychosis of schizophrenia and drug-induced cocaine and phencyclidine psychoses: a retrospective study.** Clin Neuropharmacol 1994, **17**(4):359-369.
19. StataCorp: **Stata Statistical Software.** 2009, .
20. Nordgaard J, Arnfred SM, Handest P, Parnas J: **The diagnostic status of first-rank symptoms.** Schizophr Bull 2008, **34**(1):137-154.
21. American Psychiatric Association: *Diagnostic and statistical manual of mental disorders*: 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
22. Caton C, Hasin D, Shrout P, Drake R, Dominguez B, First M, Schanzer B: **Stability of early-phase primary psychotic disorders with concurrent substance use and substance-induced psychosis.** Br J Psychiatry 2007, **190**(February):105-11.
23. Gaebel, W: **Status of Psychotic Disorders in ICD-11.** Schizophr Bull 2012, **38**(5):895-898.
24. Niemi-Pynttari, JA: **Substance-induced psychoses converting into schizophrenia: a register-based study of 18,478 Finnish inpatient cases.** J Clin Psychiatry 2013, **74**(1):e94-9.

Tables

Table 1- Demographic characteristics of sample

Variable	Methamphetamine Psychosis (N=33)		Schizophrenia (N=69)		Test statistic	df	P-value
	N	%	N	%			
Age							
18-34	29	87.8	38	55.07		-	-
35-59	4	12.12	31	44.93	Chi ² = 10.66	1	0.001
Gender							
Male	8	24.24	29	42.03		-	-
Female	25	75.76	40	57.97	Chi ² = 3.06	1	0.080
Ethnic group							
White	1	3.03	7	10.14		-	-
Coloured	22	66.67	33	47.83		-	-
Black	10	30.30	29	42.03	Chi ² = 3.71	2	0.156
Marital status							
Married or cohabitating	3	9.09	9	13.04		-	-
Never Married	29	87.88	54	78.26		-	-
Previously Married or Cohabiting	1	3.03	6	8.70	Fisher's exact test	-	0.557
Years of Education							
0 - 7	3	9.09	11*	16.18		-	-
> 7	30	90.91	57*	83.82	Fisher's exact test	-	0.540
Employment status							
Employed	8	24.24	15	21.74		-	-
Unemployed	25	75.76	54	78.26	Chi ² = 0.08	1	0.777

- n= 68. Data missing on one subject's level of education.
- df: degrees of freedom

Table 2- Adjusted and unadjusted odds ratios for the association between FRS and diagnosis.

	Schizophrenia vs. methamphetamine psychosis			
	Crude OR	95% CI	Adjusted OR^a	95% CI
Delusions of control	1.17	0.46 -2.93	1.52	0.55-4.21
Delusions of thought insertion	1.25	0.43 -3.58	1.12	0.35-3.59
Delusiosn of thought withdrawal	2.55	0.67 - 9.56	3.06	0.74-12.77
Delusions of thought broadcasting	2.27	0.89- 5.73	3.61	1.26-10.33*
Bizarre delusions	1.36	0.47-3.86	1.08	0.32-3.61
Voices giving a running commentary	0.45	0.17-1.11	0.42	0.15-1.20
Voices conversing	0.27	0.10- .66	0.27	0.10-0.75*
FRS one or more	0.99	0.40 -2.44	1.15	0.42-3.14

- *p<0.05, **p<0.01, ***p<0.001
- a. Models adjusted for age, gender, marital status, ethnicity, educational level, employment status

Figures

Figure 1. Prevalence (%) of Schneiderian first rank symptoms in methamphetamine psychosis and schizophrenia.

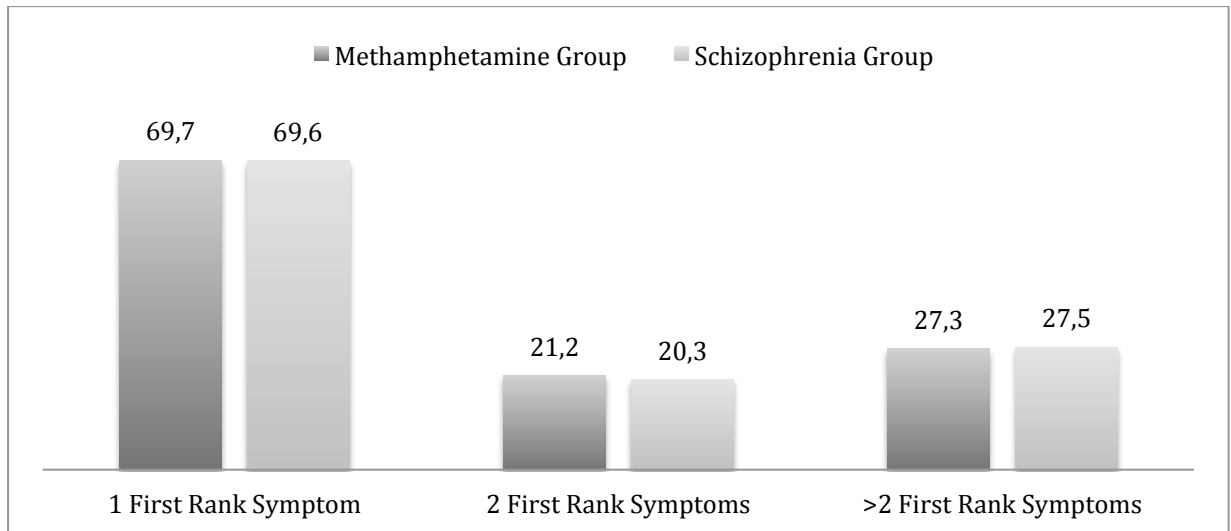
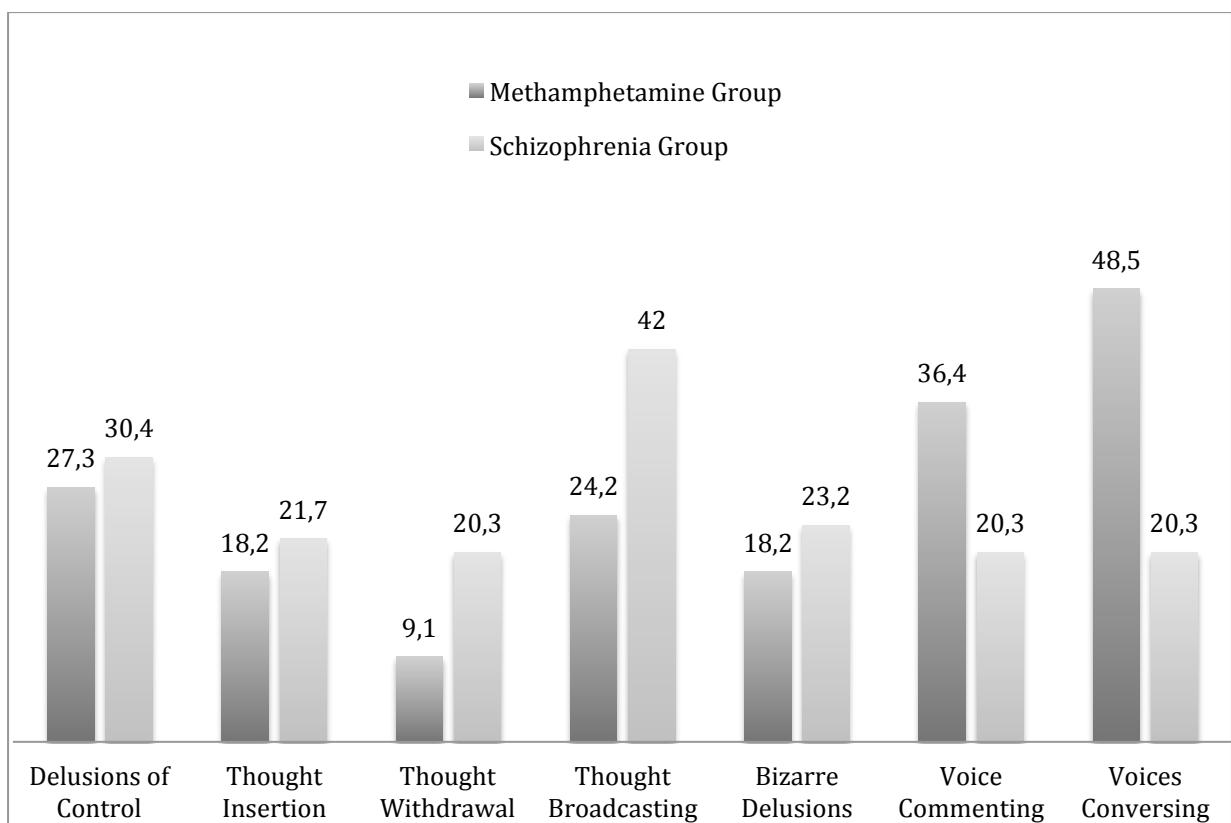


