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Contrasting the Expression of Psychotic Disorders in Ethnically Different Populations

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Abstract

Background

Schizophrenia is treated as a single (continuous) disorder diagnosed according to reliable, internationally-accepted criteria, despite contention that its optimal structure may comprise multiple distinct entities labelled ‘schizophrenia’.

Transcultural psychiatry studies that have examined the expression of schizophrenia across cultures have implicitly favoured the prevailing view that schizophrenia is universal, and consequently, that its structure is continuous.

Transethnic schizophrenia samples can inform debate at every level of the diagnostic spectrum: (1) broad theoretical (universalist vs. relativist); (2) diagnostic (nosological vs. dimensional); (3) structure of psychosis generally; and (4) structure of schizophrenia specifically. While transethnic samples have been used (primarily from an anthropological perspective) to challenge DSM-IV at the two broader levels, little work has elucidated the more specific levels. Few transethnic psychiatric studies have incorporated current diagnostic knowledge to explore the expression of demographic, clinical, and symptom variables and inform debate regarding schizophrenia’s classification.

Aims

This thesis aims to: (1) compare and contrast the way ‘schizophrenia’ is experienced by three ethnically different populations, (2) identify significant demographic, clinical and symptom differences in these populations, (3) examine these differences in the context of their relevance to the structure of schizophrenia, and (4) identify dimensions and/or clusters based on these differences, both within and across these populations, which may contribute to the discourse on the diagnostic classification of schizophrenia.

Methods

Demographic, clinical and symptom variables were analysed, and frequencies of core DSM-IV schizophrenia diagnostic criteria were contrasted in ethnically-distinct schizophrenia/schizoaffective samples from Australia (n=821), Chennai, India (n=520) and the Iban of Sarawak (n=298). Statistical methods used included $\chi 2$, T-Tests, General Linear Models and Logistic Regression. Exploratory Factor Analysis, Latent Class Analysis, and Factor Mixture Modeling were used to attempt to identify deficit

schizophrenia (DS), which has been proposed as a stable, distinct schizophrenia subtype, in each sample, and the results were then tested using taxometric analyses.

Results

Significant differences in demographic and clinical characteristics were identified between sites: (1) more individuals were living alone in Australia than India or Sarawak; (2) drug use was lower in India than Australia or Sarawak; (3) duration of untreated psychosis (DUP) was longer in India than Australia or Sarawak; (4) the rate of schizoaffective disorder was lower in India than Australia or Sarawak; and (5) mean age at psychosis onset (AAO) was approximately six years older in Sarawak than Australia or India.

More broadly, a distinct schizophrenia symptom profile was identified in the Sarawak sample. Compared with Australian and Indian populations, the Iban exhibit: low frequency of thought broadcast/insertion/withdrawal delusions, high frequency of auditory hallucinations and disorganized behaviour, with a comparatively short prodrome.

Diagnostically, differences in both DSM-IV ‘criterion A’ symptom composition and content were apparent between sites. Indian individuals with schizophrenia reported negative symptoms more frequently than those in Australia or Sarawak, whereas individuals from Sarawak reported disorganized symptoms more frequently than other sites, in particular India. Delusions of control and thought broadcast, insertion or withdrawal were less frequent in Sarawak than Australia. Curiously, a subgroup of 20 Indian individuals with schizophrenia reported no lifetime delusions or hallucinations. Nine members of this subgroup no longer meet the criteria for schizophrenia when diagnosed using DSM-5 criteria.

When the DS subtype was modelled in the three samples, there was broad consistency in the structural appearance of the best-fitting models, with both single class (no evidence of a distinct DS class) and two class (demarcation of a potential DS class) models performing well. A category was identified within the Indian and Sarawak samples that resembled DS, while the distinction in Australia was less clear-cut. Taxometric analyses suggested a two class distribution within each population, with a larger ‘deficit’ class at each site.

Conclusions

Overall, these results support schizophrenia not being a discrete, homogeneous condition. Some elements of individual experience and expression (individual socio-demographic and symptom variables, symptom profiles, diagnostic demarcations) differ between the three ethnically-distinct populations, whereas other elements (e.g. tentative evidence for a class resembling DS) appear stable across these samples. There is also evidence that some expressions are population-specific, for example the Indian subgroup (n=20) without positive symptoms.

Whereas many differences in clinical phenotype can be explained by cultural factors, the older AAO finding in the Iban is a promising candidate for genetic studies in ethnically-distinct populations, since the result is somewhat culturally counter-intuitive.

Evidence generally supporting the universality of DS, albeit with a hybrid structure across these three ethnically-distinct populations contributes to the discourse on the latent structure and diagnostic classification of ‘schizophrenia’.

Viewed in conjunction with evidence from recent genetic analyses, and mindful of the significant limitations on generalisability imposed by applying standardised assessment tools and diagnostic classifications across ethnic groups, these results expand our understanding of the nuances of schizophrenia and highlight the potential for comparing and contrasting transethnic schizophrenia samples to validate genetic clues, in order to better understand clinical heterogeneity.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

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Publications during candidature

Examinable Papers Submitted for Publication

McLean D, Linscott R, Barrett R, McGrath J, Thara R and Mowry B. Is 'Deficit schizophrenia' a distinct, universal class within the syndrome of schizophrenia? Evidence from factor mixture modeling in three ethnically distinct populations. Submitted to *Australian and New Zealand Journal of Psychiatry*.

Examinable Peer-Reviewed Papers

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McLean D, Thara R, John S, Barrett R, Loa P, McGrath J and Mowry B (2014) DSM-IV "criterion A" schizophrenia symptoms across ethnically different populations: evidence for differing psychotic symptom content or structural organization? *Culture, Medicine and Psychiatry* 38(3): 408-426.

McLean D, John S, Barrett R, McGrath J, Loa P, Thara R and Mowry B (2012) Refining clinical phenotypes by contrasting ethnically different populations with schizophrenia from Australia, India and Sarawak. *Psychiatry Research* 196(2-3): 194-200.

Non-examinable Peer-Reviewed Papers

Westcott C, Waghorn G, **McLean D**, Statham D and Mowry B. Role functioning among adults with schizophrenia. *British Journal of Occupational Therapy* In Press.

Westcott C, Waghorn G, **McLean D**, Statham D and Mowry B. Interest in employment among people with schizophrenia. *American Journal of Psychiatric Rehabilitation* In Press.

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Duncan McLean (Candidate)	Study Design (90%) Data collection/production (80%)

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Bryan Mowry	Project Design and Data Collection (30%) Study Design (10%) Data production (20%) Conceptualised manuscript design (20%) Conceptualised statistical analysis (15%) Wrote and edited paper (5%)

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Contributions by others to the thesis

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The candidate was involved with the consent and ascertainment of the Australian sample reported in this thesis, however this work is not assessable as part of the PhD, as this phase of the data collection occurred prior to 2009.

Dr. Michael McLean contributed to the formulation of a comprehensive data identification, organisation and cleaning strategy employed in this body of work. All other significant contributions are acknowledged in the publication contribution tables above.

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Keywords

psychotic disorders, schizophrenia, culture, diagnosis, taxonomy, age of onset, population characteristic

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FoR code: 2002, Cultural Studies, 30%

Table of Contents

List of Figures and Tables

List of Abbreviations Used in the Thesis

AAO	Age at psychosis onset
APA	American Psychiatric Association
ASP	Affected sibling pair
BEFD	Best estimate final diagnosis
DIGS	Diagnostic Interview for Genetic Studies
DOSMed	The Study of Determinants of Outcome of Severe Mental Disorders
DS	Deficit schizophrenia
DSM	Diagnostic and Statistical Manual of Mental Disorders
DUP	Duration of untreated psychosis
EFA	Exploratory factor analysis
FIGS	Family Interview for Genetic Studies
FMM	Factor mixture modeling
FRS	Schneiderian first rank symptoms
GWAS	Genomewide association study (analyses)
ICD	International Classification of Diseases
IPSS	The International Pilot Study of Schizophrenia
ISC	International Schizophrenia Consortium
ISOS	The International Study of Schizophrenia
LAMI	Low and middle income
LCA	Latent class analysis
LMODE	Latent mode taxometric method
MAXCOV	Maximum covariance taxometric method
MAXEIG	Maximum eigenvalue taxometric method
MGS	Molecular Genetics of Schizophrenia Studies
RDC	Research Diagnostic Criteria
SCARF	The Schizophrenia Research Foundation India
SDS	Schedule for the Deficit Syndrome
SNP	Single nucleotide polymorphism
UNODC	United Nations Office on Drugs and Crime
WHO	World Health Organisation

Background and thesis outline

The work undertaken in this thesis is necessarily grounded within the 'no-mans-land' between the disciplines of psychiatry and anthropology, although the thesis is undeniably and unapologetically conceptualised and operationalised from a psychiatry perspective. It is important however, to critically appraise and incorporate the contribution of anthropology to the topics of culture and classification, when analysing three ethnically distinct populations in seeking to modestly but meaningfully inform debate on the diagnostic classification of schizophrenia.

Chapter One reviews the literature in several key areas relevant to this thesis, including: the classification of schizophrenia (historical and current); schizophrenia subtyping; the role of transethnic samples in research; and the operationalisation of culture (in schizophrenia classification and research more generally).

Chapter Two details the establishment of cultural equivalence, data source equivalence, and data formatting equivalence across the three sites and samples examined in this thesis, as this is crucial to the validity of the results presented in subsequent chapters. Site characteristics and instruments used in subsequent chapters are discussed in detail.

Chapter Three contrasts individual demographic and clinical characteristics in transethnic schizophrenia populations from Australia (n=821), India (n=520) and Sarawak, Malaysia (n=298) and proposes cultural explanations for identified site differences. From these the authors identify candidate variables free from significant cultural confounding that are hence suitable for inclusion in genetic analyses.

Chapter Four broadens the search from individual characteristics to characteristic symptom profiles within populations, contrasting the Iban of Sarawak with both the Tamil Brahmin and proximal caste groups in Chennai, India, and a sample of European Caucasian ethnicity from Australia.

Chapter Five broadens the search even further, contrasting, from a more anthropological perspective, both lifetime frequencies of DSM-IV criterion A (the core symptom criterion of the internationally recognized DSM classification system) symptoms and types/content of delusions and hallucinations in the three available transethnic schizophrenia populations to further elucidate clinical heterogeneity.

Chapter Six takes the knowledge accumulated in the previous three chapters and uses a targeted approach to attempt to statistically identify/validate a previously proposed subtype – deficit schizophrenia – within the three ethnically-distinct samples.

Chapter Seven summarises the scope of the project, outlines the contributions to the literature made by the thesis, addresses important strengths and limitations of this work, considers application of this research (and its methods) to other settings, and maps out directions for future enquiry.

Chapter 1. General Introduction and Rationale

History of diagnostic classification of schizophrenia

"No aspect of any discipline is more fundamental than its classification capability" (Haier, 1980: 417).

Emil Kraepelin (1856-1926) used the term 'dementia praecox' to define a condition that was chronic in course and characterised by disorganisation and negative symptoms (Fischer and Carpenter, 2009). Eugen Bleuler (1857-1939) coined the term schizophrenia, which replaced dementia praecox in the literature (Sadock and Sadock, 2003). Although the existence of schizophrenia has been widely accepted in psychiatry for the past century, it has been a contested concept, as it has never been validated by biological markers, and consequently has never been 'proven' as a single disease entity (Dutta et al., 2007). This uncertainty has been further complicated in recent decades because the key criteria for diagnosing schizophrenia in current diagnostic systems have diverged significantly from those relied on by Kraepelin and Bleuler. The incorporation of the Schneiderian and Langfeldt systems into modern diagnostic classification has tended to emphasise similarities between schizophrenia and bipolar disorder as key diagnostic markers, specifically psychotic symptoms, and sideline key differences such as disorganisation and avolition which were fundamental to Kraepelin and Bleuler (Fischer and Carpenter, 2009).

Mood symptoms and schizophrenia

Kasanin coined the term schizoaffective in 1933, and there has been a controversy ever since regarding the relationship between affective disorders and schizophrenia (Spitzer et al., 1978a). Both schizophrenia and schizoaffective disorder have generally been included in most schizophrenia linkage studies on the basis of tight definitions and evidence from multiple family studies showing that both disorders cluster in families ascertained through a proband with schizophrenia (Gershon et al., 1988; Kendler et al., 1993; Maier et al., 1993; Taylor, 1992).

Although researchers have tended to group schizoaffective disorder with schizophrenia the categorical distinction between schizophrenia and bipolar disorder remains problematic, as current epidemiological (Lichtenstein et al., 2009) and molecular genetic (Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013; ISC, 2009) evidence suggest that the two conditions share genetic predisposition, challenging the dichotomous view of

functional psychoses (Craddock et al., 2009). This dichotomy has been widely accepted in Western psychiatry since the 1920s (Möller, 2008) and forms the foundation for the diagnosis of schizophrenia in both major current diagnostic systems, DSM-5 (APA, 2013a) and ICD-10 (WHO, 1992).

The relationship between mood symptoms and schizophrenia is an important consideration in exploring cross-cultural variation in schizophrenia because in many non-Western cultures there is no exclusive differentiation between thought and emotion (Lutz, 1982), which are key differential concepts in the 'Western' classification of schizophrenia. Additionally, converting thoughts and feelings across languages can be difficult (Barrett, 2004), which has implications for both the validity of diagnostic instruments used cross-culturally and for the interpretation of comparative mood data obtained between cultures.

Existing schizophrenia classification systems

Although Kraepelin acknowledged the importance of culture in psychiatric diagnosis, and his 1903 voyage to the psychiatric institutions of Singapore and Java has been regarded as the foundation of transcultural psychiatry, schizophrenia as a clinical concept has both arisen and developed in a European and North American intellectual milieu (Jenkins and Barrett, 2004). Over the course of the 20th Century, diagnostic classification systems for schizophrenia developed in parallel in Europe and the United States.

International Classification of Diseases

The International Classification of Diseases (ICD) had its origins in Europe in the 1850s, although the first edition, then known as the International List of Causes of Death was adopted by the International Statistical Institute in 1893. The World Health Organisation (WHO) took responsibility for the ICD in 1948, when the manual's sixth revision was published (WHO, 2010).

> The ICD is the international standard diagnostic classification for all general epidemiological, many health management purposes and clinical use. These include the analysis of the general health situation of population groups and monitoring of the incidence and prevalence of diseases and other health problems in relation to other variables such as the characteristics and circumstances of the individuals affected, reimbursement, resource allocation, quality and guidelines.
>
> It is used to classify diseases and other health problems recorded on many types of health and vital records including death certificates and health records. In addition to enabling the storage and retrieval of diagnostic information for clinical, epidemiological and quality purposes, these records also provide the basis for the compilation of national mortality and morbidity statistics by WHO Member States (WHO, 2010).

The current edition of the ICD is the tenth revision (ICD-10), released in 1992 and updated in 1999, with ICD-11 scheduled for release in approximately 2017 (WHO, 2015). Mental and behavioural disorders form one section of the system (Chapter V). Subsequent to the release of the ICD-10, several countries and regions have released their own adaptations, including the Chinese Classification of Mental Disorders, the Japanese Clinical Modification of ICD-10, the Cuban Glossary of Psychiatry, and the Latin American Guide for Psychiatric Diagnosis (Mezzich et al., 2001). Australia also has a version, The International Statistical Classification of Diseases and Related Health Problems: 10th Revision, Australian Modification (ICD-10-AM) (National Centre for Classification in Health, 2000). An important addition to ICD-10 from a cultural viewpoint was the Diagnostic Criteria for Research (DCR-10), released in 1993 (WHO, 1993).

Diagnostic and Statistical Manual of Mental Disorders

The Diagnostic and Statistical Manual of Mental Disorders (DSM) is the series of diagnostic manuals produced by the American Psychiatric Association (APA). Some commentators regard DSM is the American adaptation of the ICD (Mezzich et al., 2001), particularly as the APA advises on the formulation of the ICD, and revisions of both manuals are undertaken concurrently (DSM-II and ICD-8 in 1968; DSM-III and ICD-9 in 1979/80; DSM-IV and ICD-10 in 1993/94; and DSM-V and ICD-11 both being released between 2013 and 2017).

The edition of the DSM used in the analyses presented in this thesis is the fourth revision (DSM-IV), released in 1994 (APA, 1994) and updated in 2000 (APA, 2000), which was current at the time of the sample recruitment and interviews for these studies. The fifth revision of the DSM was released in 2013 (APA, 2013a). This thesis primarily focuses on DSM-IV and DSM-IV TR, with reference to changes implemented in DSM-5 where appropriate.