Figure 2. Prevalence (%) of different Schneiderian first rank symptoms in methamphetamine psychosis and schizophrenia.



Part E:
Appendices

Acknowledgements

I would like to thank Henk Temmingh for his continuous support and supervision; Anne Uhlmann, Goodman Sibeko, Gamede Benefeld, Heidi Sinclair and Nastassja Koen for their data collection; Sean Baumann, John Parker and Mohamed Coovadia for their initial inspiration in the conception of this study; and to my family for their unwavering support and patience.

UCT Faculty of Health Sciences Approval of Study Proposal

5/1/2015

Gmail - Shelly: Confirmation of Approval of Study Proposal



James Shelly <jamisjb@gmail.com>

Shelly: Confirmation of Approval of Study Proposal

1 message

Vuyi Mgoqi <vuyi.mgoqi@uct.ac.za>

9 February 2015 at 15:38

To: "jamisjb@gmail.com" <jamisjb@gmail.com>

Cc: Jackie Cogill <jackie.cogill@uct.ac.za>, Henk Temmingh <henk.temmingh@uct.ac.za>

Dear Dr Shelly

Candidature Approval (SHLJAM001)

Degree	MMed in Psychiatry
Title	Schneiderian first-rank symptoms in schizophrenia and methamphetamine psychosis: a comparative study
Department	Psychiatry
Supervisor	Dr H Temmingh
Ethics Approval	450/2013

I am pleased to advise that the Chair of the Dissertations/Doctoral & Masters Committee has approved your candidature for the above degree on behalf of the Committee. Formal approval was obtained by publication in the Dean's Circular, PG-Med Nov-Dec2014.

Yours sincerely

Vuyi Mgoqi



Vuyisela Mgoqi | Receptionist: PG Academic Administration | Faculty of Health Sciences | University of Cape Town
Town | Room N2.19, Wernher & Beit North, Health Sciences Campus, Anzio Rd, Observatory, 7925 | ☎ +27 21 406 6751 📠 +27 21 406 6584 | Office Hours: 08h30 - 16h30 Unavailable Hours: 13h00 - 13h30

UNIVERSITY OF CAPE TOWN

This e-mail is subject to the UCT ICT policies and e-mail disclaimer published on our website at <http://www.uct.ac.za/about/policies/emaildisclaimer/> or obtainable from +27 21 650 9111. This e-mail is intended only for the person(s) to whom it is addressed. If the e-mail has reached you in error, please notify the author. If you are not the intended recipient of the e-mail you may not use, disclose, copy, redirect or print

UCT Human Research Ethics Committee Approval



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492 • Facsimile [021] 406 6411
Email: Sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

29 July 2013

HREC/REF: 450/2013

Dr J Shelly
c/o Dr H Temmingh
Psychiatry & Mental Health
J-Block
GSH

Dear Mr Shelly

Project Title: SCHNEIDERIAN FIRST RANK SYMPTOMS IN SCHIZOPHRENIA AND METHAMPHETAMINE PSYCHOSIS: A COMPARATIVE STUDY LINK TO: 332/2008 & 340/2009

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above mentioned study.

Approval is granted for one year until the 28 August 2014.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

pp T. Burgess
PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Hrec/ref:450/2013

UNIVERSITY OF CAPE TOWN



Faculty of Health Sciences
Faculty of Health Sciences Human Research Ethics Committee
Room E52-24 Grootte Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: sumayah.ariefdien@uct.ac.za
www.health.uct.ac.za/research/humanethics/forms

29 July 2013

HREC REF: 450/2013

Dr J Shelly
c/o Dr H Temmingh
Psychiatry & Mental Health
J-Block
GSH

Dear Mr Shelly

PROJECT TITLE: SCHNEIDERIAN FIRST RANK SYMPTOMS IN SCHIZOPHRENIA AND METHAMPHETAMINE PSYCHOSIS: A COMPARATIVE STUDY LINK TO:322/2008

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above mentioned study.

Approval is granted for one year till the 28 August 2014.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

sAriefdien

UCT Human Research Ethics Committee Approval Renewal



UNIVERSITY OF CAPE TOWN
UNIVERSITEIT VAN KAPSTAD

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee



FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
Approved	Annual progress report	Approved until/next renewal date	28/08/2015
Not approved	See attached comments		
Signature Chairperson of the HREC	<i>[Signature]</i>	Date Signed	12/12/14

Comments to PI from the HREC	HUMAN RESEARCH ETHICS COMMITTEE 12 DEC 2014
Principal Investigator to complete the following:	HEALTH SCIENCES FACULTY UNIVERSITY OF CAPE TOWN

1. Protocol information

Date (when submitting this form)	12/12/14		
HREC REF Number	450/2013	Current Ethics Approval was granted until	28/8/14
Protocol title	Schneiderman First-Rank Symptoms in Schizophrenia and Methamphetamine Abuse: A comparative Study		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	Yes	<input checked="" type="radio"/> No	
If yes, could you please provide the HREC Refs for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	James Brady Sholly		
Department / Office Internal Mail Address	Dept of Psychiatry & mental Health J-block GSH		

1.1 Does this protocol receive US Federal funding?	Yes	<input checked="" type="radio"/> No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	Yes	No
1.3 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	Yes	<input checked="" type="radio"/> No

Participant Information Sheets and Consent Forms/Booklet – Psychosis and Methamphetamine Studies

“Participant information sheet for the project:

Presentation and Risk Factors in the Psychobiology of Psychosis

(University of Cape Town Research Ethics Committee Reference Number: 332/2008)

Please read the following document carefully as it will help you decide whether you want to take part in the above study. Please ask the investigator if there are any additional queries at any time during the study.