The validity of the *empirical foundation* supporting the DSM process has been robustly criticised. An overarching methodological criticism is that DSM does not use external validators such as quantitative biological measurements or psychological testing to evaluate diagnostic criteria or assess whether changes improve clinical validity (Dutta et al., 2007). With respect to schizophrenia there is little evidence for DSM's operational

definition as the ‘true construct’ of schizophrenia (Gaebel and Zielasek, 2008). A detailed critique of DSM-IV, focussing on how it addresses cultural issues is presented below.

Research Diagnostic Criteria

The Research Diagnostic Criteria (RDC) were developed in the 1970s to enable researchers to apply a consistent set of criteria for the description or selection of subjects in research involving functional psychiatric illnesses including schizophrenia. Previously, both clinical work and research had suffered from inconsistencies in the inclusion and exclusion criteria for psychiatric diagnoses (criterion variance). The RDC stemmed from the diagnostic work carried out at the Washington University School of Medicine in St. Louis, which came to be known as the ‘Feighner criteria’ (Spitzer et al., 1978b). The RDC were developed after DSM-II, but directly preceded the publication of DSM-III, and formed the basis for the diagnostic classification of schizophrenia in that revision. Although the RDC were extensively used in schizophrenia research, they were superseded by ICD-10 and DSM-IV.

History of subtyping schizophrenia

Substantial variability among individuals diagnosed with schizophrenia, even using ‘strict’ criteria, has always implied that schizophrenia may be a collection of disorders, with differing courses and etiologies (Haier, 1980). Kraepelin distinguished ‘catatonic’, ‘hebephrenic’ and ‘paranoid’ subtypes, which came to be known as the ‘classic’ subtypes’. An effort was made in the formulation of the RDC, and subsequently the DSM-III to subtype schizophrenia in a reliable way, based on the phenomenology of the current episode. This effort produced the following subtypes: paranoid, disorganised, catatonic, mixed and residual (Spitzer et al., 1978b), which survived into DSM-IV, but were dropped from DSM-5 due to their limited diagnostic stability, low reliability, and poor validity (APA, 2013b).

Although these subtypes have proved to be of limited use, both clinically and in schizophrenia research (Helmes and Landmark, 2003) there have been promising developments in the subtyping of schizophrenia more recently, specifically in subtyping schizophrenia as: (1) paranoid versus non-paranoid (Fiedorowicz et al., 2008), and as (2) deficit versus non-deficit (Carpenter et al., 1988; Kirkpatrick et al., 2001), a distinction that built on the dichotomy proposed by Crow (1980a, 1980b) between Type I syndrome, characterised by positive symptoms – delusions, hallucinations and thought disorder, and

Type II syndrome, characterised by negative symptoms – affective flattening and poverty of speech. Furthermore, deriving symptom dimensions or clusters statistically, utilising methods such as cluster analysis and latent class analysis has yielded mixed, but generally promising results for future research (Jablensky, 2006).

Certainly, subtyping schizophrenia in some way appears useful for detecting genetic signals, it may lead to identification of specific disease entities, and it may help to elucidate the overlap between schizophrenia and bipolar disorder. “Given the uncertainties surrounding traditional disease classifications, the use of clinical dimensions as markers should become increasingly important” (Allan et al., 2008: 340); therefore a focus on reducing phenotypic variability through splitting diagnoses into subsets based on clinical and symptom commonalities is a valid direction for further enquiry despite limited diagnostic utility in the past (Jablensky, 2006).

Although research has traditionally relied on clinical classifications of disease, future research appears likely to incorporate validated endophenotypes (Allan et al., 2008) because they appear to be more stable and persistent than symptoms. Endophenotypes are measurable components with demonstrated heritability that provide a ‘window’ between expressed clinical traits and underlying genes (Gottesman and Gould, 2003). Although endophenotypes have been successfully used in gene identification in several disorders (Jablensky, 2006), their impact on schizophrenia genetics has been less profound. Proposed schizophrenia endophenotypes have broadly fallen within three categories: neurophysiological, neuroanatomic/neuroimaging, and neuropsychological/cognitive (Fiedorowicz et al., 2008; Jablensky, 2006). Regrettably, although endophenotypes have proven useful in schizophrenia research, they remain impractical for diagnostic tests (as the deficits identified are variable and present in other disorders), and were not ready for incorporation into DSM-5 (Fiedorowicz et al., 2008). Moreover, it is not clear that any one endophenotype for schizophrenia has a less complex genetic architecture than the actual disease itself.

Statistical methods for subtyping

Various statistical methods have been commonly used in attempts to subtype schizophrenia. Several of the most widely used approaches are summarised below.

Factor analysis

“Factor analysis and related methods reduce the covariation of the primary data matrix to covariances of small numbers of latent factors which account for the interrelationships among the primary variables and explain a proportion of their variance” (Jablensky, 2006: 821). Factor analysis was instrumental in the three-factor model proposed by Liddle (1987): *psychomotor poverty* (poverty of speech, lack of spontaneous movement and various aspects of blunting of affect), *reality distortion* (particular types of delusions and hallucinations) and *disorganisation* (inappropriate affect, poverty of content of speech, and disturbances of the form of thought), which was incorporated in DSM-IV. Factor analysis is highly dependent on the content of the clinical rating scales that are used for input (Jablensky, 2006). Factor analysis assumes that underlying factors and measured variables are interval level variables, and also that the relationships among factors and between factors and variables are linear, assumptions which are often incompatible with input data (Hagenaars and Halman, 1989).

Cluster analysis

Unlike factor analysis which creates groups of *variables*, cluster analysis groups *individuals* (cases) based on their shared characteristics, which is intuitively more useful clinically (Everitt et al., 1971). Cluster analysis generally makes less restrictive assumptions than factor analysis (Hagenaars and Halman, 1989). However, statistically, clusters tend to be ill-defined, with no agreed formal ruling for cluster finding (Farmer et al., 1983). As with factor analysis, cluster analysis is dependent on the selection of input variables (Jablensky, 2006). Furthermore, studies employing cluster analysis have frequently been poor in reporting the details of the methodology used (Clatworthy et al., 2005).

Latent class analysis

Latent class analysis (LCA) groups individuals into a finite number of mutually exclusive, jointly exhaustive sets based on discrete, categorical, underlying (not directly observable) variables. Advantages of latent class analysis include: (i) types are defined on the latent rather than manifest level, which tends to better represent underlying phenomena; (ii) all variables are considered nominal scales, which accommodates input from diagnostic rating scales more appropriately than typical factor analysis methods; and (iii) no restrictions are imposed on the form of relations between variables, which gives the model more versatility than cluster analysis (Hagenaars and Halman, 1989).

Factor mixture modeling

Conceptually, factor mixture modeling (FMM) may be conceived as the simultaneous combination of factor analysis and latent class analysis. Whereas factor analysis can (and will) only find dimensions in data, and latent class analysis can (and will) only find classes (Linscott et al., 2009), FMM are latent variable models with categorical and continuous latent variables (Lubke and Neale, 2008); thus they are unbiased, and can provide evidence for either continuous or class hypotheses (Muthen and Asparouhov, 2006). By utilising all three modeling methods, and applying parameters for model fit aided by confirmation from observable data based on clinical experience (since these methods are not intelligent systems (Linscott et al., 2009)), it is possible to contrast the explanatory effectiveness of all likely combinations of factors and classes. This strategy avoids many of the subjective assumptions of methods such as cluster analysis, and avoids predetermining the structure of the data in statistical method selection.

Taxometric methods

In contrast to latent variable modeling procedures, taxometric procedures are designed to distinguish continuous latent distributions from two-class categorical distributions. Taxometric procedures vary in their specifics but most share a simple underlying principle, namely that if a class structure is present and there is conditional independence, manipulating the presence and prevalence of class members within subsets of a population sample will lead to systematic changes in statistical parameters (e.g., difference score, covariance, eigenvalue) derived from those subsets. Taxometric techniques have been shown to effectively detect existing latent class structures, and do not detect taxons (classes) where none exist (Meehl, 1995; Meehl and Yonce, 1996). As with factor mixture modeling, taxometric methods are not intelligent systems, rather they simply detect anomalies in observed variance (Linscott et al., 2009). This is both a strength and a limitation; they do not make prior assumptions about the input data used, but are highly reliant on their validity.

Role of transethnic samples in genetic research

Genetic research has a crucial role to play in clarifying the etiological pathway for schizophrenia, determining whether it is, as suspected, a collection of etiologically unrelated but dynamically interacting processes, thereby substantially recasting the present nosology (Jablensky, 2006). Eventually, it is hoped genetic research will reveal biologically valid disease markers of schizophrenia (Allan et al., 2008). “Biologic markers

are revolutionizing diagnosis and treatment. The majority of studies of psychopharmacology and biologic markers are conducted on Western populations, and have neglected [other] ethnic populations" (Flaskerud, 2000: 6).

At a population level, differences in the expression of schizophrenia have been noted, for example the hebephrenic subtype has been identified as common in Japan and catatonia has been identified as common in India (Flaskerud, 2000). At a genetic level, differences in expression have been identified in different ethnicities. Recent schizophrenia genome-wide association studies and subsequent replication studies have found significant genetic differences between Caucasians and African-Americans (ISC, 2009), with polygenic risk scores explaining more variance in European than African-American ancestral groups. Significant genetic differences have also been identified between Caucasians and Han Chinese (Li et al., 2010; Yue et al., 2011), with some significant loci shared and others identified in the Han Chinese only, results differing from those reported by the Psychiatric Genomics Consortium.

Thus, the importance of studying non-European populations in genetics arises because (a) no single population is sufficient for uncovering variants underlying disease in all populations (Rosenberg et al., 2010); (b) the same genetic variant will likely have different prevalence across populations which may facilitate prospects for its discovery (McCarthy, 2008); and (c) there will be a percentage of new variants identified that are population-specific (e.g. Li et al., 2010), even though a majority of genetic variation is shared across ethnicities.

Importance of transethnic research in understanding psychoses

Whereas genetic studies of psychoses tend to contrast ethnicities at a broad population (trans-national) level, transethnic research has the ability to interrogate datasets in greater detail at the demographic, clinical and symptom levels, using ethnicity to explore differential impacts of environment and culture, and assess the limitations of diagnostic assessment. From an anthropological perspective, "what light can be thrown on psychotic illness without interview data, ethnographic description, videotape recording, or clinical interaction" (Jenkins and Barrett, 2004: 16)? Contrasting well-ascertained transethnic schizophrenia samples at the level of individual experience and expression allows researchers to meaningfully incorporate the data generated from these anthropologically-driven methods, particularly in populations where extensive cross-cultural work has been

undertaken, such as in the Iban of Sarawak, Malaysia (Barrett, 2004) and in Southern India (Corin et al., 2004).

The phenomenological differences identified are crucial to understanding and accommodating the different ways in which culture is involved in psychiatric assessment and diagnosis: (1) culture shapes the phenomenology of symptoms themselves; (2) culture is manifested through ethnopsychiatric diagnostic practices and rationales; (3) culture provides the matrix for the interpersonal situation of the diagnostic interview; (4) the dynamics of cross-cultural work are crucial for understanding and refining diagnostic categories and practices; and (5) culture informs the overall conceptualisation of diagnostic systems (Mezzich et al., 1999).

In summary, given the uncertain diagnostic validity of schizophrenia, the search for genetic variants across populations must take place in parallel with the recognition of potential differences in etiology, environment and diagnostic assessment across populations. Transethnic samples are useful for subjecting any diagnostic system to a cross-cultural validity test. An overview of the theoretical divide between anthropology and psychiatry, and a synopsis of the debate on the cross-cultural validity of DSM-IV are provided below.

Schizophrenia, Culture and Ethnicity

Academic interest in the intersection between schizophrenia and culture has been traced to Harry Stack Sullivan, a psychiatrist, and Edward Sapir, an anthropologist, in New York in the 1930s. Yet the relationship between schizophrenia and culture has, until recently, remained somewhat neglected in academic debate. This lack of sustained, coherent effort to elucidate what is a nebulous concept has been attributed to two fundamental areas of contention.

The first of these has been the inability of psychiatrists and anthropologists to successfully ‘straddle’ the theoretical divide between the disciplines, in fact, it has been argued that “the interaction between nosologists and cultural experts has been traditionally antagonistic” (Mezzich et al., 2001: 407). Recent developments in the diagnostic classification of schizophrenia, summarised below, have brought renewed focus to this theoretical impasse. Historically, psychiatry takes a universalist perspective in relation to psychiatric diagnoses, which contends that disorders such as schizophrenia are essentially the same across societies, with culture mediating the content or expression, but not the form of

symptoms. This was traditionally known as the pathoplastic model of mental illness. The tacit assumption is that biology determines the cause and structure of the disorder (Kulhara and Chakrabarti, 2001). Anthropology, in contrast, takes a relativist perspective, contending that culture mediates all aspects of schizophrenia.

> Culture is critical in nearly *every* aspect of schizophrenic illness experience: the identification, definition and meaning of the illness during the prodromal, acute, and residual phases; the timing and type of onset; symptom formation in terms of content, form, and constellation; clinical diagnosis; gender and ethnic differences; the personal experience of schizophrenic illness; social response, support, and stigma; and, perhaps most important, the course and outcome of disorders with respect to symptomatology, work, and social functioning (Jenkins and Barrett, 2004: 6-7).

In summary, psychiatry strives to find similarities in psychiatric presentations across cultures, whereas anthropology strives to elucidate differences.

The second source of difficulty in integrating schizophrenia and culture in a meaningful way has been the imprecision with which schizophrenia is defined in psychiatry and culture is defined in anthropology. The discipline of psychiatry has attempted to define both these concepts more precisely and meaningfully for clinicians and researchers, with mixed success; the diagnostic classification of schizophrenia was robustly debated prior to the release of DSM-V, and culture in psychiatry was meaningfully incorporated for the first time into DSM-IV (summarised below).

Summary of Relevant Research on Culture and Schizophrenia

Despite the major methodological issues outlined above there have been many meaningful attempts to study the relationship between schizophrenia and culture. These efforts have generally focused on two areas: (1) studies of migrant groups within a (generally 'Western') country in comparison to non-migrants; and (2) international studies based on cross-cultural comparisons of groups from developing countries with groups from developed, 'Western' countries. The focus of this summary is the latter body of literature, as this is directly relevant to the data included in this thesis.

Early cross-cultural research studies (prior to the 1970s) generally hypothesised the universality of schizophrenia, but they were plagued by methodological inadequacies (Thakker and Ward, 1998), inextricably linked to the ethnocentric, essentialist, racist discourse within which they were undertaken, and which had underpinned medical science since the 18th Century (Pfeffer, 1998).

The World Health Organization Cross-Cultural Research Program significantly improved the quality of cross-cultural schizophrenia research (Thakker and Ward, 1998). This involved three major undertakings: the first across nine countries in the early 1970s (The International Pilot Study of Schizophrenia – IPSS); the second including more than 1300 cases across 10 countries in the 1980s (The Study of Determinants of Outcome of Severe Mental Disorders – DOSMed); and the third beginning in 1990 (with results published in 2007) and following up subjects from the first two studies across 12 countries (The International Study of Schizophrenia – ISOS). Although these studies have also been criticised on methodological grounds (Edgerton and Cohen, 1994), they were ground-breaking in the field, were conducted with reasonable sophistication and rigor (Kleinman, 1987), and are still widely referenced today.

The major finding of the IPSS, supported by the DOSMed and ISOS, was that the outcome for individuals with schizophrenia is better in developing countries than developed countries (Alem et al., 2009; Sartorius et al., 1986). It was argued at the time of the second WHO study that this represented the single most important finding in cross-cultural psychiatry (Lin and Kleinman, 1988). A subsequent reanalysis of the DOSMeD data still identified type of centre (i.e. developing versus developed) as an important predictor of good outcome (along with acute mode of onset as found in the original study), but it suggested that there were complexities that make the original findings less convincing (Craig et al., 1997). Several studies from developing countries undertaken since the IPSS and DOSMed have supported the favourable outcome hypothesis (Kulhara and Chakrabarti, 2001), while recent challenges to the hypothesis have also been forthcoming (Alem et al., 2009). The distinction between Western/developed and non-Western/developing cultures has pervaded the research ever since the first two WHO studies, and although this is not an ideal comparison, its ubiquity in the transcultural psychiatry literature has made it a sensible reference point for beginning to understand cross-cultural complexities in schizophrenia (Kulhara and Chakrabarti, 2001).

With the notable exception of the WHO Cross-Cultural Research Program most modern schizophrenia ethnic comparison studies use ethnic minorities within a single Western country and health care system to provide contrasting samples. Genetic collaborative studies and pooling available datasets are certainly providing opportunities for ethnic comparative studies utilising multiple ethnicities, for example Lo et al. (2007) contrasted

Japanese (n=304) and German Caucasian (n=301) samples examining gamma-aminobutyric acid receptor subunit beta-2 isoform 2 precursor (*GABRB2*) against Leonhard's clinical subgroups (Leonhard, 1999), to validate previous findings from a Chinese sample (Lo et al., 2004). There have also been comparative studies across international sites examining different treatment centres, for example Iyer et al. (2010) contrasted first episode psychosis treatment in Montreal, Canada (n=88) and Chennai, India (n=61). However, recent studies across multiple sites with large sample sizes assessing individuals with schizophrenia using the same ascertainment method are scarce.

Culture in DSM-IV

Prior to the publication of DSM-IV the only mention of culture was one or two paragraphs in the introduction of DSM-III, supplied from a letter by Professor Kleinman, criticising the original draft (Good, 1996). The imperative to explicitly integrate culture into DSM-IV was brought about by the political reality of the increasing awareness of multiculturalism in the United States, the increased pace of intercultural exchange in the latter half of the 20th Century, and advances in the academic fields of cross-cultural psychiatry, psychology, medical anthropology, and sociology (Mezzich et al., 1999). The process of cultural incorporation was undertaken by an NIMH-sponsored multidisciplinary Group on Culture and Psychiatric Diagnosis, which had semi-official status compared to other DSM-IV workgroups; this limited direct access to decision-making processes, but allowed scholarly independence (Mezzich et al., 1999). An overarching concern for this group was the realisation that inadequate cultural understanding leads to misdiagnosis and perpetuation of inequality and differential class-based service access given that culture is inextricably linked with class/socioeconomic status, particularly in migrant groups in a country (Good, 1996). The complex relationship between culture and socioeconomic status is highly contested and problematic for researchers (Dein, 2006).

Below is a summary of the inclusion of culture in DSM-IV:

> Cultural concerns are represented in a significant manner in the text of DSM-IV – in the Introduction, in the introduction to the multi-axial structure, in the text associated with particular categories (as 'cultural considerations'), in a glossary of cultural terms ('culture-bound syndromes'), and in an 'outline for cultural formulation' appearing in Appendix I (Good, 1996: 128).

The cultural formulation proposed five category headings to consider for a diagnostic assessment: cultural identity of the individual; cultural explanations of the individual's

illness; cultural factors related to psychosocial environment and levels of functioning; cultural elements of the relationship between the individual and the clinician; and the overall cultural assessment for diagnosis and care (APA, 1994).

Criticism of the way culture was incorporated into the DSM-IV has come from both the Group on Culture and Psychiatric Diagnosis, and from those outside the DSM-IV process. The criticism focuses on three areas: (1) The 'sidelining' placement of cultural material within the manual and the selective omission of recommendations in the final version; (2) The ethnocentric bias of the DSM-IV exemplified by the inclusion of 'Western' culture-bound syndromes as core conditions; and (3) The lack of acknowledgement of the theoretical assumptions underpinning the manual and the resulting ambiguity in relation to the universalist/relativist debate for psychiatric diagnosis. Each of these criticisms is summarised below.

In some ways culture was sidelined in DSM-IV from its inception; the Group on Culture and Psychiatric Diagnosis only had semi-official status (Mezzich et al., 1999). When recommendations from the cultural workgroup were included, they were selectively chosen, such that key components were omitted e.g. proposed definitions for ethnicity and culture were deleted from the introduction (Mezzich et al., 1999). Furthermore, placement of cultural content further sidelined it as 'optional' rather than universally important (Kleinman, 1997); e.g. cultural formulation guidelines were included as the 9th appendix (Mezzich et al., 1999).

The DSM-IV inevitably represents the values and perspectives of certain segments of U.S. society (Fabrega, 1994; Fabrega, 1995). Although DSM-IV did not overtly claim to be atheoretical as DSM-III and DSM-III-R had, its guiding theory was not outlined (Thakker and Ward, 1998). Although DSM-IV is frequently portrayed as atheoretical, universal or culture-free, and this is implied in the introduction (Mezzich et al., 1999), a stark example of its cultural bias can be seen in the fact that 'Western' culture-bound syndromes such as anorexia nervosa and chronic fatigue syndrome are included as universal conditions and not as culture-bound syndromes (Rogler, 1996; Thakker and Ward, 1998), even though anorexia nervosa has been rarely reported outside the 'West' (Thakker and Ward, 1998), although the prevalence of eating disorders in developing countries is rising (e.g. Sharan and Sundar, 2015).

Ambiguity regarding the theoretical underpinnings of DSM-IV results in multiple unresolved conundrums and apparent contradictions. First, how can we rely on a biological theoretical model when our signs of pathology are overwhelmingly behavioural (Thakker and Ward, 1998)? And, given this anomaly, how can we rely on 'evidence' presented for underlying pathological mechanisms, and how can we claim the manual is atheoretical (Mezzich et al., 1999)? Second, DSM-IV is a universalist venture (criteria based on similarities), attempting (in a non-comprehensive way) to incorporate relativism through sporadic recognition of cultural mediation (Thakker and Ward, 1998). This recognition of the significance of culture necessarily generates hypothetical questions that may undermine the universalist theoretical framework of the DSM system: what is the cultural effect on symptom application; what is the cultural effect on disorder attribution and assignment; and what is the cultural effect on the diagnostic process?

These ambiguities highlight a fundamental conceptualisation of diagnostic classification that aligns well with the current direction of schizophrenia research, but which DSM-IV has not successfully evolved to accommodate: "Recognition of phenomenological diversity is essential to complement our understanding of core commonalities and both are required for a nosology that is comprehensive and has broad national and international relevance" (Alarcon et al., 2009: 560).

Culture in DSM-5

The 'Emerging Measures and Models' section of the DSM-5 attempts to address variation in a clinically meaningful way, specifically through the 'Clinician-Rated Dimensions of Psychosis Symptom Severity' scales, and the 'Cultural Formulation Interview' (APA, 2013a), although a categorical classification system will inevitably inadequately incorporate real world complexity, as it is not designed for that purpose (Fiedorowicz et al., 2008; Möller, 2008). Therefore, cultural impact is still peripheral to the DSM-5 (relegated to Section III, separated from the diagnostic criteria). It could be argued that embracing a dimensional approach to characterizing the expression of schizophrenia, without strict qualifications regarding applicability, would be incompatible with the very diagnostic foundation of the DSM.

Culture in ICD-10

Although culture has been incorporated into the core ICD-10 manual to a lesser extent than DSM-IV, several countries and regions have released their own, culturally relevant *versions* of the ICD-10, including China, Japan, Cuba and Latin America. The most prominent cultural element in ICD-10 is a list of culture-specific disorders that forms Annex 2 of the DCR-10 (WHO, 1993). It includes a brief definition and discussion of the concept of culture-specific disorders, and then lists twelve of these disorders. Of these eight are also listed in DSM-IV (Mezzich et al., 2001). The limited inclusion of culture in the ICD-10 has been attributed to the diagnostic system being more suited to finding cross-cultural similarities and convergences than recognising variations in clinical presentations and needs (Mezzich et al., 2001). This criticism has also been levelled at the DSM-IV (Thakker and Ward, 1998).

Operationalising Culture in other disciplines

One key question pervades the debate regarding culture and schizophrenia: How can we meaningfully operationalise the concept of 'culture' without losing the value of the subjective experience of schizophrenia by individuals, which is fundamental to an anthropological understanding of the condition? Is it even possible?

Other disciplines have attempted to measure culture in a manner that makes it meaningful for research, notably economics and epidemiology. Fernandez, an economist, proposed a working definition in order to express culture as a useful analytical concept: "think of *differences* in culture as systematic variation in beliefs and preferences across time, space, or social groups" (Fernandez, 2007: 305). The inappropriateness of using uniform, society-wide definitions of culture, especially to operationalise these concepts to generate 'cultural factors' has been vigorously argued within the anthropology literature (Hopper, 2004), although economists utilise proxy variables routinely.

Epidemiology falls between economics and anthropology on the continuum of whether culture can be measured, and if so, how? Psychiatric epidemiology recognises the importance of being able to measure concepts such as race, ethnicity and culture, but acknowledges the complex meanings of these terms, their subtle differences, and the impossibility of breaking them down into three or four easily defined categories (Singh, 1997).

Ethnicity versus Culture

It is important, being mindful of the contested nature of the concept, to develop a working definition of culture in order to meaningfully interpret the rich multi-site data available. As early as 1871, E.B. Tylor formulated a definition of culture that is still widely quoted today, “that complex whole which includes knowledge, belief, art, morals, law, custom, and any other capabilities and habits acquired by man as a member of society” (Chestnut, 2000: 110). Pasick et al. gave the following definition of culture specific to health behaviours, “unique shared values, beliefs, and practices that are directly associated with a health-related behavior, indirectly associated with a behavior, or influence acceptance and adoption of a health education message” (Egede, 2006: 668). Importantly, as is captured by most definitions, the nature of culture and its effects are both implicit and explicit. In order to operationalise the concept in a way useful to research, it is necessary to understand the different levels on which culture can be understood: (1) Pragmatic: What we must know and do to function in a society; (2) Learning: Norms, values, beliefs and behaviours that are socially transmitted; and (3) Statistical: Norms, values, beliefs and behaviours that are common in a population (Hruschka and Hadley, 2008). The statistical dimension offers the most promise for finding a meaningful definition of culture that can assist data interpretation within this thesis.

Culture is extremely challenging to measure, which explains why proxy measures such as race and ethnicity are commonly used (Hruschka and Hadley, 2008). The Centers for Disease Control recommended using ethnicity as the preferred measure, due to the decline of distinct racial groups, although measuring ‘ethnicity’ is also problematic (Flaskerud, 2000). Furthermore, even if ‘ethnicity’ can be accurately ascertained, its use in research is a fine balance between grouping individuals to make useful observations without committing essentialism: using ethnicity to incorrectly overgeneralise (Dein, 2006).

Ethnicity as a categorising term has been used in many different ways and in many spheres, professional and non-professional, academic and non-academic. Most academics and policy makers stress some degree of cultural distinctiveness as the mark of an ethnic group (Dein, 2006), and most definitions suggest that common criteria for membership of an ethnic group include: shared national or territorial identity, shared racial identity, and shared language (Chestnut, 2000).

Self-reported ethnicity is considered the research ‘gold-standard’ (Ma et al., 2007). Not only is a subjective sense of belonging important to ethnic identity (Chestnut, 2000), there

are also important ethical reasons underpinning self-selection stemming from the use of the categories ‘race’, ‘ethnicity’ and ‘culture’ to support racist essentialism in past health research (Dein, 2006; Pfeffer, 1998). Defining group boundaries is also simpler when ethnicity is self-selected (Dein, 2006). Major criticisms of relying on ethnicity as a category include: (a) that it only superficially dissociates research from the racist ideology of the past (Pfeffer, 1998; Singh, 1997), and (b) that a person’s ethnic identity or national origin does not reliably predict their beliefs and attitudes (Egede, 2006), which necessarily limits the generalisability of findings.

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Chapter 2. Establishing Cultural and Data Equivalence

A great strength of the datasets presented in this thesis is their equivalence, not only their cultural equivalence, but also their data source equivalence and their data format equivalence. As establishment of sample similarity across these three domains is crucial to the validity of the analyses presented in Chapters 3-6, and cultural equivalence is a predictable source of critique, these issues will now be explored. Since much of the work on equivalence was undertaken prior to the candidate's PhD, and is therefore not directly assessable, this chapter will focus on the theoretical underpinning of cultural equivalence, and the candidate's experience and assessment of the data sources.

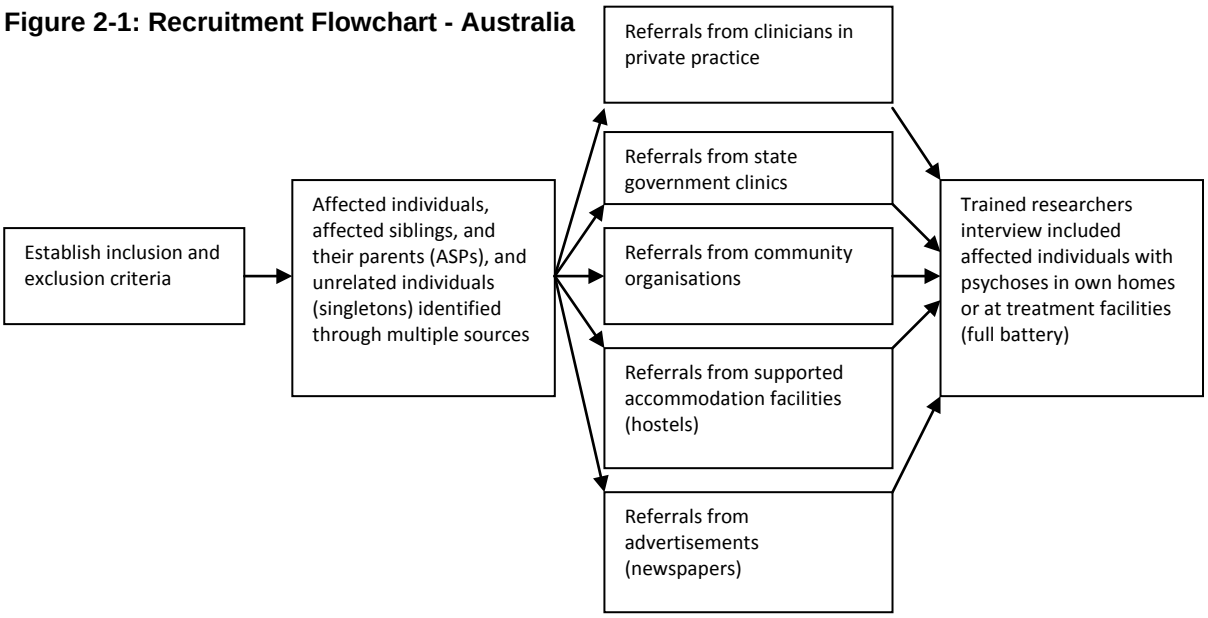
Overview of Site and Sample Characteristics

The three ethnically-distinct schizophrenia populations were drawn from Caucasian Australians; Tamil Brahmin and proximal caste groups from Tamil Nadu, India; and the Iban of Sarawak, Malaysia.

Australia: Sample characteristics and attitudes to mental illness and psychoses

The Australian sample was recruited from two collaborative US/Australian studies examining genes and schizophrenia, known as the Molecular Genetics of Schizophrenia Studies (MGS). The first study (MGS1) examined affected sibling pairs (ASPs) for a linkage analysis, including families with a proband with schizophrenia, at least one other sibling with schizophrenia or schizoaffective disorder, and their parents if available. The second study (MGS2) examined unrelated probands (singletons) with schizophrenia or schizoaffective disorder for a genome-wide association study. Eligible participants were recruited from a range of sources, as outlined in Figure 2-1.

Figure 2-1: Recruitment Flowchart - Australia



Most participants were recruited in South East Queensland (78%), although included individuals and families were also recruited from Melbourne (11%), Adelaide (6%), Sydney and surrounds (4%), Tasmania (<1%) and North Queensland (<1%). The total sample comprised 821 affected individuals, 654 of whom were unrelated singletons and 167 of whom were first-degree related individuals (ASPs) from 79 independent families (McLean et al., 2012).