What is the study about?

The above study looks at whether there are certain factors in the lives of people that make them more vulnerable to develop conditions that require treatment in a psychiatric hospital.

The aim of this study is to carefully describe your current and past experiences and symptoms. This will allow the investigators to make a more accurate medical diagnosis of the suspected illness (es) involved. Your views and experiences will also be explored in order to increase our understanding of how you view events and experiences that made it necessary for you to receive treatment at a psychiatric hospital. If applicable this study will also explore your habits and patterns of drug use as well as your view of these habits. Should you agree, we may approach your family or close friends to clarify some of the information.

This study also aims to investigate whether there are inherited factors that make persons more vulnerable to develop psychotic illnesses. For this aim, should you provide us with permission; a blood sample will be taken for genetic analysis and a series of facial photographs will be taken.

What does participation in this study entail?

Should you choose to participate the investigator will interview you to obtain certain information. This will take approximately 60 to 90 minutes of your time. The investigator may have to visit you more than once. It may also be necessary for the investigator to contact your family to obtain additional information. Should you agree a blood sample will be also being taken and a series of facial photographs will be taken.

Potential risks and benefits:

Risks of taking part in this study vary from minimal to no risk at all. Should you feel tired at any time during the interview you should feel free to discuss this with the investigator and the interview can be completed at another time. You and the doctor responsible for your treatment will make decisions regarding your treatment independently of this study. Blood samples will be drawn by the doctor and facial photographs will be taken by a researcher as directed by the doctor.

Possible benefits include increased knowledge of the resources and help contacts in your community. The information you provide will also help us to understand your illness better and will assist us to better plan the treatment of other patients in future.

Compensation

You will not be paid for participation in the study.

What will happen with the information you provided?

All personal information obtained during the study will be treated as strictly confidential. In cases where the results are written up in academic dissertations and publications, your identity will not be revealed in any way.

Your participation in this study is *entirely voluntary* and *you can withdraw from this study at any time*. This will not affect your present or future treatment.

Should you have any questions regarding this study you can contact Dr. HS Temmingh on Tel: 021 4403185”



REQUEST FOR PATIENT/FAMILY INTERVIEW, MOLECULAR STUDIES (DNA) and FACIAL MORPHOMETRY (UCT Rec. Ref 332/2008-v3.Apr.2013)



Molecular Laboratory

**Division of Human Genetics
IIDMM, LEVEL 3
UCT Medical School, Observatory 7925**

Tel: (021) 406 6425 Fax: (021) 406 6826

Blood should be drawn in 2 plastic EDTA Tubes (Purple top) +/- 10ml each using a yellow barrel. Each tube should be inverted to mix and should be clearly labelled with the patient's study number. Keep blood in fridge at 4°C until able to send to laboratory

Please DO NOT send specimens on ice or frozen.

Please fill in all the information requested:

Surname: _____ First Name(s): _____

Gender: M F Date of Birth: Year: _____ Month: _____ Day: _____

Ethnic Origin: Black Indian Mixed ancestry Caucasian Other _____

Contact Address: _____

Town: _____ Tel: _____ Fax: _____

Referring Doctor/Sister: _____ Town: _____ Tel/Fax: _____

Hospital or Address: _____ Town: _____ Tel/Fax: _____

For Clinician/Psychiatric Nurse:

Participants unique research code number: _ _ _ _ . _ _ _ _ _

Affected At Risk Carrier Spouse Query Unaffected

Bipolar disorder Schizophrenia Other psychotic disorder Control

Volume of Blood: _____ Number of 10 ml / 5ml EDTA tubes _____ (ml) Volume in each of the EDTA tubes

Date of Blood drawing: Year: _____ Month: _____ Day: _____

New Family: Yes No (If no, please fill in family name) Family name: _____

Have samples from this patient been sent to a DNA lab before? (DELETE WHERE NOT APPLICABLE)

Yes No Unsure If Yes, where: _____

For Laboratory use only:

Date Blood sample(s) received: Year: _____ Month: _____ Day: _____

Date of DNA extraction: Year: _____ Month: _____ Day: _____

Volume of DNA in Eppendorff 1: _____ DNA lab coding: _____

Volume of DNA in Eppendorff 2: _____ DNA lab coding: _____

CONSENT FORM A (UCT Rec. Ref 332/2008-v.7 Nov.2013)

FOR DNA ANALYSIS AND STORAGE **Yes No**

1. I, _____ agree to participate in a study that will use my genetic material, to assess the genetic relationship to psychiatric disorders that are under investigation in this study.
2. I understand that the genetic material for analysis is to be obtained from: blood cells/skin sample/other (specify) (DELETE WHERE NOT APPLICABLE) :
3. I request that **no** portion of the [_____]sample be stored for later use and that my [_____] sample be destroyed immediately following conclusion of analysis
Or
I request that a portion of the sample be stored for a period of 50 years following the closure of this study, for (DELETE WHERE NOT APPLICABLE):
 - (a) possible re-analysis
 - (b) research purposes, subject to the approval of the University of Cape Town Research Ethics Committee, provided that any information from such research will remain confidential ,
 - (c) AND that such research will be on the same subject as the current research that investigates the relationship between genetic variations and its association with particular psychiatric disorders.
 - (c) AND as per the original study protocol, these disorders exclude any primary disorder characterized by intellectual disability/ mental retardation.
- 4.a I authorise / do not authorise my doctor(s) (DELETE WHERE NOT APPLICABLE) to provide relevant clinical details to the Division of Human Genetics, UCT.
- 4.b I want my identity removed from/ kept with my [type of sample _____]
5. I have been informed that:
 - (a) there are risks and benefits associated with genetic analysis and storage of biological material and these have been explained to me.
 - (b) the analysis procedure is specific to the disorders mentioned above and cannot determine the complete genetic makeup of an individual.
 - (c) the genetics laboratory is under an obligation to respect medical confidentiality .
 - (d) genetic analysis may not be informative for some families or family members.
 - (e) even under the best conditions, current technology of this type is not perfect and could lead to incorrect results.
 - (f) where biological material is used for research purposes, there may be no direct benefit to me.
6. I understand that I may withdraw my consent for any aspect of the above at any time without this affecting my future medical care.
7. I am willing/ not willing to be re-contacted by the researcher about possible future use of my tissue samples in future research.
8. **ALL OF THE ABOVE HAS BEEN EXPLAINED TO ME IN A LANGUAGE THAT I UNDERSTAND AND MY QUESTIONS ANSWERED BY:**

Researcher signature _____ **Date :** _____
Witness signature _____ **Date:** _____
Patient signature _____ **Date:** _____

CONSENT FORM B (UCT Rec. Ref 332/2008-v.7 Nov2013)

1) CLINICAL INTERVIEW **Yes No**

1. I/the participant.....have read the attached information sheet to the study called "*Presentation and Risk Factors in the Psychobiology of Psychosis*"/ the purpose and procedures of this project has been explained to me by the researcher in a language that I understand. I understand that the results will be used for research purposes, that all information will be treated as strictly confidential, and that I might withdraw from the

study at any time.