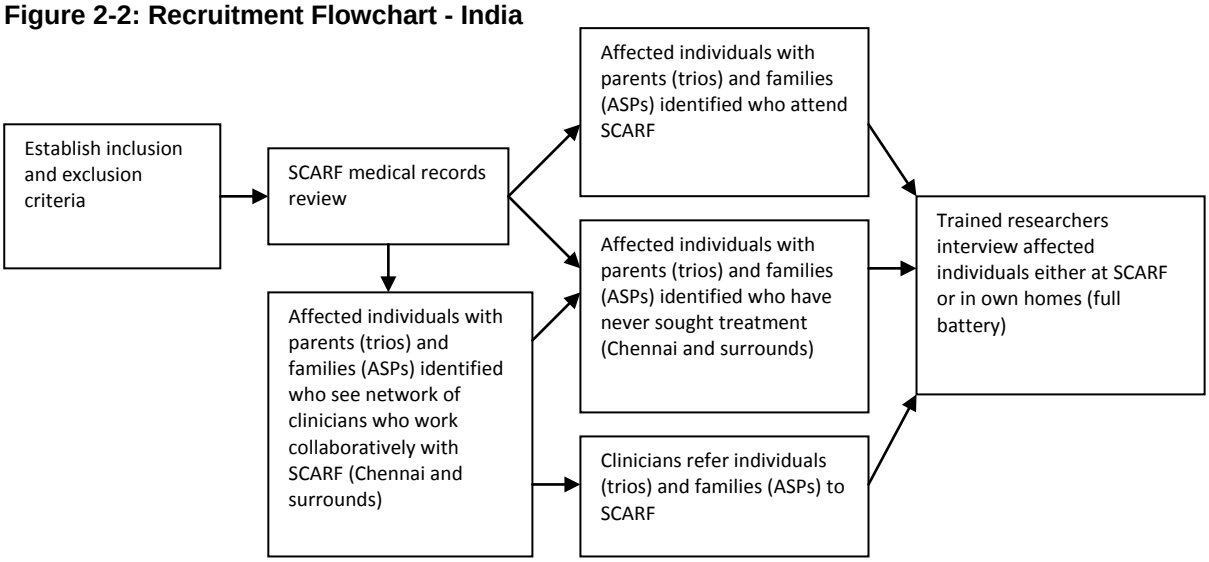
A SANE Australia survey (SANE Australia, 2007) reported that most individuals affected by mental illness believe that societal attitudes to mental illness in Australia are slowly improving, despite 74% experiencing stigma. A recent national survey carried out with 5220 Australians, 1381 of whom reported a mental health problem or scored high on a symptom screening questionnaire, concluded that "the social environments of friends, families, workplaces and educational institutions in particular are sources of both discrimination and support, depending on the circumstances of the individual" (Reavley and Jorm, 2015: 910). It is noteworthy that 41.4% of the Australian individuals included in this thesis were living alone at the time of assessment, with only 34.7% living with family, in stark contrast to India and Sarawak, where almost all participants were living with family (India, 93.1%; Sarawak, 96.0%). This is potentially indicative of less social support being available for individuals with psychosis in Australia in comparison with other sites.

India: Sample characteristics and attitudes to mental illness and psychoses

For the Indian sample, affected sibling pairs (ASPs) and trio pedigrees (affected proband with both parents) were identified by caste/ethnicity for a genetic linkage analysis. The sample comprised those belonging to the Brahmin caste from Tamil, Kerala, Karnataka, or Andhra Pradesh, and those from geographically proximal caste groups from Tamil Nadu (Mudaliars, Chettiars, and Dalits) (Thara et al., 2009). Individuals and families were recruited both directly through the Schizophrenia Research Foundation, India (SCARF), a major psychiatric research facility in Chennai, and also through a network of clinicians in and around Chennai. A recruitment flowchart for the Indian sample is provided as Figure 2-2. Several characteristics of the Indian sample are unusual (see Thara et al., 2009). The extremely low rates of alcohol, cannabis and other drug abuse and dependence are striking, as is the diagnostic homogeneity – there were only two cases of schizoaffective disorder diagnosed in a sample of 520 individuals (0.4%), contrasted with schizoaffective proportions of 6.8% in Australia and 19.1% in Sarawak (see Chapter Three). Also (as

noted above), 93.1% of included individuals were living with family at the time of assessment.

Figure 2-2: Recruitment Flowchart - India



In India, psychiatric hospital facilities are meagre and generally confined to urban areas, and community services are generally non-existent. Most individuals with psychoses live at home, and families tend to seek hospital admission only when their relative becomes violent or aggressive (Thara et al., 2009).

A qualitative study in which eleven patients attending SCARF in the early stages of schizophrenia were interviewed about their experiences (Corin et al., 2004), offers insight into the individual experience of schizophrenia in the population included in this thesis. There were shared themes identified across the interviews: the most common was a feeling of fear or terror that threatened the core of the person. This experience subsequently resulted in three associated themes: “a sense of hostility of the outside world; a feeling that personal limits and boundaries had become porous; and a confusion that attacked the core of the person and undermined the possibility of that person forming an image of him or herself” (Corin et al., 2004: 118).

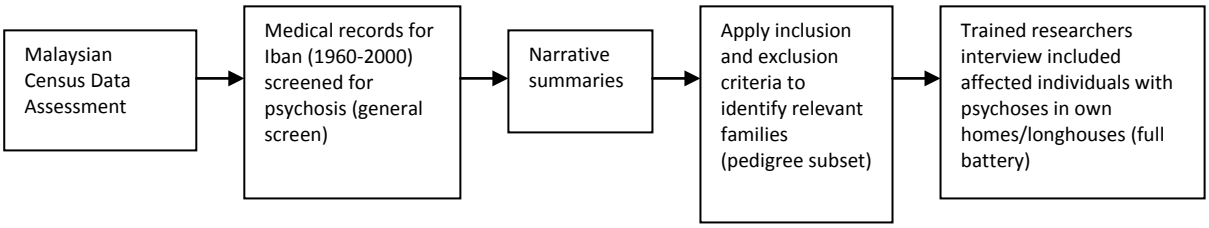
Sarawak: Sample characteristics and attitudes to mental illness and psychoses

The Iban are a people of proto-Malay stock who migrated from the central highlands of Borneo to Sarawak over ten generations, beginning 400 years ago. The Iban almost completely annihilated the pre-existing inhabitants there (the Bukitan and Seru). It was estimated there were 450,000 Iban in Sarawak in 1991. The Iban live in longhouses,

comprising a series of up to 50 apartments joined under one roof, housing up to 300 individuals of a common kinship group (Barrett et al., 2005). Almost all individuals (96.0%) included in this thesis were living with family at the time of assessment.

A review of Malaysian census data identified Iban individuals in Sri Aman and Betong (where a majority of Iban live), and all available medical records were screened for the presence of psychoses. Narrative summaries were compiled for all individuals who screened positive, and then a detailed pedigree subset was identified and interviewed using the full diagnostic battery outlined in this thesis. There were 298 included individuals (from a total of 486 individuals with psychoses) identified through the medical records screen with schizophrenia or schizoaffective disorder; of these, 145 were included in pedigree subset. A flowchart of recruitment in Sarawak is provided as Figure 2-3.

Figure 2-3: Recruitment Flowchart - Sarawak



The Iban have a preoccupation with bodily symptoms and illness, which leads them to present early and often for medical attention. With regard to their attitudes to psychoses, patients and their families uniformly seek assistance from both traditional healers and government health services, in spite of the stigma attached to mental illness (Barrett et al., 2005).

Establishing Cultural Equivalence: A framework for transcultural research

Unlike absolutism, which contends that schizophrenia does not vary significantly across cultures, and relativism, which contends that *all* aspects of schizophrenia vary across cultures, universalism acknowledges that there are commonalities in the form of symptoms, but differences in the expression or content. The great challenge, from a universalist approach, is therefore to develop a research method that is culturally equivalent across populations in order to appropriately accommodate differing conceptualisations of similar concepts across societies.

Herdman et al. (1998) propose a useful framework to establish cultural equivalence in universalist research. They propose six types of equivalence that should be established when converting (diagnostic) instruments across cultural groups. In summary they include: conceptual equivalence – are concepts of health and illness understood the same way across groups; item equivalence – are questions that assess domains equally relevant and acceptable across groups; semantic equivalence – do key concepts translate appropriately across languages; operational equivalence – is the format of instruments equally valid across groups; measurement equivalence – do different versions of instruments have equal reliability, responsiveness and construct validity; and functional equivalence – overall, does the instrument achieve its purpose equally well across groups?

Establishing cultural equivalence across these six domains thereby gives a stable 'reference point' from which to explore identified differences, with a degree of confidence that all findings are not confounded by culture and associated measurement bias.

Anthropological Contributions Relevant to These Datasets

A major strength of the datasets analysed in this thesis is the ability of the research site coordinators in both India and Sarawak to successfully traverse the theoretical gulf between psychiatry and anthropology. Both Professor Barrett, in Sarawak, and Dr. Thara, in India, have conducted qualitative research and written extensively on how culture mediates the experience of psychosis, and the implications for using standardised diagnostic instruments and applying universal diagnostic criteria within these cultures (Barrett, 2004; Corin et al., 2004). An appreciation of the relational or interactional notion of 'self' in both Sarawak (Barrett, 2004) and India (Corin et al., 2004; Kakar, 1991), in contrast to individual uniqueness defining 'self' in post-Enlightenment Western cultures (Kakar, 1991) such as Australia, is central to establishing diagnostic equivalence across sites. The establishment of cultural equivalence across the three datasets analysed in this thesis is dealt with in greater detail in Chapter Five.

Establishing and Confirming Data Source Equivalence

Five main data sources were available for each of the three ethnically-distinct schizophrenia populations.

Diagnostic Interview for Genetic Studies (DIGS)

Trained clinicians used the semi-structured DIGS (Nurnberger et al., 1994) to obtain information relevant to the diagnosis of psychotic, mood, and substance-use disorders in accordance with DSM-IV criteria (APA, 1994), the comorbidity of these disorders, proband medical history, and ratings of the positive and negative symptoms of schizophrenia. DIGS interviews were obtained in all populations except individuals from the initial Sarawak medical records-based screen.

The DIGS was developed and piloted as a collaborative effort of investigators form sites in the National Institute of Mental Health (NIMH) Genetics Initiative in the United States. It has the following features: (1) polydiagnostic capacity; (2) a detailed assessment of the course of illness, chronology of mood and psychotic symptoms, and comorbidity; (3) additional phenomenological assessment of symptoms; and (4) algorithmic scoring capacity. The interview is semi-structured, often requiring clinical judgement to code responses properly (Nurnberger et al., 1994). The sections of the DIGS included in the work presented in the thesis include: demographics, medical history, overview of psychiatric disturbance, major depression, mania, dysthymia, alcohol and drug abuse and dependence, psychosis, comorbidity, suicidal behaviour, global assessment scale, SANS, SAPS, and interviewer's reliability assessment.

An initial two phase reliability study showed that: (1) reliabilities for assessing major depression, bipolar disorder, schizophrenia and schizoaffective disorder were excellent (0.73 to 0.95), except for schizoaffective disorder, for which disagreement on estimates of duration of mood syndromes relative to psychosis reduced reliability; and (2) cross-site training procedures were successful in producing clinical interviewers who would apply a skilled and uniform approach to this ascertainment (Nurnberger et al., 1994). With regard to validity, the agreement between two DIGS interviewers' generated diagnoses, and the baseline referral diagnosis (three independent assessments) was high for depression (45/53; 85%) and bipolar disorder (42/55; 76%), adequate for schizophrenia (29/51; 57%), and poor for schizoaffective disorder (2/48; 4%) for the reason noted above (Nurnberger et al., 1994).

Family Interview for Genetic Studies (FIGS)

A family informant, when possible, or the proband was interviewed about the family psychiatric history using the FIGS (Gershon et al., 1988; Maxwell, 1992). FIGS ratings were obtained in all populations except individuals from the initial Sarawak medical

records-based screen. Approximately 60% of FIGS were from both proband and family informants, the remainder being from probands only. The candidate found that the additional corroborating information provided by the FIGS was particularly rich in both India and Sarawak, where a greater proportion of study participants were living with family than in Australia.

“The FIGS is a guide for gathering diagnostic information about relatives in the pedigrees being studied. This diagnostic information becomes part of a pool of data on each individual relative, to be added to data from the completed Diagnostic Interview for Genetic Studies (DIGS) and from medical records” (Maxwell, 1992: 1). Whereas the DIGS is designed to be used verbatim, the FIGS is designed to be a guide for interviewers. It has three main parts: a pedigree drawing, a set of general screening questions, and symptom checklists for each first-degree relative of interest (Maxwell, 1992). Symptom checklists include depression, mania, psychosis, drug and alcohol misuse, and personality disorders.

The cumulative importance of FIGS verification of information from the DIGS is shown in results of a study by Gershon and Guroff (1984). For major affective disorders, informant/relative information (n=1093) agreed on the presence of a disorder for 96% of probands (n=159). Additionally, of those diagnosed with a major affective disorder by diagnostic interview, there was only diagnostic agreement in only 15% of cases when there was a single informant, this rose to 64% agreement with four or more informants. Thus, additional sources of diagnostic information increase the accuracy of diagnosis.

The cultural equivalence of the DIGS and FIGS was extensively addressed by the chief investigators at the three sites, with specific focus on conceptual equivalence, item equivalence, and functional equivalence. Professor Barrett completed his PhD in Anthropology/Psychiatry, living for several years immersed in Iban culture; Dr. Thara has a long track record of schizophrenia research in India; and Professor Mowry oversaw diagnostic equivalence across all sites by reviewing every case.

The DIGS and FIGS were translated into both Iban (Sarawak) and Tamil (India) with appropriate back-translation procedures. Interview schedules were translated into Tamil and Iban, affected individuals were interviewed by experienced research clinicians, and responses to questions were recorded and back-translated into English. This process was

repeated several times until the research teams were sure that the final version accurately reflected clinical phenomenology.

Inter-rater reliability was assessed within the Australian/American sample (Suarez et al., 2006); within the Indian sample; within the Sarawak sample; between the Australian and Indian samples (disagreement in one of 20 cases; κ=0.886); and between the Australian and Sarawak samples (disagreement in one of 20 cases; κ=0.828).

Crucially, the candidate had access to the original paper copies of the DIGS interviews for all three sites (containing all handwritten notes from the interviewer), and these could be (and were) consulted during data cleaning (see Appendix C).

There are several good examples of the site-specific DIGS interview for Sarawak reflecting subtle, culturally-influenced differences in clinical phenomenology (broadly discussed in Chapter Five). These include, but are not limited to, the questions relating to auditory hallucinations, erotomanic delusions, religious delusions and delusions of magic.

In the US/Australian DIGS (2.0 modified), there were eight questions relating to auditory hallucinations and related phenomena:

1. Auditory – Voices, Noises, Music: Have you ever heard sounds or voices other people could not hear?
2. (If yes:) Did they say bad things about you or threaten you?
3. Auditory – Running Commentary: Have you ever heard voices that described or commented on what you were doing or thinking?
4. Auditory – Two or More Voices: Have you ever heard two or more voices talking with each other?
5. Thought Echo: Have you ever experienced hearing your thoughts repeated or echoed?
6. Audible Thoughts: Have you ever heard your own thoughts as a voice spoken out loud?
7. Did you ever talk to any voices you heard?
8. When you heard the voices, did you also see the person talking, even though others did not see that person?

The English translation of the Iban DIGS also contained these eight core questions, given in a different order, with five additional questions. Prior to the first question (Auditory – Voices, Noises, Music), the Iban DIGS contained a question formulated by Professor Barrett:

1. Talking to self?

There were three additional questions asked after the Auditory – Running Commentary question:

2. Voices wanting you to follow them?
3. Voices commanding?
4. Nice voices?

Following the question on talking visions (question 8 above), the Iban DIGS had an additional question:

5. Talking Noises?

The question relating to erotomanic delusions in the US/Australian DIGS had an additional interviewer instruction inserted in the Iban DIGS in order to differentiate the experience from other reported experiences: *Only mark it as an erotomanic delusion if the patient is convinced a **living person** has fallen in love with them.*

A question relating to delusions of magic was inserted into the Iban DIGS that had no equivalent question in the US/Australian version. Both this question, and the question rating religious delusions had additional interviewer instructions inserted in the Iban DIGS to assess the cultural appropriateness of these experiences:

> *Check whether the family agree or disagree with the patient. Record what they think.*
>
> ***If they agree**, then mark it as a cultural belief "1".*
>
> ***If they disagree**, then mark it as a delusion "2".*

It is evident from these subtle modifications to the Iban version of the DIGS (and FIGS) that having fluent Iban-speaking interviewers familiar with Iban cultural beliefs and experienced in Iban clinical presentations was crucial to the validity of these diagnostic instruments. This ascertainment rigor was replicated in both India and Australia, which is a great strength of these studies.

Thus, although the majority of work adapting the DIGS and FIGS to achieve cultural equivalence was undertaken prior to the candidate's PhD, it is undeniably crucial to the validity of Chapters Two to Six. A detailed decision framework was employed by Professor Mowry and the late Professor Barrett in regard to Iban/Australian equivalence. As has been previously noted Professor Barrett completed his PhD in Anthropology/Psychiatry, living for several years immersed in Iban culture, and he published extensively on Iban culture as it relates to schizophrenia (see Barrett, 2004; Barrett et al., 2005), and the cross-cultural interpretation of schizophrenia more generally (see Barrett, 1988a, 1988b). With regard to the equivalence of the Australian and Indian DIGS, the candidate painstakingly compiled a worksheet containing each variable (685 in total) in the Australian interview booklet, and then mapped each variable in the Indian interview to its equivalent item in Australia.