2. I understand that the results of the analyses carried out during the clinical interview and from the questionnaires will not be made known to me, as the analyses are for research purposes only. I understand therefore that I will gain no immediate benefit from the research in the event of any scientific breakthrough.

2) FAMILY INTERVIEW

Yes No

1. I.....hereby grant the researcher permission to approach my family/close friend/associate (delete where not applicable), concerned with my well being, with the aim of conducting an interview to obtain collateral information if this is deemed necessary.

3) FACIAL MORPHOMETRY

Yes No

1. I, _____ agree to participate in a study that will use my facial features from stereo-photogrammetric images, to assess the physical relationship to psychiatric disorders.
2. I understand that the facial photographs will only be utilised for research purposes, subject to the approval of the University of Cape Town Research Ethics Committee, and that any information from such research will remain confidential.

APPLICABLE TO ALL OF THE ABOVE (Consent A and B)

1. I understand that I may withdraw my consent from any aspect of the above at any time without this affecting my current or future medical care.
2. In addition, I will allow researchers from this project to share information about my identity with other researchers who work as part of the psychosis research team. This may lead to them contacting me to invite me to participate in related research projects.
AGREE / DISAGREE
3. All of the above has been explained to me in a language that I understand and my questions answered by the researcher involved in the present study.

Researcher signature _____ Date : _____
Witness signature: _____ Date: _____
Patient signature _____ Date: _____"

“PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

TITLE OF THE RESEARCH PROJECT:

Neural correlates of deficits in affect regulation in methamphetamine abusers with a history of psychosis

REFERENCE NUMBER: 340/2009

Version: 2

Date: 01/07/2010

PRINCIPAL INVESTIGATOR: Dr Donald Wilson

ADDRESS: University of Cape Town, Dept of Psychiatry and Mental Health, Groote Schuur Hospital (J2), Anzio Road, Observatory 7925, Cape Town, South Africa

CONTACT: E-mail:d.wilson@uct.ac.za, Phone: +27-21-404-2182, Fax: +27-21-448-8158

Dear Volunteer

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is *entirely voluntary* and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the Faculty of Health Sciences Human Research Ethics Committee (FHS HREC) of the University of Cape Town, and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

This project is being run at the Department of Psychiatry, University of Cape Town. We aim to recruit a total of 60 participants over a period of 3 years.

What is this research study all about?

Background: The increasing use of methamphetamine (MA, also “tik” or “meth”) is a cause for concern for a number of reasons. On the personal level the chronic use of MA has been associated with brain damages resulting in potentially long-lasting mental health effects including confusion, impaired concentration and memory. Imaging studies have shown that MA use is associated with imbalances in the neurochemistry of the brain. Thus long-term abuse of “tik” or “meth” is associated with the development of paranoid, often violent psychotic states accompanied by auditory, visual and/or tactile hallucinations. MA abuse also has profound consequences on an interpersonal level, due to associated impairments in emotion regulation. For instance, aggression and hostility have been consistently identified in chronic users of MA and such emotional

disturbances have been associated with abnormalities in functional and structural neuroanatomy.

Methods: Participants will have to complete questionnaires and a series of behavioural tasks used to determine whether MA abuse and MA-induced psychosis is associated with defects in social awareness and regulation of emotions. In addition, brain imaging techniques will be used to determine the effect of MA abuse, with and without a history of psychosis, on brain structure and function. Specifically, structural magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) will be employed to investigate how brain structure and metabolism change in MA abusers in comparison to healthy controls. DNA analyses of blood samples will be conducted to examine whether specific genes account for structural and functional brain abnormalities after methamphetamine abuse and for increased vulnerability to psychosis.

In addition, associations between “tik” abuse and the disability of controlling emotions will be assessed. Participants will therefore perform two simple tasks measuring emotional processing and impulsivity (called Affective Labelling task and Delay Discounting task) as part of the functional MRI scan. Those tasks will be used to assess differences in brain activation corresponding to impairments in regulating behaviour.

Procedures

If you agree to take part in the study and if you meet all of the conditions required for entering the study (assessed in a screening interview), you will complete the following 3 phases and procedures:

- At your first visit the study will be explained and written consent to take part will be obtained. Your study investigator will ask you some questions about your psychiatric and neurological history and you will have to fill out several questionnaires. If you are eligible and agree to participate in the study you will be asked to attend the second testing session at the Cape Universities Brain Imaging Centre (www.sun.ac.za/cubic).
- During the second testing day, you will be asked to complete behavioural tasks. Following completion of these tasks the brain scanning session, Magnetic Resonance Imaging (MRI) and Spectroscopy (MRS), will take place.
- During the third visit you will undergo neuropsychological testing including tasks about your memory, attention and risk taking behaviour.

It is estimated that none of the testing sessions should take more than 3 hours to complete.

The psychiatric interview will take place either at Valkenberg Hospital or in the Psychiatric department at Groote Schuur Hospital. Brain imaging will be conducted using a 3T Siemens Magnetom Allegra at CUBIC, Stellenbosch. Each scanning session will last approximately one hour. Structural and functional imaging data will be acquired. Stimuli for each cognitive-affective protocol will be computerized and displayed to you in the scanner via a screen display. The neuropsychological assessment, which will be computer based tests, will take place in the Psychiatric Department of Groote Schuur Hospital.

Urine screens will be performed on both days of testing to verify methamphetamine abstinence and to determine the degree of cannabis use, as well as for a pregnancy test (if you are female). You will have to pee in a cup for those tests. The results of those tests are not for legal medicine or police purpose, and will only be used for our study.

Blood samples will be collected for routine laboratory testing and for possible future gene and protein expression studies. Approximately 50ml (10 teaspoons) of blood will be drawn from your arm. We may need to contact you again to get another blood sample should we fail to get a DNA sample from your blood. Candidate polymorphisms identified to be associated with drug dependency or psychosis and possibly playing a role in explaining variance in the MRI results will be investigated later on. This process will take place at the Division of Human Genetics at the University of Cape Town.

Magnetic Resonance Imaging

With an MRI you can obtain very detailed images of organs and tissues throughout the body, even of the brain, as in our study. MRS provides a tool to investigate metabolites in the living brain. Both MRI and MRS testing cause no pain and the magnetic fields produce no known tissue damage of any kind.

The MRI and MRS examination are performed in a special room that houses the MR system or "scanner". You will be escorted into the room by a staff member of the MRI facility and asked to lie down on a comfortably padded table that gently glides you into the scanner. This is typically a large, tunnel magnet that is open at both ends, so you won't be completely enclosed at any time.

As the scan is done in a relatively confined space, occasionally people feel closed-in or frightened. This does not happen often, and if you feel anxious, we will spend time allowing you to get used to the surroundings. Another side-effect might be a tingling feeling in your teeth if you have metal fillings.

The most important thing for you to do is to **relax and lie perfectly still** during the time the imaging takes place. For the functional imaging you will be asked to perform some simple tasks of emotional processing and attention, which will enable the investigators to determine your brain function. During the structural and diffusion tensor imaging you will be able to close your eyes and rest. Given that the testing session will take one hour to complete, you might get sleepy or uncomfortable after a while, but you are asked to stay awake and not to move throughout the scanning.

A radiologist will operate the scanner from behind a window, and will be able to see and hear you during the scan. You will be able to communicate with the radiologist or the study assistant at any time using an intercom system. You will also be given an alarm call button to hold during the scan, which you can press to get attention.

The MR scanner may produce loud tapping or knocking noises at times during the testing, which is normal and should not worry you. Especially when the magnet in the machine is switched on, it will make some loud banging noises, but you will be clearly warned when this will take place. You will feel nothing and the noise is not harmful to you in any way. To minimise the possible discomfort associated with this, we will give you some soft earplugs to put in.

MRI and MRS scans are commonly performed and a safe procedure if you have been screened correctly for the presence of any magnetic material on or inside you such as pace-makers, surgical clips and metal objects in the eyes. A formal screen for this will be done at the screening visit by a member of the study team.

Why have you been invited to participate?

Three groups of participants will be included in this study: methamphetamine (MA) abusers with a history of psychosis, MA abusers without a history of psychosis and non-substance-abusing healthy control subjects. Each of the groups will consist of 20 participants. You may fit into one of these categories as assessed during your initial screening.

What will your responsibilities be?

The study investigator will be required to ask you about medications that you may be taking currently or that you may have taken recently. Your study investigator will explain to you which medications need to be stopped during the entire length of the study and how soon before you take part in the study these medications must be stopped.

Your doctor will also advise you on which prescription or over-the-counter medications or any other remedies or foods that you will be required to either stop or restrict your consumption of during the entire length of the study. This will include a restriction on the amount of alcohol that can be consumed.

At each visit you may be asked to complete questionnaires or tasks to check the status of your symptoms. These will measure your mood, emotional responses, trust, sociability and emotional resilience.

Please ensure that you are punctual at all times, as we are using specialized equipment during each of the sessions, for which costs are incurred. If for some reason you are unable to complete a visit on a particular day we may reschedule to complete the assessments at another time.

Will you benefit from taking part in this research?

There are no direct benefits to you for participating in this study. However, you will be making an important contribution to this research that may benefit others in the future. We expect that the results of this study will help us understand the effects of methamphetamine on brain structure and function and how their abuse can lead to the development of psychosis.

Are there any risks involved in your taking part in this research?

There are no major risks involved in participation in this study. There will be several questionnaires, including some about past traumatic events that ask for information of a very personal and sensitive nature. This may cause some emotional discomfort.

Who will have access to your medical records?

Maintaining your confidentiality is important. Your personal information (for example your gender, age, the details of your medical conditions) and other information (the data collected by the investigators as part of the study) will be identified by a number (i.e. coded). Your name will not appear in any publications or reports produced from this

study. The investigators will keep the information and the results collected about you in this study. This information about you will be kept in a secure place.

By agreeing to take part in this study, you will be allowing certain persons to see the information about you (both personal, including your name, and other information) held by the study doctor. You have the right to withdraw your consent to participate in this study at any time.

If you withdraw your consent to participate in this study no new information will be collected from you and added to existing data or to a database. Your information will be processed electronically (i.e. by a computer) or manually and analysed to determine the outcome of this study. Your information may/could be sent to regulatory authorities and to the Ethics Committees. You have the right to ask the study doctor about the data being collected on you for the study and about the purpose of this data. You have the right to ask the study doctor to allow you to see your personal information and to have any necessary corrections made to it.

What will happen in the unlikely event of some form of injury occurring as a direct result of your taking part in this research study?

If you become ill or injured as a direct result of your participation in this clinical study, you will be referred for appropriate medical treatment. The University of Cape Town's insurance policy will cover the costs of such treatment. If you have any questions concerning the availability of compensation/medical care or if you think you have experienced a research-related illness or injury, contact details are below. Your legal right to claim compensation for injury where you can prove negligence is not affected.

If you have any questions about your rights as a research subject, you should contact the Faculty of Health Sciences Human Research Ethics Committee (FHS HREC), Tel: (021)4066492, Fax: (021)4066411.

If you have questions about this study you should first discuss them with your study doctor or the Faculty of Health Sciences Human Research Ethics Committee (FHS HREC), UCT.

Dr D. Wilson: (021)4042182

Dr H. Temmingh: (021)4403185

After you have consulted your doctor or the FHS HREC and if they have not provided you with answers to your satisfaction, you should write to the South African Medical Research Council at: Head Office Cape Town, Corporate Communications Office, Sarah Bok, PO Box 19070, Tygerberg, 7505, South Africa or Fax: (021)9380200.

Will you be paid to take part in this study and are there any costs involved?

All evaluations will be provided, hence there will be no costs involved for you or your medical aid, if you do take part in the study. You will be compensated for taking part in the study as your transport and meal costs will be covered with supermarket vouchers to exchange for food, amounting to R150.

Is there any thing else that you should know or do?

- You can contact the Committee for Human Research at (021)4066492 if you have any concerns or complaints that have not been adequately addressed by your study doctor.
- You will receive a copy of this information and consent form for your own records.

Informed Consent Form for Study Participants

Title of the Research Project: *“Neural correlates of deficits in affect regulation in methamphetamine abusers with a history of psychosis.”*

Declaration by participant

1. By signing below, I agree to be interviewed and asked personal information as part of the above named study and that the information I give will be correct. Furthermore, I declare that:
 - I have read, or had read to me, the “Participant Information Leaflet and Consent Form” and it is written in a language with which I am fluent and comfortable.
 - I have had a chance to ask questions and all my questions have been adequately answered.
 - I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
 - I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
 - I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) on (*date*) 20 .

.....

Signature of participant

2. By signing below, I agree to have my blood taken for the proposed genetic tests as described in the “Participant Information Leaflet and Consent Form”.

Signed at (*place*) on (*date*) 20 .

.....

Signature of participant

3. By signing below, I agree to undergo brain scans (MRI/MRS) as described in the "Participant Information Leaflet and Consent Form".

Signed at (*place*) on (*date*) 20 .

.....

Signature of participant

4. By signing below, I agree to Neuropsychological testing as described in the "Participant Information Leaflet and Consent Form".

Signed at (*place*) on (*date*) 20 .

.....

Signature of participant

Declaration by investigator

I (*name*) declare that:

- I explained the information in this document to
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above.

Signed at (*place*) on (*date*) 20 .

.....

Signature of investigator"

BioMed Central Psychiatry - Instructions for authors

“Research articles

[Criteria](#) | [Submission process](#) | [Preparing main manuscript text](#) | [Preparing illustrations and figures](#) | [Preparing tables](#) | [Preparing additional files](#) | [Style and language](#)

Assistance with the process of manuscript preparation and submission is available from [BioMed Central customer support team](#). See [‘About this journal’](#) for information about policies and the refereeing process. We also provide a collection of links to [useful tools](#) and resources for scientific authors on our page.

Criteria

Research articles should report on original primary research, but may report on systematic reviews of published research provided they adhere to the appropriate reporting guidelines which are detailed in our [Editorial Policies](#). Please note that non-commissioned pooled analyses of selected published research will not be considered.

Submission process

Manuscripts must be submitted by one of the authors of the manuscript, and should not be submitted by anyone on their behalf. The submitting author takes responsibility for the article during submission and peer review.