Medical records assessment

All available medical records were retrieved for each participant and then assessed by trained clinicians. Medical records formed the primary source of diagnostic information for the general screening population in Sarawak, for whom DIGS interviews were unavailable. Although the quality and quantity of medical records obtained varied between and within sites, both the records themselves and the clinician summaries for the Iban were of a general high standard, which was important given the candidate's reliance on them for a significant number of Iban participants (n=153).

Narrative summary

A trained clinician, usually the interviewer who conducted the DIGS, prepared a case summary based on all information obtained from the DIGS, FIGS and medical records assessment. The narrative summary was typically between two and ten pages in length, and was invaluable in recording the first-hand impressions of the interviewer. This facilitated diagnostic assessment by augmenting the DIGS interview information, especially when the participant's responses lacked clarity. Narrative summaries were available for over 90% of participants in Australia and Sarawak, and over 75% in India. These reports were crucial in data cleaning (see Appendix C), and the candidate read and took notes on every narrative summary across the three sites.

Best Estimate Final Diagnosis (BEFD)

DIGS interview, interviewer narrative, available medical records, and FIGS reports formed the basis for diagnostic review. Diagnoses were assigned using the BEFD procedure (Leckman et al., 1982), with two experienced psychiatrists independently reviewing all available information then conferring to assign a consensus diagnosis. Outstanding questions were resolved through discussion and sometimes involved collection of further clinical information. Best estimate diagnoses were formulated for all populations, except the detailed family subset in Sarawak, where diagnosis was routinely formulated by one experienced psychiatrist, with a BEFD generated in a random subset (20 cases). The BEFD diagnostic sheets recorded not only primary diagnostic information, but also comorbid diagnoses, which the candidate relied on heavily when extracting variables such as intellectual disability, mania, depression, and substance abuse and/or dependence.

Establishing and Confirming Data Formatting Equivalence

Overall, the data identification, extraction, cleaning and formatting steps for this thesis took eighteen months. The candidate was the recruitment coordinator for the Australian site for the second Molecular Genetics of Schizophrenia (MGS2) study (which provided all data for the majority of the Australian individuals included in this thesis), and he personally conducted ~100 diagnostic interviews. While this data collection preceded the candidate's PhD, this experience gave him an intimate knowledge of all data sources, instruments used in the study, and the nuances of the dataset, such as the theoretical underpinnings of coding conventions. This knowledge was vital in guiding the exhaustive data identification, extraction, cleaning and formatting strategy used in this thesis (see Appendix C).

Addressing Equivalence Issues Throughout the Thesis

Certain 'global' measures were taken to establishing cultural and data equivalence, as outlined above and in Appendix C. A key component of creating a valid starting point for comparing and contrasting the samples was ascertaining and confirming the ethnicity of all included individuals across the three sites (see Chapters Five and Seven for more detail). There were also Chapter-specific equivalence issues that were addressed during the thesis. Table 2-4 shows the aims of the following four chapters, the samples included for each study, and how study-specific potential equivalence issues and biases were addressed.

Table 2-4 Addressing Equivalence Issues in Each Chapter

Chapter Title	Aims	Samples	Addressing Potential Biases
Chapter 3 Refining Clinical Phenotypes in Schizophrenia	Identify candidate variables free from significant cultural confounding that are hence suitable for inclusion in genetic analyses.	Australia n=821 India n=520 Sarawak n=298 Total n=1639	Report 'raw' differences and then discuss and acknowledge potential sources of bias: direct cultural, indirect cultural, measurement bias.
Chapter 4 Identifying Characteristic Symptom Profiles	Explore symptom variables reported to be characteristic of schizophrenia in the Iban. Test site differences to confirm previous research, and to explore implications of differences across populations for future investigations.	Australia n=609 India n=310 Sarawak n=205 Total n=1124	Sample contains only unrelated individuals to remove familial relatedness as a confounder (i.e. individuals within families may be more similar with regard to demographic and symptom characteristics than unrelated individuals owing to shared socioeconomic and environmental circumstances). This accounts for the smaller sample sizes.
Chapter 5 DSM-IV "criterion A" schizophrenia symptoms across ethnically different populations: evidence for differing psychotic symptom content or structural organization?	Contrast lifetime frequencies of DSM-IV criterion A symptoms and types/content of delusions and hallucinations (with a particular focus on Schneiderian First Rank Symptoms) to elucidate clinical heterogeneity.	Australia n=776 India n=504 Sarawak n=259 Total n=1539	Acknowledge and discuss the transcultural importance of Schneiderian First Rank Symptoms in highlighting culturally-contingent versus culturally-robust characteristics. Acknowledge and discuss the role of culturally formed notions of self in illness expression.
Chapter 6 Is 'Deficit schizophrenia' a distinct class within the syndrome of schizophrenia? Evidence from factor mixture modeling in three ethnically distinct population	Test the underlying statistical demarcation of deficit schizophrenia (DS). Analyse twelve characteristic DS variables by exploratory factor analysis, latent class analysis, and factor mixture modelling (FMM). Test results using taxometric analyses: MAXCOV, MAXEIG, LMODE.	Australia n=812 India n=474 Sarawak n=145 Total n=1431	FMM and taxometric methods not intelligent systems (i.e. they are not influenced by data content). Thus, equivalence issues are discussed in the discussion (and specifically the limitations) section in terms of their effect on data distribution.

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Chapter 3. Refining Clinical Phenotypes in Schizophrenia

McLean D, John S, Barrett R, McGrath J, Loa P, Thara R and Mowry B (2012) Refining clinical phenotypes by contrasting ethnically different populations with schizophrenia from Australia, India and Sarawak. *Psychiatry Research* 196(2-3): 194-200.

Abstract

We contrasted demographic and clinical characteristics in transethnic schizophrenia populations from Australia (n=821), India (n=520) and Sarawak, Malaysia (n=298) and proposed cultural explanations for identified site differences. From these we aimed to identify candidate variables free from significant cultural confounding that are hence suitable for inclusion in genetic analyses. We observed five phenomena: (1) more individuals were living alone in Australia than India or Sarawak; (2) drug use was lower in India than Australia or Sarawak; (3) duration of untreated psychosis (DUP) was longer in India than Australia or Sarawak; (4) the rate of schizoaffective disorder was lower in India than Australia or Sarawak; and (5) age at psychosis onset (AAO) was older in Sarawak than Australia or India. We suggest that site differences for living arrangements, drug use and DUP are culturally confounded. The schizoaffective site difference likely results from measurement bias. The AAO site difference, however, has no obvious cultural or measurement bias explanation. Therefore, this may be an ideal candidate for use in genetic studies, given that genetic variants affecting AAO have already been proposed.

Key words: psychotic disorders, age of onset, culture

Introduction

Similarities and differences in the expression of psychotic illness across cultural groups have attracted significant interest, primarily from social scientists and anthropologists (Larsen, 2004). Transethnic samples are also important in identifying genetic variants underlying complex disorders, such as type 2 diabetes (Unoki et al., 2008; Yasuda et al., 2008) and schizophrenia (ISC, 2009; Li et al., 2010). The importance of studying non-European populations in genetics arises because (i) no single population is sufficient for uncovering variants underlying disease in all populations (Rosenberg et al., 2010); (ii) the same genetic variant will likely have different prevalence across populations which may facilitate prospects for its discovery (McCarthy, 2008); and (iii) there will be a percentage of new variants identified that are population-specific (e.g. Li et al., 2010).

In the clinic schizophrenia is treated as a single entity diagnosed according to reliable, internationally accepted criteria consisting of symptoms, duration, illness course, and exclusion of allied disorders (APA, 1994; WHO, 1992). However, current epidemiological (Lichtenstein et al., 2009) and molecular genetic (ISC, 2009) evidence suggest that it shares genetic predisposition with bipolar disorder, challenging the dichotomous view of functional psychoses (Craddock et al., 2009); indeed the concept of schizophrenia may well represent a group of heterogeneous disorders (Fiedorowicz et al., 2008).

Given uncertain diagnostic validity, one approach to facilitate progress in correlating genotypes with phenotypes is to identify homogeneous sub-groups or dimensional phenotypes (Allan et al., 2008; Holliday et al., 2009; Jablensky, 2006). This approach has proven effective in other complex disorders (Nyholt et al., 2005; Todd et al., 2005). Moreover, given clinical (Thakker and Ward, 1998) and genetic (Li et al., 2010; Suarez et al., 2006) variation in schizophrenia across populations, the search for refined clinical phenotypes is incomplete if we neglect the study of transethnic samples.

Traditionally in psychiatric research non-European populations have either been neglected (Flaskerud, 2000) or simply used to validate Western diagnostic classification (Thakker and Ward, 1998). Phenomenological diversity and commonality are both important if we are to develop a comprehensive nosological understanding (Alarcon et al., 2009). Thus, evaluating demographic and clinical differences across populations complements genetic research, since these differences may have relevance in identifying homogeneous phenotypes.

However, cultural factors may confound our ability to identify relevant differences. First, cultural factors can influence behavior and create true group differences that are unrelated to genetic variation; for example a societal preference to support mentally ill individuals in the workplace may result in less measurable disability in individuals with schizophrenia in that society contrasted with a society where those supports are absent. Second, cultural factors can influence both behavior and resource allocation, indirectly resulting in group differences through measurement differences; for example help-seeking behavior and/or greater availability of mental health services in a society may result in higher reported rates of schizophrenia and higher hospitalization rates in contrast to a society where services are unavailable or services are not actively sought. Third, cultural factors can influence interpretation of clinical diagnostic concepts, thereby resulting in group differences due to measurement bias resulting from the different conceptualization and/or application of diagnostic instruments. Arguably, culture is critical in almost every aspect of the experience of schizophrenia, including identification, diagnosis, symptomatology, ethnic differences and social responses (Jenkins, 1998).

Some clinical and demographic differences across schizophrenia populations may not be confounded, however, and hence truly correlate with genetic variation. To isolate these, we can use clinical judgment and cultural insight in conjunction with previously published evidence (where available). Whenever no cultural confounding explanation is apparent, a demographic or clinical group difference across sites may be a promising candidate phenotype for investigating phenotype-genotype correlations.

The Genetics Research group at the Queensland Centre for Mental Health Research (QCMHR) recruited three cohorts of individuals with psychosis for genetic analyses. We studied demographic and clinical characteristics of schizophrenia in three ethnic groups: Caucasian Australians (*n*=821); Tamil Brahmin and proximal caste groups from Tamil Nadu, India (*n*=520); and the Iban of Sarawak, Malaysia (*n*=298). We examined a broad cross-section of variables that characterize each population, and based on previous research and clinical experience across the three sites we expected to observe five phenomena.

First, a greater proportion of individuals in Australia would be living alone (Jablensky et al., 1999) than in Tamil Nadu, India (Thara et al., 2009) or Sarawak (Barrett et al., 2005).

Second, drug use in India would be significantly lower than in Australia or Sarawak. International drug statistics suggest a higher prevalence of drug abuse in Australia than India (United Nations Office on Drugs and Crime, UNODC, 2008), and a previous Chennai schizophrenia study revealed extremely low drug use (Thara, 2004).

Third, the duration of untreated psychosis (DUP) would be significantly longer in India than in Australia or Sarawak. The average mean DUP from low-and-middle-income (LAMI) countries, including India and Malaysia, is significantly higher than for high-income countries, including Australia (Large et al., 2008), and DUP is lower for indigenous groups, including the Iban, than other Malaysian sub-groups (Chee et al., 2010).

Fourth, the rate of schizoaffective disorder would be significantly lower in India (Thara et al., 2009) than in Australia or Sarawak.

Fifth, the age of onset of psychosis (AAO) would be significantly older in Sarawak (Chee et al., 2010) than in Australia (Kessler et al., 2007) or India (Thara et al., 2009). Schizophrenia AAO is an attractive variable to examine because heritability has been reported in a Mexican/Central American sample (Hare et al., 2010), and AAO-associated genetic variants have been observed in an American-Caucasian sample (Renou et al., 2007).

Utilizing three large, uniformly ascertained, ethnically distinct schizophrenia samples we aimed to identify clinical variables of potential genetic relevance. A focus on clinical variation complementary to the search for genetic variants may eventually assist in refining the complex schizophrenia phenotype.

Methods

Sample recruitment

At each site we included all probands and relatives who had a Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (APA, 1994) diagnosis of schizophrenia or schizoaffective disorder. To standardise schizoaffective diagnoses, we operationalized the mood syndrome duration criterion at ≥30% of total illness duration, consistent with other major genetic studies (Suarez et al., 2006). Individuals were included if they met the ethnicity criterion for each study: Australia – self-reported European

Caucasian ancestry; India – membership of Brahmin caste from Tamil, Kerala, Karnataka, or Andhra Pradesh, or membership of geographically proximal caste groups from Tamil Nadu (Mudaliars, Chettiars, and Dalits) (for details see Thara et al., 2009); and Sarawak – self reported Iban ethnicity. Ethnicity was subsequently confirmed through genetic analysis across all three samples. In Sarawak, individuals diagnosed with psychotic disorders other than schizophrenia or schizoaffective disorder were excluded from this study.

Exclusion criteria for individuals were: (i) inability to give informed consent to all aspects of the study; (ii) psychosis judged to be secondary to substance use or a known neurological disorder such as epilepsy; and (iii) severe intellectual disability (any impairment that precluded informed consent, and any individual with an IQ assessed below 55 according to formal testing/medical record evidence).

The Australian sample was recruited during two related collaborative US/Australian studies examining genes and schizophrenia, collectively termed the Molecular Genetics of Schizophrenia Study. The first examined affected sibling pairs for a linkage analysis (for details see Suarez et al., 2006), where included families had a proband with schizophrenia, and one or more siblings of the proband with schizophrenia or schizoaffective disorder. The second examined unrelated individuals with schizophrenia or schizoaffective disorder for a genome-wide association study (for details see Shi et al., 2009). Eligible families and individuals were recruited from a range of sources, including local treatment facilities, physician referrals, community organizations, supported accommodation facilities and advertisements.

The Indian sample was recruited as an ethnically homogeneous sample for genetic studies of schizophrenia. Both affected sibling pairs and trios (a single affected offspring and both parents) were recruited. Eligible families were identified and invited to participate through The Schizophrenia Research Foundation India's (SCARF's) well-established recruitment network of clinicians (for details see Thara et al., 2009).

The Sarawak sample was recruited through Malaysian census data from the two major regional divisions (Sri Aman and Betong) where the Iban live (for details see Barrett et al., 2005). Institutional Review Board approval was obtained, and then medical records (1960-2000) for individuals in the Sri Aman and Betong divisions were screened for psychosis and narrative summaries and research diagnoses generated. Families where individuals

were identified as having any psychotic illness were then approached using the same clinical ascertainment battery that was used for the studies in Australia and India. Although the Sarawak sample was based on treated rates (approximating population prevalence) of schizophrenia, whereas the Australian and Indian samples were opportunistically recruited, the similarities in the ascertainment methods across sites still make comparison of these groups valuable.

All participants in Australia and India gave written informed consent, and individuals in Sarawak who participated in the detailed screening follow-up gave verbal, videotaped informed consent (given that the Iban is traditionally a preliterate society). Individuals consented to an interview, a blood sample for DNA, and review of their psychiatric records. Local Institutional Review Board approval was obtained for each study.

Clinical ascertainment

The following routine sources of information were obtained across the studies in each country.

Diagnostic Interview for Genetic Studies (DIGS)

Trained clinicians used the semi-structured DIGS (Nurnberger et al., 1994) to obtain information relevant to the diagnosis of psychotic, mood, and substance-use disorders in accordance with DSM-IV criteria (APA, 1994), the comorbidity of these disorders, proband medical history, and ratings of the positive and negative symptoms of schizophrenia. DIGS interviews were obtained in all populations except individuals from the initial Sarawak medical records-based screen.

Family Interview for Genetic Studies (FIGS)

A family informant, when possible, or the proband was interviewed about the family psychiatric history using the FIGS (Gershon et al., 1988; Maxwell, 1992). FIGS ratings were obtained in all populations except individuals from the initial Sarawak medical records-based screen. Approximately 60% of FIGS were from both proband and family informants, the remainder being from probands only.

The cultural equivalence of the DIGS and FIGS was extensively addressed by the chief investigators at the three sites, with specific focus on conceptual equivalence, item equivalence, and functional equivalence (for details of a cultural equivalence framework

see Herdman et al., 1998). Professor Barrett completed his PhD in Anthropology/Psychiatry, living for several years immersed in Iban culture; Dr. Thara has a long track record of schizophrenia research in India; and Professor Mowry oversaw diagnostic equivalence across all sites by reviewing every case.

The DIGS and FIGS were translated into both Iban (Sarawak) and Tamil (India) with appropriate back-translation procedures. Interview schedules were translated into Tamil and Iban, affected individuals were interviewed by experienced research clinicians, and responses to questions were recorded and back-translated into English. This process was repeated several times until the research teams were sure that the final version accurately reflected clinical phenomenology.

Medical records assessment

All available medical records were retrieved for each participant and then assessed by trained clinicians. Medical records were obtained for all populations.

Narrative summary

A trained clinician, usually the interviewer who conducted the DIGS, prepared a case summary based on all information obtained from the DIGS, FIGS and medical records assessment. The narrative summary was invaluable in recording the first-hand impressions of the interviewer. This facilitated diagnostic assessment by augmenting the DIGS interview information, especially when the participant's responses lacked clarity. Narrative summaries were obtained in all populations.

Best Estimate Final Diagnosis (BEFD)

DIGS interview, interviewer narrative, available medical records, and FIGS reports formed the basis for diagnostic review. Diagnoses were assigned using the BEFD procedure (Leckman et al., 1982), with two experienced psychiatrists independently reviewing all available information then conferring to assign a consensus diagnosis. Outstanding questions were resolved through discussion and sometimes involved collection of further clinical information. Best estimate diagnoses were formulated for all populations, except the detailed family subset in Sarawak, where diagnosis was routinely formulated by one experienced psychiatrist, with a BEFD generated in a random subset (20 cases).

Diagnostic inter-rater reliability

Inter-rater reliability was assessed within the Australian/American sample (Suarez et al., 2006); within the Indian sample; within the Sarawak sample; between the Australian and Indian samples (disagreement in one of 20 cases; κ=0.886); and between the Australian and Sarawak samples (disagreement in one of 20 cases; κ=0.828). One psychiatrist (BM) was a Principal Investigator on all five studies, and has reviewed all included cases.

Data analysis

We analyzed a broad range of variables potentially relevant to the five phenomena outlined in the introduction, including: demographic variables, (i) age, (ii) marital status, (iii) living arrangements, (iv) years of formal schooling, (v) current employment status, (vi) five-year employment history; illness variables, (vii) DSM-IV diagnosis, (viii) age at onset of psychosis, (ix) age at first psychiatric treatment, (x) duration of illness in years, (xi) duration of untreated psychosis, (xii) whether ever hospitalized for psychiatric treatment, (xiii) number of lifetime hospitalizations; and drug use variables, (xiv) lifetime DSM-IV alcohol abuse or dependence, (xv) lifetime DSM-IV cannabis abuse or dependence, (xvi) lifetime DSM-IV other drug abuse or dependence.

Age at onset of psychosis was assessed as the age at which active psychotic symptoms were first recognized, and duration of untreated psychosis was assessed as the period between the onset of psychosis, and the age at which formal psychiatric treatment was first accessed.

Sources of data were audited (both electronic and hard copy), and all potential cases were identified for whom diagnostic information was available. Data were extracted from diagnostic interview databases, where possible, then responses were checked, corrected, and missing values retrieved from all available sources. These variables were tested for significant differences by site (Australia, India, Sarawak), by sex, and by site controlling for sex. Statistical analyses used SAS software, version 9.2 for Windows (SAS Institute Inc.), and the tests used included: Chi-Square for nominal and ordinal variables, Proc T-Test when comparing two means for interval variables, and Proc GLM when comparing more than two means for interval variables. Adequate statistical power for assessing the sixteen variables utilizing three-way tests was confirmed using a Bonferroni correction.

Results

The present study was drawn from 1831 individuals from Australia (*n*=821), India (*n*=524) and Sarawak (*n*=486). We excluded 192 individuals because their DSM-IV diagnosis was a psychotic disorder other than schizophrenia or schizoaffective disorder (Australia, *n*=0; India, *n*=4; Sarawak, *n*=188). Therefore, the final sample comprised 1639 individuals from Australia (*n*=821), India (*n*=520) and Sarawak (*n*=298). DIGS and FIGS data were available for over 90% of participants in Australia and India, and approximately 50% of participants in Sarawak. Narrative summaries were available for over 90% of participants in Australia and Sarawak, and for over 75% of participants in India. Best-estimate final diagnoses were available for all participants across the three sites (except as previously noted).

A summary of demographic and clinical variables by site is provided in table 3-1.

Table 3-1: Demographic and Clinical Characteristics of Affected Individuals by Site

Variable	Australia	India	Sarawak	Total	Test statistic	df/df_{err}	*P*
N [a]	821 (50.1%)	520 (31.7%)	298 (18.2%)	1639 (100%)			
Demographic variables							
Age, Mean ± SD	39.10 ± 11.86	38.00 ± 11.98	46.73 ± 14.70		$F = 51.38$	2, 1627	< 0.001
Marital status [b]					$\chi^2 = 180.55$	4	< 0.001
Married	56 (6.9%)	163 (32.3%)	96 (34.5%)	315 (19.8%)			
Never married	637 (78.5%)	283 (56.2%)	137 (49.3%)	1057 (66.3%)			
Separated/divorced	119 (14.7%)	58 (11.5%)	45 (16.2%)	222 (13.9%)			
Living arrangements					$\chi^2 = 604.47$	6	< 0.001
Alone	334 (41.4%)	6 (1.3%)	8 (2.9%)	348 (22.3%)			
Facility	118 (14.6%)	23 (4.8%)	1 (0.4%)	142 (9.1%)			
Family	280 (34.7%)	444 (93.1%)	265 (96.0%)	989 (63.4%)			
Others	75 (9.3%)	4 (0.8%)	2 (0.7%)	81 (5.2%)			
Years of formal schooling, Mean ± SD	10.95 ± 2.24	12.60 ± 3.39	5.62 ± 3.95		$F = 345.56$	2, 1422	< 0.001
Current employment status					$\chi^2 = 720.75$	10	< 0.001
Disabled: formerly worked, no longer able	474 (58.0%)	123 (25.8%)	7 (2.9%)	604 (39.3%)			

	Homemaker	5 (0.6%)	72 (15.1%)	17 (7.0%)	94 (6.1%)		
	Never worked	231 (28.2%)	102 (21.4%)	13 (5.4%)	346 (22.5%)		
	Student	10 (1.2%)	22 (4.6%)	0 (0%)	32 (2.1%)		
	Unemployed	21 (2.6%)	57 (12.0%)	30 (12.4%)	108 (7.0%)		
	Working	77 (9.4%)	101 (21.2%)	176 (72.4%)	354 (23.0%)		
Occupational dysfunction (past five years)						$\chi^2 = 189.36$	8	< 0.001
	Always worked	18 (2.2%)	68 (14.4%)	24 (16.6%)	110 (7.7%)		
	Periods of unemployment not related to illness	6 (0.7%)	17 (3.6%)	0 (0%)	23 (1.6%)		
	Minor occupational dysfunction	79 (9.7%)	103 (21.7%)	20 (13.8%)	202 (14.1%)		
	Moderate occupational dysfunction	115 (14.1%)	98 (20.7%)	24 (16.6%)	237 (16.5%)		
	Severe occupational dysfunction	600 (73.4%)	188 (39.7%)	77 (53.1%)	865 (60.2%)		
Illness variables							
Diagnosis						$\chi^2 = 114.09$	4	< 0.001
	Schizoaffective, depressed	24 (2.9%)	1 (0.2%)	38 (12.8%)	63 (3.8%)		
	Schizoaffective, bipolar	32 (3.9%)	1 (0.2%)	19 (6.4%)	52 (3.2%)		
	Schizophrenia	765 (93.2%)	518 (99.6%)	241 (80.9%)	1524 (93.0%)		
Age at onset, Mean ± SD		22.09 ± 6.39	23.25 ± 7.60	29.14 ± 11.37		$F = 79.38$	2, 1623	< 0.001
Age at first treatment, Mean ± SD		22.99 ± 6.69	25.85 ± 10.10	29.45 ± 11.32		$F = 53.87$	2, 1604	< 0.001
Illness duration (years)		17.01 ± 10.68	14.71 ± 10.47	17.50 ± 10.15		$F = 11.72$	2, 1628	< 0.001
Duration of untreated psychosis (DUP) (years)		0.89 ± 2.76	2.63 ± 6.99	0.31 ± 1.88		$F = 30.65$	2, 1604	< 0.001
Hospitalized (ever)		787 (96.0%)	215 (46.6%)	255 (95.2%)	1257 (81.2%)	$\chi^2 = 511.10$	2	< 0.001
Hospitalizations (lifetime)		8.10 ± 11.09	1.01 ± 1.69	6.07 ± 8.65		$F = 89.36$	2, 1543	< 0.001
Substance use variables							
Alcohol abuse/dependence (lifetime)		333 (40.7%)	3 (0.8%)	28 (10.5%)	364 (24.5%)	$\chi^2 = 265.53$	2	< 0.001
Cannabis abuse/dependence (lifetime)		372 (45.5%)	0 (0%)	2 (0.8%)	374 (25.3%)	$\chi^2 = 397.06$	2	< 0.001
Other drug abuse/dependence (lifetime)		216 (26.5%)	0 (0%)	7 (2.6%)	223 (15.1%)	$\chi^2 = 185.94$	2	< 0.001

[a] Sample size varies across variables due to exclusion of missing data

[b] Widowed individuals not included in marital status analysis (n=26)

Note: A breakdown of the demographic and clinical characteristics of affected females by site (table 3-2S) and affected males by site (table 3-3S) are provided as supplementary material.

Sex breakdown by site

There were 1055 males (64%) and 584 females included in the sample, comprising: Australia, 580 males (71%) and 241 females; India, 302 males (58%) and 218 females; and Sarawak, 173 males (58%) and 125 females.

Age by site

There was a significant age effect (see table 3-4S) across all tested demographic and clinical variables, except diagnosis. We tested site differences for each of the 15 non-age variables controlling for age (see supplemental tables 3-5S and 3-6S), and our site differences remained significant in all instances.

Demographic variables

The site effects for marital status, living arrangements, current employment status, and occupational dysfunction all remained significant once sex was controlled for. Current age was significant by site and by sex, however, the relationship between current age and both site and sex was not significant, indicating that sex does not confound the site effect. Although years of formal schooling was significant by site and by sex, the relationship between years of school and both site and sex was also significant, $F(2, 1422) = 14.86$, $p < 0.001$, which indicates that sex may confound the site effect. All site combinations (Sarawak-Australia, Sarawak-India, Australia-India) were significant at 0.05 level using Scheffe's Test for years of formal schooling, whereas two site combinations (Sarawak-Australia, Sarawak-India) were significant at 0.05 level for current age.

Illness variables

The site effects for diagnosis and whether hospitalized (ever) remained significant after controlling for sex. The site effects for age at onset, age at first treatment, illness duration, DUP, and mean hospitalizations do not appear confounded by sex, as the relationship between each of these variables by both site and sex was not significant. All site combinations (Sarawak-Australia, Sarawak-India, Australia-India) were significant at 0.05 level using Scheffe's Test for age at onset, age at first treatment, and mean

hospitalizations. Two site combinations (India-Australia, India-Sarawak) were significant at 0.05 level for both illness duration and DUP.

Substance abuse variables

The site difference for alcohol, cannabis, and other drug abuse/dependence remained significant after controlling for sex.

Power analyses

All sixteen variables remained significant using a corrected p-value=0.001.

Discussion

Each of the five studied phenomena was strongly supported by the data, although there were interesting variations from what may have been expected from the literature. The virtual absence of lifetime drug abuse/dependence in India was lower than expected from international figures (UNODC, 2008), although comparable with other studies from Chennai (Thara, 2004; Thara et al., 2009). The rate of cannabis abuse/dependence in the Iban was very low (<1%); conversely the rate in Australia was very high, with more individuals rating for lifetime cannabis abuse/dependence (*n*=372) than for lifetime alcohol abuse/dependence (*n*=333).

Although the mean DUP reported for indigenous groups in Malaysia was 117 weeks (Chee et al., 2010), the mean DUP in our Iban sample was significantly shorter at 16 weeks. Our reported DUP for Australian individuals was also somewhat shorter, 46 weeks, than expected from the reported average for high-income countries, 63 weeks (Large et al., 2008).

While our reported mean age at onset of psychosis in Australia (22.1 years) was comparable with international literature (Kessler et al., 2007), our Indian AAO was younger (23.3 years) than the reported mean for LAMI countries (27.3 years), although closer to the reported mean for low-income countries (25.7 years), which included India (Large et al., 2008). Our Sarawak AAO (29.1 years) was older than both the LAMI figure, and that reported for indigenous groups in Malaysia (28.3 years) (Chee et al., 2010).

Potential cofounders for each candidate variable are discussed subsequently, mindful of their suitability as phenotypes for genetic studies.

Living arrangements

Culture likely plays an important role in differences in living arrangements by site, with the family unit being far more important socially and support-wise in both Sarawak and India. This trend was consistently reflected in the narrative summaries, and has been identified in the literature (Barrett et al., 2005; Thara et al., 2009). Indian individuals who lack family support frequently find other community supports non-existent and consequently reside in state-run institutions.

Drug use

We suggest that the almost non-existent rate of alcohol and drug use in our Indian sample is likely due in part to a higher proportion of individuals with schizophrenia and related conditions recruited for this study living with family, which limits their access to drugs. There have now been two schizophrenia studies based in Chennai reporting extremely low drug use (Thara, 2004; Thara et al., 2009). Caste may also play a role in this phenomenon; there is a disinclination in the Tamil Brahmin community to use substances such as alcohol, although cannabis use has been noted historically (Sharma, 1996).

Duration of untreated psychosis

The significantly longer mean DUP in India is likely cultural; India was the only site where some individuals had never accessed any psychiatric treatment at the time of study assessment. Previous Indian schizophrenia studies have identified many individuals who have never accessed treatment (McCreadie et al., 2005; Srinivasan et al., 2004). Indian individuals were frequently looked after at home with family, a premise supported by the analysis of the hospitalization variables, with a lower proportion of Indian individuals having ever been hospitalized, and Indian individuals also having the fewest mean number of hospitalizations.

Schizoaffective rate

The comparatively low rate of schizoaffective disorder in India and the conversely high rate in Sarawak in contrast to Australia may be indirectly cultural in genesis, resulting from different weighting given to mood symptoms either by the local diagnosticians or study participants. Alternatively, there may be measurement bias involved which is not cultural in origin; the site differences may stem from the different sampling methods and inclusion criteria used in Sarawak. A proportion of individuals interviewed in a psychosis-wide

assessment protocol (Sarawak) may have an illness course that would not bring them into contact with the research team in an opportunistic, schizophrenia-focused recruitment setting (India) (Thara et al., 2009). Further analysis of symptom and illness course data will be necessary to test this explanation.

Age at onset

The AAO site difference is puzzling. The mean AAO in Sarawak is almost six years older than in either Australia or India, with our reported AAOs similar to those reported in other studies in Australia (Kessler et al., 2007) and Malaysia (Chee et al., 2010). Sarawak was a representative sample, whereas Australia and India were convenience samples comprising both singletons and sib-pairs, although how this would account for such a large difference is not apparent. Furthermore, our Australian and Indian AAOs are broadly consistent with those reported in systematic review (Large et al., 2008) and representative sample data (Kessler et al., 2007). Culturally influenced measurement bias appears unlikely; conversely, the societal tendency toward help-seeking behaviour in Sarawak would be expected to result in a younger AAO, with cases of psychosis identified and documented reliably at an early stage. This phenomenon has been noted with regard to shorter DUP for indigenous Malaysians, including the Iban, compared to other groups in Malaysia (Chee et al., 2010).

Older AAO has been noted in LAMI countries than high-income countries (Large et al., 2008), although the difference was not as great as the difference we report, and our AAO difference was also seen between India and Sarawak (Malaysia), which are both LAMI countries. Thus, while a trend similar to what we report has been identified in the literature, there has been no definitive explanation proffered.

Cultural considerations

Categorization of research participants by ethnicity and/or culture is problematic and highly contested (Egede, 2006; Ma et al., 2007). The fact that our cohorts are both ethnically homogeneous and geographically constrained enables assessment of cultural confounders because these two factors represent the best available proxy for culture (Azuonye, 1994). Our sample is large for a transethnic comparative schizophrenia study (*n*=1639) and individuals were assessed with uniform instruments and diagnostic methods including the benchmark BEFD. We assessed ethnicity by self-report, which is considered the research ‘gold standard’ in transcultural research (Ma et al., 2007). Furthermore, we

ascertained birthplace for individuals' parents and grandparents, confirmed ethnic homogeneity genetically, and interviewed individuals in their home countries using local interviewers. These measures avoid many confounding factors frequently experienced in cross-cultural research, which can limit generalizability of findings (McKenzie and Crowcroft, 1996a, 1996b).