Please note that *BMC Psychiatry* levies an article-processing charge on all accepted Research articles; if the submitting author's institution is a [BioMed Central member](#) the cost of the article-processing charge may be covered by the membership (see [About](#) page for detail). Please note that the membership is only automatically recognised on submission if the submitting author is based at the member institution.

To facilitate rapid publication and to minimize administrative costs, *BMC Psychiatry* prefers [online submission](#).

Files can be submitted as a batch, or one by one. The submission process can be interrupted at any time; when users return to the site, they can carry on where they left off.

See below for examples of [word processor](#) and [graphics file formats](#) that can be accepted for the main manuscript document by the online submission system. Additional files of any type, such as [asmovies](#), animations, or [original data files](#), can also be submitted as part of the manuscript.

During submission you will be asked to provide a cover letter. Use this to explain why your manuscript should be published in the journal, to elaborate on any issues relating to our editorial policies in the [‘About BMC Psychiatry’](#) page, and to declare any potential competing interests. You will be also asked to provide the contact details (including email addresses) of potential peer reviewers for your manuscript. These should be experts in their field, who will be able to provide an objective assessment of the manuscript. Any suggested peer reviewers should not have published with any of the authors of the manuscript within the past five years, should not be current collaborators, and should not be members of the same research institution. Suggested reviewers will be considered alongside potential reviewers recommended by the Editorial team, Editorial Advisors, Section Editors and Associate Editors.

Assistance with the process of manuscript preparation and submission is available from [BioMed Central customer support team](#).

We also provide a collection of links to useful tools and resources for scientific authors on our [Useful Tools](#) page.

File formats

The following word processor file formats are acceptable for the main manuscript document:

- Microsoft word (DOC, DOCX)
- Rich text format (RTF)
- Portable document format (PDF)
- TeX/LaTeX (use [BioMed Central's TeX template](#))
- DeVice Independent format (DVI)

TeX/LaTeX users: Please use [BioMed Central's TeX template](#) and BibTeX stylefile if you use TeX format. During the TeX submission process, please submit your TeX file as the main manuscript file and your bib/bbl file as a dependent file. Please also convert your TeX file into a PDF and submit this PDF as an additional file with the name 'Reference PDF'. This PDF will be used by internal staff as a reference point to check the layout of the article as the author intended. Please also note that all figures must be coded at the end of the TeX file and not inline.

If you have used another template for your manuscript, or if you do not wish to use BibTeX, then please submit your manuscript as a DVI file. We do not recommend converting to RTF.

For all TeX submissions, all relevant editable source must be submitted during the submission process. Failing to submit these source files will cause unnecessary delays in the publication procedures.

Publishing Datasets

Through a special arrangement with [LabArchives](#), LLC, authors submitting manuscripts to BMC Psychiatry can obtain a [complimentary subscription to LabArchives](#) with an allotment of 100MB of storage. LabArchives is an

Electronic Laboratory Notebook which will enable scientists to share and publish data files in situ; you can then link your paper to these data. Data files linked to published articles are assigned digital object identifiers (DOIs) and will remain available in perpetuity. Use of LabArchives or similar data publishing services does not replace preexisting data deposition requirements, such as for nucleic acid sequences, protein sequences and atomic coordinates. Instructions on assigning DOIs to datasets, so they can be permanently linked to publications, can be found on the LabArchives website. Use of LabArchives' software has no influence on the editorial decision to accept or reject a manuscript.

Authors linking datasets to their publications should include an [Availability of supporting data](#) section in their manuscript and cite the dataset in their reference list.

Preparing main manuscript text

General guidelines of the journal's style and language are given [below](#).

Overview of manuscript sections for Research articles

Manuscripts for Research articles submitted to *BMC Psychiatry* should be divided into the following sections (in this order):

- [Title page](#)
- [Abstract](#)
- [Keywords](#)
- [Background](#)
- [Methods](#)
- [Results and discussion](#)
- [Conclusions](#)
- [List of abbreviations used](#) (if any)
- [Competing interests](#)
- [Authors' contributions](#)
- [Authors' information](#)
- [Acknowledgements](#)
- [Endnotes](#)
- [References](#)
- [Illustrations and figures](#) (if any)
- [Tables and captions](#)
- [Preparing additional files](#)

The **Accession Numbers** of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript should be provided, in square brackets and include the corresponding database name; for example, [EMBL:AB026295, EMBL:AC137000, DDBJ:AE000812, GenBank:U49845, PDB:1BFM, Swiss-Prot:Q96KQ7, PIR:S66116].

The databases for which we can provide direct links are: EMBL Nucleotide Sequence Database ([EMBL](#)), DNA Data Bank of Japan ([DDBJ](#)), GenBank at the NCBI ([GenBank](#)), Protein Data Bank ([PDB](#)), Protein Information Resource ([PIR](#)) and the Swiss-Prot Protein Database ([Swiss-Prot](#)).

You can [download a template](#) (Mac and Windows compatible; Microsoft Word 98/2000) for your article.

For reporting standards please see the information in the [About](#) section.

Title page

The title page should:

- provide the title of the article
- list the full names, institutional addresses and email addresses for all authors
- indicate the corresponding author

Please note:

- the title should include the study design, for example "A versus B in the treatment of C: a randomized controlled trial X is a risk factor for Y: a case control study"
- abbreviations within the title should be avoided

Abstract

The Abstract of the manuscript should not exceed 350 words and must be structured into separate sections: **Background**, the context and purpose of the study; **Methods**, how the study was performed and statistical tests used; **Results**, the main findings; **Conclusions**, brief summary and potential implications. Please minimize the use of abbreviations and do not cite references in the abstract. **Trial registration**, if your research article reports the results of a controlled health care intervention, please list your trial registry, along with the unique identifying number (e.g. **Trial registration**: Current Controlled Trials ISRCTN73824458). Please note that there should be no space between the letters and numbers of your trial registration number. We recommend manuscripts that report randomized controlled trials follow the [CONSORT extension for abstracts](#).

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should be written in a way that is accessible to researchers without specialist knowledge in that area and must clearly state - and, if helpful, illustrate - the background to the research and its aims. Reports of clinical research should, where appropriate, include a summary of a search of the literature to indicate why this study was necessary and what it aimed to contribute to the field. The section should end with a brief statement of what is being reported in the article.

Methods

The methods section should include the design of the study, the setting, the type of participants or materials involved, a clear description of all interventions and comparisons, and the type of analysis used, including a power calculation if appropriate. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses in the Methods section.

For studies involving human participants a statement detailing ethical approval and consent should be included in the methods section. For further details of the journal's editorial policies and ethical guidelines see '[About this journal](#)'. For further details of the journal's data-release policy, see the policy section in '[About this journal](#)'.

Results and discussion

The Results and discussion may be combined into a single section or presented separately. Results of statistical analysis should include, where appropriate, relative and absolute risks or risk reductions, and confidence intervals. The Results and discussion sections may also be broken into subsections with short, informative headings.

Conclusions

This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance. Summary illustrations may be included.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations can be provided, which should precede the competing interests and authors' contributions.

Competing interests

A competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organizations. Authors must disclose any financial competing interests; they should also reveal any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript.

Authors are required to complete a declaration of competing interests. All competing interests that are declared will be listed at the end of published articles. Where an author gives no competing interests, the listing will read 'The author(s) declare that they have no competing interests'.