We acknowledge that elucidating the complex confounding role of culture in cross-cultural research is problematic; therefore, we have not attempted this. Rather, with many demographic and clinical site differences available for further investigation, we simply eliminated those with readily apparent plausible cultural explanations in order to focus on those with no plausible cultural or measurement bias explanations. The stark difference in age at onset in Sarawak is such a finding.

Methodological limitations

First, a lack of measurement equivalence was unavoidable. The samples were collected for specific genetic studies, thus there were differences in selection methods of included individuals. Both the Indian and Sarawak samples were chosen from ethnically homogeneous populations, whereas the Australian sample was not specifically recruited as such. Furthermore, the Australian and Indian cohorts included sib-pairs as well as unrelated individuals recruited opportunistically, while only the Sarawak sample can be considered relatively epidemiologically sound. A high rate of recruitment from hostels in Australia, for example, may result in overrepresentation of drug abuse and dependence in that sample, although increased drug abuse in boarding house accommodation was not identified in a study of substance abuse and schizophrenia in Australia (Fowler et al., 1998). The opportunistic recruitment methods may have accessed a population with a higher level of disability in Australia, which will be investigated in future analyses. The different recruitment methods also resulted in DIGS and FIGS data being unavailable for approximately half the Sarawak sample (i.e. those from the initial medical records screen).

Second, the limited precision or validity of diagnostic criteria may be problematic. Caution must always be exercised when using instruments across cultures, as converting thoughts and feelings across languages can be difficult (Barrett, 2004). To address this issue we employed state-of-the-art methods, translating and back-translating the DIGS, and using local interviewers who interviewed in the native language across the three sites, and recorded responses in Iban (Sarawak) and English (India and Australia). The reliability of

the instrument (inter-rater reliability within and across the samples) was also tested to establish reliability and validity across sites, although diagnostic inter-rater reliability was not assessed between India and Sarawak, nor was inter-rater reliability assessed on individual diagnostic components other than the DIGS.

Third, the generalizability of our findings is limited, particularly given that both the Iban in Malaysia and the Brahmin in India are homogeneous groups within diverse societies. Furthermore, we did not specifically collect socioeconomic data across our samples, which further limits the generalizability of any findings attributed to ethnicity/culture, as socioeconomic position has been proposed as a stronger determinant of health outcomes than ethnicity (Egede, 2006).

However, given that we were seeking specific site differences and using cultural explanations to prioritize candidates for further investigation, we argue that these limitations do not detract from the exploratory value of our methodology or findings. Moreover, we hope that our study will energize discourse on tackling the confounding role of culture in transethnic psychiatric research - an inherently worthwhile though challenging task. Given the clinical heterogeneity of schizophrenia there is ample scope to test a range of potential refinements to this complex phenotype in order to facilitate genetic analyses.

Concluding remark

Our finding that the age of onset in Sarawak is significantly older than in Australia or India is worthy of further investigation. As there is no obvious cultural or measurement bias explanation to explain this, age at onset emerges as a promising phenotypic candidate for genetic studies across ethnically distinct schizophrenia populations.

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Declaration of Interest

No conflicts declared.

Chapter 3 Supplemental Tables

This material supplements but does not replace the content of the peer-reviewed paper published in *Psychiatry Research*.

Table 3-2S: Demographic and Clinical Characteristics of Affected Individuals (Females) by Site

Variable	Australia	India	Sarawak	Total	Test statistic	df/df_{err}	*P*
N [a]	241 (41.3%)	218 (37.3%)	125 (21.4%)	584 (100%)			
Demographic variables							
Age, Mean ± SD	40.63 ± 12.38	37.77 ± 12.86	48.49 ± 14.71		$F = 26.75$	2, 577	< 0.001
Marital status [b]					$\chi^2 = 62.51$	4	< 0.001
Married	25 (10.7%)	80 (38.1%)	49 (43.0%)	154 (27.6%)			
Never married	159 (68.0%)	90 (42.9%)	42 (36.8%)	291 (52.2%)			
Separated/divorced	50 (21.4%)	40 (19.1%)	23 (20.2%)	113 (20.3%)			
Living arrangements					$\chi^2 = 211.88$	6	< 0.001
Alone	97 (40.9%)	2 (1.0%)	1 (0.9%)	100 (18.1%)			
Facility	28 (11.8%)	9 (4.4%)	0 (0%)	37 (6.7%)			
Family	97 (40.9%)	193 (94.6%)	110 (98.2%)	400 (72.3%)			
Others	15 (6.3%)	0 (0%)	1 (0.9%)	16 (2.9%)			
Years of formal schooling, Mean ± SD	10.99 ± 2.06	11.93 ± 3.59	4.04 ± 4.42		$F = 148.04$	2, 488	< 0.001
Current employment status					$\chi^2 = 280.18$	10	< 0.001
Disabled: formerly worked, no longer able	117 (48.8%)	41 (20.3%)	2 (2.0%)	160 (29.5%)			
Homemaker	5 (2.1%)	71 (35.2%)	15 (15.0%)	91 (16.8%)			
Never worked	77 (32.1%)	40 (19.8%)	10 (10.0%)	127 (23.4%)			
Student	4 (1.7%)	15 (7.4%)	0 (0%)	19 (3.5%)			
Unemployed	9 (3.8%)	16 (7.9%)	10 (10.0%)	35 (6.5%)			
Working	28 (11.7%)	19 (9.4%)	63 (63.0%)	110 (20.3%)			
Occupational dysfunction (past five years)					$\chi^2 = 64.26$	8	< 0.001
Always worked	8 (3.3%)	31 (15.4%)	14 (25.0%)	53 (10.7%)			
Periods of unemployment not related to illness	4 (1.7%)	8 (4.0%)	0 (0%)	12 (2.4%)			
Minor occupational dysfunction	36 (15.0%)	50 (24.9%)	7 (12.5%)	93 (18.7%)			
Moderate occupational dysfunction	38 (15.8%)	47 (23.4%)	9 (16.1%)	94 (18.9%)			
Severe occupational dysfunction	154 (64.2%)	65 (32.3%)	26 (46.4%)	245 (49.3%)			
Illness variables							

Diagnosis					χ^2 = 45.61	4	< 0.001
Schizoaffective, depressed	12 (5.0%)	1 (0.5%)	19 (15.2%)	32 (5.5%)			
Schizoaffective, bipolar	15 (6.2%)	1 (0.5%)	6 (4.8%)	22 (3.8%)			
Schizophrenia	214 (88.8%)	216 (99.1%)	100 (80.0%)	530 (90.8%)			
Age at onset, Mean ± SD	22.69 ± 6.14	23.49 ± 7.70	29.24 ± 11.51		*F* = 28.46	2, 575	< 0.001
Age at first treatment, Mean ± SD	23.45 ± 6.43	25.99 ± 10.59	29.73 ± 11.40		*F* = 18.66	2, 566	< 0.001
Illness duration (years)	17.94 ± 11.18	14.19 ± 10.72	19.00 ± 10.60		*F* = 10.03	2, 578	< 0.001
Duration of untreated psychosis (DUP) (years)	0.75 ± 2.45	2.35 ± 6.97	0.49 ± 2.38		*F* = 8.88	2, 566	< 0.001
Hospitalized (ever)	233 (97.1%)	91 (46.7%)	104 (93.7%)	428 (78.4%)	χ^2 = 180.69	2	< 0.001
Hospitalizations (lifetime)	8.44 ± 11.27	0.94 ± 1.68	5.25 ± 9.15		*F* = 40.95	2, 543	< 0.001
Substance use variables							
Alcohol abuse/dependence (lifetime)	60 (25.1%)	0 (0%)	0 (0%)	60 (11.7%)	χ^2 = 78.43	2	< 0.001
Cannabis abuse/dependence (lifetime)	74 (31.1%)	0 (0%)	1 (0.9%)	75 (14.6%)	χ^2 = 96.88	2	< 0.001
Other drug abuse/dependence (lifetime)	43 (18.1%)	0 (0%)	1 (0.9%)	44 (8.6%)	χ^2 = 51.25	2	< 0.001

[a] Sample size varies across variables due to exclusion of missing data

[b] Widowed individuals not included in marital status analysis (n=19)

Table 3-3S: Demographic and Clinical Characteristics of Affected Individuals (Males) by Site

Variable	**Australia**	**India**	**Sarawak**	**Total**	**Test statistic**	**df/df$_{err}$**	***P***
N [a]	580 (55.0%)	302 (28.6%)	173 (16.4%)	1055 (100%)			
Demographic variables							
Age, Mean ± SD	38.47 ± 11.59	38.16 ± 11.33	45.47 ± 14.60		*F* = 25.02	2, 1050	< 0.001
Marital status [b]					χ^2 = 109.39	4	< 0.001
Married	31 (5.4%)	83 (28.2%)	47 (28.7%)	161 (15.5%)			
Never married	478 (82.7%)	193 (65.7%)	95 (57.9%)	766 (73.9%)			
Separated/divorced	69 (11.9%)	18 (6.1%)	22 (13.4%)	109 (10.5%)			
Living arrangements					χ^2 = 382.11	6	< 0.001
Alone	237 (41.6%)	4 (1.5%)	7 (4.3%)	248 (24.6%)			
Facility	90 (15.8%)	14 (5.1%)	1 (0.6%)	105 (10.4%)			
Family	183 (32.1%)	251 (91.9%)	155 (94.5%)	589 (58.5%)			
Others	60 (10.5%)	4 (1.5%)	1 (0.6%)	65 (6.5%)			
Years of formal schooling,	10.93 ± 2.31	13.08 ± 3.16	6.59 ± 3.31		*F* = 204.27	2, 934	< 0.001

Mean ± SD							
Current employment status					χ^2 = 439.48	10	< 0.001
Disabled: formerly worked, no longer able	357 (61.8%)	82 (29.8%)	5 (3.5%)	444 (44.6%)			
Homemaker	0 (0%)	1 (0.4%)	2 (1.4%)	3 (0.3%)			
Never worked	154 (26.6%)	62 (22.6%)	3 (2.1%)	219 (22.0%)			
Student	6 (1.0%)	7 (2.6%)	0 (0%)	13 (1.3%)			
Unemployed	12 (2.1%)	41 (14.9%)	20 (14.0%)	73 (7.3%)			
Working	49 (8.5%)	82 (29.8%)	113 (79.0%)	244 (24.5%)			
Occupational dysfunction (past five years)					χ^2 = 119.50	8	< 0.001
Always worked	10 (1.7%)	37 (13.6%)	10 (11.2%)	57 (6.1%)			
Periods of unemployment not related to illness	2 (0.4%)	9 (3.3%)	0 (0%)	11 (1.2%)			
Minor occupational dysfunction	43 (7.4%)	53 (19.4%)	13 (14.6%)	109 (11.6%)			
Moderate occupational dysfunction	77 (13.3%)	51 (18.7%)	15 (16.9%)	143 (15.2%)			
Severe occupational dysfunction	446 (77.2%)	123 (45.1%)	51 (57.3%)	620 (66.0%)			
Illness variables							
Diagnosis					χ^2 = 74.42	4	< 0.001
Schizoaffective, depressed	12 (2.1%)	0 (0%)	19 (11.0%)	31 (2.9%)			
Schizoaffective, bipolar	17 (2.9%)	0 (0%)	13 (7.5%)	30 (2.8%)			
Schizophrenia	551 (95.0%)	302 (100.0%)	141 (81.5%)	994 (94.2%)			
Age at onset, Mean ± SD	21.85 ± 6.48	23.07 ± 7.53	29.06 ± 11.30		*F* = 57.54	2, 1048	< 0.001
Age at first treatment, Mean ± SD	22.79 ± 6.79	25.75 ± 9.75	29.25 ± 11.30		*F* = 40.73	2, 1038	< 0.001
Illness duration (years)	16.63 ± 10.46	15.07 ± 10.29	16.42 ± 9.70		*F* = 2.33	2, 1050	0.098
Duration of untreated psychosis (DUP) (years)	0.95 ± 2.88	2.82 ± 7.00	0.18 ± 1.42		*F* = 25.72	2, 1038	< 0.001
Hospitalized (ever)	554 (95.5%)	124 (46.6%)	151 (96.2%)	829 (82.7%)	χ^2 = 327.89	2	< 0.001
Hospitalizations (lifetime)	7.97 ± 11.03	1.06 ± 1.69	6.65 ± 8.25		*F* = 53.76	2, 1000	< 0.001
Substance use variables							
Alcohol abuse/dependence (lifetime)	273 (47.2%)	3 (1.3%)	28 (18.0%)	304 (31.4%)	χ^2 = 177.85	2	< 0.001
Cannabis abuse/dependence (lifetime)	298 (51.5%)	0 (0%)	1 (0.7%)	299 (30.9%)	χ^2 = 285.25	2	< 0.001
Other drug abuse/dependence (lifetime)	173 (29.9%)	0 (0%)	6 (3.9%)	179 (18.5%)	χ^2 = 125.14	2	< 0.001

[a] Sample size varies across variables due to exclusion of missing data

[b] Widowed individuals not included in marital status analysis (n=7)

Table 3-4S: Demographic and Clinical Characteristics of Affected Individuals by Age[a]

Variable	Old (>37 years)	Young (<38 years)	Total	Test statistic	df	*P*

N [b]	860 (52.7%)	773 (47.3%)	1633 (100%)			
Demographic variables						
Marital status [c]				χ^2 = 166.39	2	< 0.001
Married	234 (28.3%)	77 (10.1%)	311 (19.6%)			
Never married	429 (51.8%)	627 (82.4%)	1056 (66.5%)			
Separated/divorced	165 (19.9%)	57 (7.5%)	222 (14.0%)			
Living arrangements				χ^2 = 34.80	3	< 0.001
Alone	233 (28.1%)	115 (15.8%)	348 (22.3%)			
Facility	67 (8.1%)	75 (10.3%)	142 (9.1%)			
Family	492 (59.4%)	495 (67.9%)	987 (63.4%)			
Others	37 (4.5%)	44 (6.0%)	81 (5.2%)			
Years of formal schooling				χ^2 = 57.93	2	< 0.001
Primary (<9 years)	158 (21.8%)	57 (8.1%)	215 (15.1%)			
Secondary (9-12 years)	413 (56.9%)	427 (60.8%)	840 (58.8%)			
Tertiary (>12 years)	155 (21.4%)	218 (31.1%)	373 (26.1%)			
Current employment status				χ^2 = 44.02	5	< 0.001
Disabled: formerly worked, no longer able	313 (38.6%)	291 (40.1%)	604 (39.3%)			
Homemaker	59 (7.3%)	34 (4.7%)	93 (6.1%)			
Never worked	170 (21.0%)	176 (24.2%)	346 (22.5%)			
Student	2 (0.3%)	30 (4.1%)	32 (2.1%)			
Unemployed	52 (6.4%)	56 (7.7%)	108 (7.0%)			
Working	215 (26.5%)	139 (19.2%)	354 (23.0%)			
Occupational dysfunction (past five years)				χ^2 = 17.97	4	0.001
Always worked	67 (9.2%)	43 (6.1%)	110 (7.7%)			
Periods of unemployment not related to illness	12 (1.6%)	11 (1.6%)	23 (1.6%)			
Minor occupational dysfunction	90 (12.3%)	112 (15.9%)	202 (14.1%)			
Moderate occupational dysfunction	99 (13.5%)	138 (19.6%)	237 (16.5%)			
Severe occupational dysfunction	463 (63.3%)	402 (56.9%)	865 (60.2%)			
Illness variables						
Diagnosis				χ^2 = 2.87	2	0.238
Schizoaffective, depressed	39 (4.5%)	24 (3.1%)	63 (3.9%)			
Schizoaffective, bipolar	30 (3.5%)	22 (2.9%)	52 (3.2%)			
Schizophrenia	791 (92.0%)	727 (94.1%)	1518 (93.0%)			
Age at onset				χ^2 = 235.72	3	< 0.001
< 19 years	146 (17.1%)	298 (38.6%)	444 (27.3%)			
19 to 28 years	416 (48.6%)	427 (55.2%)	843 (51.8%)			
29 to 38 years	200 (23.4%)	48 (6.2%)	248 (15.2%)			
39+ years	94 (11.0%)	0 (0%)	94 (5.8%)			
Age at first treatment				χ^2 = 257.63	3	< 0.001
< 19 years	106 (12.5%)	238 (31.2%)	344 (21.4%)			
19 to 28 years	393 (46.5%)	457 (59.8%)	850 (52.8%)			
29 to 38 years	221 (26.1%)	69 (9.0%)	290 (18.0%)			