When completing your declaration, please consider the following questions:

Financial competing interests

- In the past five years have you received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? Is such an organization financing this manuscript (including the article-processing charge)? If so, please specify.
- Do you hold any stocks or shares in an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? If so, please specify.
- Do you hold or are you currently applying for any patents relating to the content of the manuscript? Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript? If so, please specify.
- Do you have any other financial competing interests? If so, please specify.

Non-financial competing interests

Are there any non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript? If so, please specify.

If you are unsure as to whether you, or one your co-authors, has a competing interest please discuss it with the editorial office.

Authors' contributions

In order to give appropriate credit to each author of a paper, the individual contributions of authors to the manuscript should be specified in this section.

According to [ICMJE guidelines](#), An 'author' is generally considered to be someone who has made substantive intellectual contributions to a published study. To qualify as an author one should 1) have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) have been involved in drafting the manuscript or revising it critically for important intellectual content; 3) have given final approval of the version to be published; and 4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of

the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

We suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

All contributors who do not meet the criteria for authorship should be listed in an acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support.

Authors' information

You may choose to use this section to include any relevant information about the author(s) that may aid the reader's interpretation of the article, and understand the standpoint of the author(s). This may include details about the authors' qualifications, current positions they hold at institutions or societies, or any other relevant background information. Please refer to authors using their initials. Note this section should not be used to describe any competing interests.

Acknowledgements

Please acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for each author, and for the manuscript preparation. Authors must describe the role of the funding body, if any, in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Please also acknowledge anyone who contributed materials essential for the study. If a language editor has made significant revision of the manuscript, we recommend that you acknowledge the editor by name, where possible.

The role of a scientific (medical) writer must be included in the acknowledgements section, including their source(s) of funding. We suggest wording such as 'We thank Jane Doe who provided medical writing services on behalf of XYZ Pharmaceuticals Ltd.'

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

Endnotes

Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

References

All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. Each reference must have an individual reference number. Please avoid excessive referencing. If automatic numbering systems are used, the reference numbers must be finalized and the bibliography must be fully formatted before submission.

Only articles, datasets, clinical trial registration records and abstracts that have been published or are in press, or are available through public e-print/preprint servers, may be cited; unpublished abstracts, unpublished data and personal communications should not be included in the reference list, but may be included in the text and referred to as "unpublished observations" or "personal communications" giving the names of the involved researchers. Obtaining permission to quote personal communications and unpublished data from the cited colleagues is the responsibility of the author. Footnotes are not allowed, but endnotes are permitted. Journal abbreviations follow Index Medicus/MEDLINE. Citations in the reference list should include all named authors, up to the first 30 before adding 'et al.'.

Any *in press* articles cited within the references and necessary for the reviewers' assessment of the manuscript should be made available if requested by the editorial office.

Style files are available for use with popular bibliographic management software:

- [BibTeX](#)
- [EndNote style file](#)
- [Reference Manager](#)
- [Zotero](#)

Examples of the *BMC Psychiatry* reference style are shown below. Please ensure that the reference style is followed precisely; if the references are not in the correct style they may have to be retyped and carefully proofread.

All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and the URL, in the following format: **The Mouse Tumor Biology Database** [http://tumor.informatics.jax.org/mtbwi/index.do]. If an author or group of authors can clearly be associated with a web link, such as for weblogs, then they should be included in the reference.

Examples of the *BMC Psychiatry* reference style

Article within a journal
 Koonin EV, Altschul SF, Bork P: **BRCA1 protein products: functional motifs.** *Nat Genet* 1996,**13**:266-267.

Article within a journal supplement
 Orengo CA, Bray JE, Hubbard T, LoConte L, Sillitoe I: **Analysis and assessment of ab initio three-dimensional prediction, secondary structure, and contacts prediction.** *Proteins* 1999, **43**(Suppl 3):149-170.

In press article
 Kharitonov SA, Barnes PJ: **Clinical aspects of exhaled nitric oxide.** *Eur Respir J*, in press.

Published abstract
 Zvaifler NJ, Burger JA, Marinova-Mutafchieva L, Taylor P, Maini RN: **Mesenchymal cells, stromal derived factor-1 and rheumatoid arthritis [abstract].** *Arthritis Rheum* 1999, **42**:s250.

Article within conference proceedings
 Jones X: **Zeolites and synthetic mechanisms.** In *Proceedings of the First National Conference on Porous Sieves: 27-30 June 1996; Baltimore.* Edited by Smith Y. Stoneham: Butterworth-Heinemann; 1996:16-27.

Book chapter, or article within a book
 Schnepf E: **From prey via endosymbiont to plastids: comparative studies in dinoflagellates.** In *Origins of Plastids. Volume 2.* 2nd edition. Edited by Lewin RA. New York: Chapman and Hall; 1993:53-76.

Whole issue of journal
 Ponder B, Johnston S, Chodosh L (Eds): **Innovative oncology.** In *Breast Cancer Res* 1998, **10**:1-72.

Whole conference proceedings
 Smith Y (Ed): *Proceedings of the First National Conference on Porous Sieves: 27-30 June 1996; Baltimore.* Stoneham: Butterworth-Heinemann; 1996.

Complete book
 Margulis L: *Origin of Eukaryotic Cells.* New Haven: Yale University Press; 1970.

Monograph or book in a series
 Hunninghake GW, Gadek JE: **The alveolar macrophage.** In *Cultured Human Cells and Tissues.* Edited by Harris TJR. New York: Academic Press; 1995:54-56. [Stoner G (Series Editor): *Methods and Perspectives in Cell Biology*, vol 1.]

Book with institutional author
 Advisory Committee on Genetic Modification: *Annual Report.* London; 1999.

PhD thesis
 Kohavi R: **Wrappers for performance enhancement and oblivious decision graphs.** *PhD thesis.* Stanford University, Computer Science Department; 1995.

Link / URL
The Mouse Tumor Biology Database [<http://tumor.informatics.jax.org/mtbwi/index.do>]

Link / URL with author(s)
 Corpas M: **The Crowdfunding Genome Project: a personal genomics community with open source values** [<http://blogs.biomedcentral.com/bmcblog/2012/07/16/the-crowdfunding-genome-project-a-personal-genomics-community-with-open-source-values/>]

Dataset with persistent identifier
 Zheng, L-Y; Guo, X-S; He, B; Sun, L-J; Peng, Y; Dong, S-S; Liu, T-F; Jiang, S; Ramachandran, S; Liu, C-M; Jing, H-C (2011): **Genome data from sweet and grain sorghum (Sorghum bicolor).** *GigaScience.* <http://dx.doi.org/10.5524/100012>.

Clinical trial registration record with persistent identifier
 Mendelow, AD (2006): **Surgical Trial in Lobar Intracerebral Haemorrhage.** *Current Controlled Trials.* <http://dx.doi.org/10.1186/ISRCTN22153967>

Preparing illustrations and figures

Illustrations should be provided as separate files, not embedded in the text file. Each figure should include a single illustration and should fit on a single page in portrait format. If a figure consists of separate parts, it is important that a single composite illustration file be submitted which contains all parts of the figure. There is no charge for the use of color figures.

Please read our [figure preparation guidelines](#) for detailed instructions on maximising the quality of your [figures](#).

Formats

The following file formats can be accepted:

- PDF (preferred format for diagrams)
- DOCX/DOC (single page only)
- PPTX/PPT (single slide only)
- EPS
- PNG (preferred format for photos or images)
- TIFF
- JPEG
- BMP

Figure legends

The legends should be included in the main manuscript text file at the end of the document, rather than being a part of the figure file. For each figure, the following information should be provided: Figure number (in sequence, using Arabic numerals - i.e. Figure 1, 2, 3 etc); short title of figure (maximum 15 words); detailed legend, up to 300 words.

Please note that it is the responsibility of the author(s) to obtain permission from the copyright holder to reproduce figures or tables that have previously been published elsewhere.

Preparing tables

Each table should be numbered and cited in sequence using Arabic numerals (i.e. Table 1, 2, 3 etc.). Tables should also have a title (above the table) that summarizes the whole table; it should be no longer than 15 words. Detailed legends may then follow, but they should be concise. Tables should always be cited in text in consecutive numerical order.

Smaller tables considered to be integral to the manuscript can be pasted into the end of the document text file, in A4 portrait or landscape format. These will be typeset and displayed in the final published form of the article. Such tables should be formatted using the 'Table object' in a word processing program to ensure that columns of data are kept aligned when the file is sent electronically for review; this will not always be the case if columns are generated by simply using tabs to separate text. Columns and rows of data should be made visibly distinct by ensuring that the borders of each cell display as black lines. Commas should not be used to indicate numerical values. Color and shading may not be used; parts of the table can be highlighted using symbols or bold text, the meaning of which should be explained in a table legend. Tables should not be embedded as figures or spreadsheet files.

Larger datasets or tables too wide for a portrait page can be uploaded separately as additional files. Additional files will not be displayed in the final, laid-out PDF of the article, but a link will be provided to the files as supplied by the author.

Tabular data provided as additional files can be uploaded as an Excel spreadsheet (.xls) or comma separated values (.csv). As with all files, please use the standard file extensions.

Preparing additional files

Although *BMC Psychiatry* does not restrict the length and quantity of data included in an article, we encourage authors to provide datasets, tables, movies, or other information as additional files.

Please note: All Additional files **will be published** along with the article. Do not include files such as patient consent forms, certificates of language editing, or revised versions of the main manuscript document with tracked changes. Such files should be sent by email to editorial@biomedcentral.com, quoting the Manuscript ID number.

Results that would otherwise be indicated as "data not shown" can and should be included as additional files. Since many weblinks and URLs rapidly become broken, *BMC Psychiatry* requires that supporting data are included as additional files, or deposited in a recognized repository. Please do not link to data on a personal/departmental website. The maximum file size for additional files is 20 MB each, and files will be virus-scanned on submission.

Additional files can be in any format, and will be downloadable from the final published article as supplied by the author. We recommend CSV rather than PDF for tabular data.

Certain supported files formats are recognized and can be displayed to the user in the browser. These include most movie formats (for users with the Quicktime plugin), mini-websites prepared according to our guidelines, chemical structure files (MOL, PDB), geographic data files (KML).

If additional material is provided, please list the following information in a separate section of the manuscript text:

- File name (e.g. Additional file 1)
- File format including the correct file extension for example .pdf, .xls, .txt, .pptx (including name and a URL of an appropriate viewer if format is unusual)
- Title of data
- Description of data

Additional files should be named "Additional file 1" and so on and should be referenced explicitly by file name within the body of the article, e.g. 'An additional movie file shows this in more detail [see Additional file 1]'.

Additional file formats

Ideally, file formats for additional files should not be platform-specific, and should be viewable using free or widely available tools. The following are examples of suitable formats.

- Additional documentation
 - PDF (Adobe Acrobat)
- Animations
 - SWF (Shockwave Flash)
- Movies
 - MP4 (MPEG 4)
 - MOV (Quicktime)

- Tabular data
 - XLS, XLSX (Excel Spreadsheet)
 - CSV (Comma separated values)

As with figure files, files should be given the standard file extensions.

Mini-websites

Small self-contained websites can be submitted as additional files, in such a way that they will be browsable from within the full text HTML version of the article. In order to do this, please follow these instructions:

1. Create a folder containing a starting file called index.html (or index.htm) in the root.
2. Put all files necessary for viewing the mini-website within the folder, or sub-folders.
3. Ensure that all links are relative (ie "images/picture.jpg" rather than "/images/picture.jpg" or "http://yourdomain.net/images/picture.jpg" or "C:\Documents and Settings\username\My Documents\mini-website\images\picture.jpg") and no link is longer than 255 characters.
4. Access the index.html file and browse around the mini-website, to ensure that the most commonly used browsers (Internet Explorer and Firefox) are able to view all parts of the mini-website without problems, it is ideal to check this on a different machine.
5. Compress the folder into a ZIP, check the file size is under 20 MB, ensure that index.html is in the root of the ZIP, and that the file has .zip extension, then submit as an additional file with your article.

Style and language

General

Currently, *BMC Psychiatry* can only accept manuscripts written in English. Spelling should be US English or British English, but not a mixture.

There is no explicit limit on the length of articles submitted, but authors are encouraged to be concise.

BMC Psychiatry will not edit submitted manuscripts for style or language; reviewers may advise rejection of a manuscript if it is compromised by grammatical errors. Authors are advised to write clearly and simply, and to have their article checked by colleagues before submission. In-house copyediting will be minimal. Non-native speakers of English may choose to make use of a copyediting service.

Language editing

For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends [Edanz](#). BioMed Central has arranged a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. Please contact [Edanz](#) directly to make arrangements for editing, and for pricing and payment details.

Help and advice on scientific writing

The abstract is one of the most important parts of a manuscript. For guidance, please visit our page on [Writing titles and abstracts for scientific articles](#).

Tim Albert has produced for BioMed Central a [list of tips](#) for writing a scientific manuscript. *American Scientist* also provides a list of resources for science writing. For more detailed guidance on preparing a manuscript and writing in English, please visit the [BioMed Central author academy](#).

Abbreviations

Abbreviations should be used as sparingly as possible. They should be defined when first used and a list of abbreviations can be provided following the main manuscript text.

Typography

- Please use double line spacing.
- Type the text unjustified, without hyphenating words at line breaks.
- Use hard returns only to end headings and paragraphs, not to rearrange lines.
- Capitalize only the first word, and proper nouns, in the title.
- All lines and pages should be numbered. Authors are asked to ensure that line numbering is included in the main text file of their manuscript at the time of submission to facilitate peer-review. Once a manuscript has been accepted, line numbering should be removed from the manuscript before publication. For authors submitting their manuscript in Microsoft Word please do not insert page breaks in your manuscript to ensure page numbering is consistent between your text file and the PDF generated from your submission and used in the review process.
- Use the *BMC Psychiatry* [reference format](#).
- Footnotes are not allowed, but endnotes are permitted.
- Please do not format the text in multiple columns.
- Greek and other special characters may be included. If you are unable to reproduce a particular special character, please type out the name of the symbol in full. **Please ensure that all special characters used are embedded in the text, otherwise they will be lost during conversion to PDF.**

Units

SI units should be used throughout (liter and molar are permitted, however)."