39+ years	126 (14.9%)	0 (0%)	126 (7.8%)			
Illness duration (years)				$\chi^2 = 436.28$	3	< 0.001
< 6 years	31 (3.6%)	222 (28.7%)	253 (15.5%)			
6 to 25 years	532 (62.0%)	551 (71.3%)	1083 (66.4%)			
26 to 45 years	282 (32.9%)	0 (0%)	282 (17.3%)			
46+ years	13 (1.5%)	0 (0%)	13 (0.8%)			
Duration of untreated psychosis (DUP) (years)				$\chi^2 = 45.98$	2	< 0.001
< 1 year	668 (79.0%)	550 (72.0%)	1218 (75.7%)			
1 to 4 years	99 (11.7%)	178 (23.3%)	277 (17.2%)			
5+ years	79 (9.3%)	36 (4.7%)	115 (7.1%)			
Hospitalized (ever)	682 (83.1%)	573 (78.9%)	1255 (81.1%)	$\chi^2 = 4.32$	1	0.038
Hospitalizations (lifetime)				$\chi^2 = 44.58$	4	< 0.001
None	139 (16.9%)	153 (21.1%)	292 (18.9%)			
One	105 (12.8%)	152 (20.9%)	257 (16.6%)			
2-3	167 (20.3%)	154 (21.2%)	321 (20.8%)			
4-9	223 (27.2%)	179 (24.7%)	402 (26.0%)			
10+	187 (22.8%)	88 (12.1%)	275 (17.8%)			
Substance use variables						
Alcohol abuse/dependence (lifetime)	168 (21.0%)	196 (28.8%)	364 (24.6%)	$\chi^2 = 12.02$	1	< 0.001
Cannabis abuse/dependence (lifetime)	118 (14.8%)	256 (37.7%)	374 (25.3%)	$\chi^2 = 101.78$	1	< 0.001
Other drug abuse/dependence (lifetime)	70 (8.8%)	153 (22.5%)	223 (15.1%)	$\chi^2 = 53.82$	1	< 0.001

[a] Age stratified into binary variable based on median age of sample (38 years)

[b] Sample size varies across variables due to exclusion of missing data

[c] Widowed individuals not included in marital status analysis (n=26)

Table 3-5S: Demographic and Clinical Characteristics of Affected Individuals by Site Controlling for Age (Old: Age > 37 Years)

Variable	**Australia**	**India**	**Sarawak**	**Total**	**Test statistic**	**df**	***P***
N [a]	423 (49.2%)	232 (27.0%)	205 (23.8%)	860 (100%)			
Demographic variables							
Marital status [b]					$\chi^2 = 133.55$	4	< 0.001
Married	43 (10.4%)	105 (47.1%)	86 (45.3%)	234 (28.3%)			
Never married	271 (65.3%)	89 (39.9%)	69 (36.3%)	429 (51.8%)			
Separated/divorced	101 (24.3%)	29 (13.0%)	35 (18.4%)	165 (19.9%)			
Living arrangements					$\chi^2 = 393.19$	6	< 0.001
Alone	220 (52.8%)	6 (2.7%)	7 (3.7%)	233 (28.1%)			
Facility	57 (13.7%)	9 (4.1%)	1 (0.5%)	67 (8.1%)			

Family	108 (25.9%)	203 (91.9%)	181 (94.8%)	492 (59.4%)			
Others	32 (7.7%)	3 (1.4%)	2 (1.1%)	37 (4.5%)			
Years of formal schooling					$\chi^2 = 276.16$	4	< 0.001
Primary (<9 years)	56 (13.4%)	29 (13.4%)	73 (79.4%)	158 (21.8%)			
Secondary (9-12 years)	299 (71.7%)	96 (44.2%)	18 (19.6%)	413 (56.9%)			
Tertiary (>12 years)	62 (14.9%)	92 (42.4%)	1 (1.1%)	155 (21.4%)			
Current employment status					$\chi^2 = 514.25$	10	< 0.001
Disabled: formerly worked, no longer able	260 (61.8%)	49 (22.3%)	4 (2.4%)	313 (38.6%)			
Homemaker	2 (0.5%)	43 (19.6%)	14 (8.2%)	59 (7.3%)			
Never worked	122 (29.0%)	43 (19.6%)	5 (2.9%)	170 (21.0%)			
Student	0 (0%)	2 (0.9%)	0 (0%)	2 (0.3%)			
Unemployed	8 (1.9%)	30 (13.6%)	14 (8.2%)	52 (6.4%)			
Working	29 (6.9%)	53 (24.1%)	133 (78.2%)	215 (26.5%)			
Occupational dysfunction (past five years)					$\chi^2 = 136.44$	8	< 0.001
Always worked	12 (2.9%)	35 (16.0%)	20 (22.0%)	67 (9.2%)			
Periods of unemployment not related to illness	3 (0.7%)	9 (4.1%)	0 (0%)	12 (1.6%)			
Minor occupational dysfunction	28 (6.7%)	50 (22.8%)	12 (13.2%)	90 (12.3%)			
Moderate occupational dysfunction	44 (10.5%)	40 (18.3%)	15 (16.5%)	99 (13.5%)			
Severe occupational dysfunction	334 (79.3%)	85 (38.8%)	44 (48.4%)	463 (63.3%)			
Illness variables							
Diagnosis					$\chi^2 = 61.47$	4	< 0.001
Schizoaffective, depressed	15 (3.6%)	0 (0%)	24 (11.7%)	39 (4.5%)			
Schizoaffective, bipolar	13 (3.1%)	0 (0%)	17 (8.3%)	30 (3.5%)			
Schizophrenia	395 (93.4%)	232 (100.0%)	164 (80.0%)	791 (92.0%)			
Age at onset					$\chi^2 = 98.07$	6	< 0.001
< 19 years	93 (22.0%)	39 (17.0%)	14 (6.9%)	146 (17.1%)			
19 to 28 years	237 (56.0%)	103 (44.8%)	76 (37.4%)	416 (48.6%)			
29 to 38 years	71 (16.8%)	68 (29.6%)	61 (30.1%)	200 (23.4%)			
39+ years	22 (5.2%)	20 (8.7%)	52 (25.6%)	94 (11.0%)			
Age at first treatment					$\chi^2 = 76.15$	6	< 0.001
< 19 years	70 (16.6%)	24 (10.9%)	12 (5.9%)	106 (12.5%)			
19 to 28 years	234 (55.5%)	84 (38.0%)	75 (37.0%)	393 (46.5%)			
29 to 38 years	90 (21.3%)	68 (30.8%)	63 (31.0%)	221 (26.1%)			
39+ years	28 (6.6%)	45 (20.4%)	53 (26.1%)	126 (14.9%)			
Illness duration (years)					$\chi^2 = 19.64$	6	0.003
< 6 years	10 (2.4%)	11 (4.7%)	10 (4.9%)	31 (3.6%)			
6 to 25 years	246 (58.2%)	147 (63.4%)	139 (68.5%)	532 (62.0%)			
26 to 45 years	161 (38.1%)	67 (28.9%)	54 (26.6%)	282 (32.9%)			
46+ years	6 (1.4%)	7 (3.0%)	0 (0%)	13 (1.5%)			
Duration of untreated psychosis (DUP) (years)					$\chi^2 = 77.73$	4	< 0.001
< 1 year	337 (79.9%)	137 (62.0%)	194 (95.6%)	668 (79.0%)			
1 to 4 years	55 (13.0%)	42 (19.0%)	2 (1.0%)	99 (11.7%)			
5+ years	30 (7.1%)	42 (19.0%)	7 (3.5%)	79 (9.3%)			
Hospitalized (ever)	406 (96.2%)	96 (45.1%)	180 (96.8%)	682 (83.1%)	$\chi^2 = 295.32$	2	< 0.001
Hospitalizations (lifetime)					$\chi^2 = 395.09$	8	< 0.001

None	16 (3.8%)	117 (54.9%)	6 (3.2%)	139 (16.9%)			
One	28 (6.6%)	44 (20.7%)	33 (17.7%)	105 (12.8%)			
2-3	81 (19.2%)	38 (17.8%)	48 (25.8%)	167 (20.3%)			
4-9	152 (36.0%)	11 (5.2%)	60 (32.3%)	223 (27.2%)			
10+	145 (34.4%)	3 (1.4%)	39 (21.0%)	187 (22.8%)			
Substance use variables							
Alcohol abuse/dependence (lifetime)	150 (35.7%)	3 (1.5%)	15 (8.1%)	168 (21.0%)	$\chi^2 = 117.87$	2	< 0.001
Cannabis abuse/dependence (lifetime)	117 (27.9%)	0 (0%)	1 (0.5%)	118 (14.8%)	$\chi^2 = 121.15$	2	< 0.001
Other drug abuse/dependence (lifetime)	68 (16.3%)	0 (0%)	2 (1.1%)	70 (8.8%)	$\chi^2 = 61.77$	2	< 0.001

[a] Sample size varies across variables due to exclusion of missing data

[b] Widowed individuals not included in marital status analysis (n=26)

Table 3-6S: Demographic and Clinical Characteristics of Affected Individuals by Site Controlling for Age (Young: Age < 38 Years)

Variable	**Australia**	**India**	**Sarawak**	**Total**	**Test statistic**	**df**	***P***
N [a]	398 (51.5%)	285 (36.9%)	90 (11.6%)	773 (100%)			
Demographic variables							
Marital status [b]					$\chi^2 = 64.07$	4	< 0.001
Married	13 (3.3%)	55 (19.8%)	9 (10.5%)	77 (10.1%)			
Never married	366 (92.2%)	194 (69.8%)	67 (77.9%)	627 (82.4%)			
Separated/divorced	18 (4.5%)	29 (10.4%)	10 (11.6%)	57 (7.5%)			
Living arrangements					$\chi^2 = 226.27$	6	< 0.001
Alone	114 (29.2%)	0 (0%)	1 (1.2%)	115 (15.8%)			
Facility	61 (15.6%)	14 (5.5%)	0 (0%)	75 (10.3%)			
Family	172 (44.1%)	241 (94.1%)	82 (98.8%)	495 (67.9%)			
Others	43 (11.0%)	1 (0.4%)	0 (0%)	44 (6.0%)			
Years of formal schooling					$\chi^2 = 183.71$	4	< 0.001
Primary (<9 years)	13 (3.3%)	22 (8.6%)	22 (39.3%)	57 (8.1%)			
Secondary (9-12 years)	295 (75.6%)	98 (38.3%)	34 (60.7%)	427 (60.8%)			
Tertiary (>12 years)	82 (21.0%)	136 (53.1%)	0 (0%)	218 (31.1%)			
Current employment status					$\chi^2 = 213.21$	10	< 0.001
Disabled: formerly worked, no longer able	214 (53.9%)	74 (28.8%)	3 (4.2%)	291 (40.1%)			
Homemaker	3 (0.8%)	29 (11.3%)	2 (2.8%)	34 (4.7%)			
Never worked	109 (27.5%)	59 (23.0%)	8 (11.1%)	176 (24.2%)			
Student	10 (2.5%)	20 (7.8%)	0 (0%)	30 (4.1%)			
Unemployed	13 (3.3%)	27 (10.5%)	16 (22.2%)	56 (7.7%)			
Working	48 (12.1%)	48 (18.7%)	43 (59.7%)	139 (19.2%)			
Occupational dysfunction (past five years)					$\chi^2 = 67.85$	8	< 0.001
Always worked	6 (1.5%)	33 (12.9%)	4 (7.4%)	43 (6.1%)			

Periods of unemployment not related to illness	3 (0.8%)	8 (3.1%)	0 (0%)	11 (1.6%)			
Minor occupational dysfunction	51 (12.9%)	53 (20.8%)	8 (14.8%)	112 (15.9%)			
Moderate occupational dysfunction	71 (17.9%)	58 (22.8%)	9 (16.7%)	138 (19.6%)			
Severe occupational dysfunction	266 (67.0%)	103 (40.4%)	33 (61.1%)	402 (56.9%)			
Illness variables							
Diagnosis					$\chi^2 = 66.59$	4	< 0.001
Schizoaffective, depressed	9 (2.3%)	1 (0.4%)	14 (15.6%)	24 (3.1%)			
Schizoaffective, bipolar	19 (4.8%)	1 (0.4%)	2 (2.2%)	22 (2.9%)			
Schizophrenia	370 (93.0%)	283 (99.3%)	74 (82.2%)	727 (94.1%)			
Age at onset [c]					*********	**	******
< 19 years	165 (41.5%)	107 (37.5%)	26 (28.9%)	298 (38.6%)			
19 to 28 years	215 (54.0%)	161 (56.5%)	51 (56.7%)	427 (55.2%)			
29 to 38 years	18 (4.5%)	17 (6.0%)	13 (14.4%)	48 (6.2%)			
39+ years	0 (0%)	0 (0%)	0 (0%)	0 (0%)			
Age at first treatment [c]					*********	**	******
< 19 years	133 (33.4%)	79 (28.6%)	26 (28.9%)	238 (31.2%)			
19 to 28 years	242 (60.8%)	164 (59.4%)	51 (56.7%)	457 (59.8%)			
29 to 38 years	23 (5.8%)	33 (12.0%)	13 (14.4%)	69 (9.0%)			
39+ years	0 (0%)	0 (0%)	0 (0%)	0 (0%)			
Illness duration (years) [c]					*********	**	******
< 6 years	94 (23.6%)	99 (34.7%)	29 (32.2%)	222 (28.7%)			
6 to 25 years	304 (76.4%)	186 (65.3%)	61 (67.8%)	551 (71.3%)			
26 to 45 years	0 (0%)	0 (0%)	0 (0%)	0 (0%)			
46+ years	0 (0%)	0 (0%)	0 (0%)	0 (0%)			
Duration of untreated psychosis (DUP) (years)					$\chi^2 = 43.45$	4	< 0.001
< 1 year	291 (73.1%)	173 (62.7%)	86 (95.6%)	550 (72.0%)			
1 to 4 years	95 (23.9%)	79 (28.6%)	4 (4.4%)	178 (23.3%)			
5+ years	12 (3.0%)	24 (8.7%)	0 (0%)	36 (4.7%)			
Hospitalized (ever)	381 (95.7%)	119 (48.0%)	73 (91.3%)	573 (78.9%)	$\chi^2 = 217.61$	2	< 0.001
Hospitalizations (lifetime)					$\chi^2 = 296.42$	8	< 0.001
None	17 (4.3%)	129 (52.0%)	7 (8.8%)	153 (21.1%)			
One	61 (15.3%)	67 (27.0%)	24 (30.0%)	152 (20.9%)			
2-3	98 (24.6%)	34 (13.7%)	22 (27.5%)	154 (21.2%)			
4-9	145 (36.4%)	18 (7.3%)	16 (20.0%)	179 (24.7%)			
10+	77 (19.4%)	0 (0%)	11 (13.8%)	88 (12.1%)			
Substance use variables							
Alcohol abuse/dependence (lifetime)	183 (46.0%)	0 (0%)	13 (16.3%)	196 (28.8%)	$\chi^2 = 145.60$	2	< 0.001
Cannabis abuse/dependence (lifetime)	255 (64.1%)	0 (0%)	1 (1.3%)	256 (37.7%)	$\chi^2 = 285.49$	2	< 0.001
Other drug abuse/dependence (lifetime)	148 (37.2%)	0 (0%)	5 (6.3%)	153 (22.5%)	$\chi^2 = 120.40$	2	< 0.001

[a] Sample size varies across variables due to exclusion of missing data

[b] Widowed individuals not included in marital status analysis (n=26)

[c] No statistics computed for these tables due to a row sum being zero.

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Chapter 4. Identifying Characteristic Symptom Profiles

McLean D, Barrett R, Loa P, Thara R, John S, McGrath J, Gratten J and Mowry B (2015) Comparing schizophrenia symptoms in the Iban of Sarawak with other populations to elucidate clinical heterogeneity. *Asia-Pacific Psychiatry* 7(1): 36-44.

Abstract

Introduction

The symptom profile of schizophrenia can vary between ethnic groups. We explored selected symptom variables previously reported to be characteristic of schizophrenia in the Iban of Sarawak in transethnic populations from Australia, India and Sarawak, Malaysia. We tested site differences to confirm previous research, and to explore implications of differences across populations for future investigations.

Methods

We recruited schizophrenia samples in Australia (n=609), India (n=310) and Sarawak (n=205) primarily for the purposes of genetic studies. We analyzed seven identified variables and their relationship to site using logistic regression, including: global delusions, bizarre delusions, thought broadcast/insertion/withdrawal delusions, global hallucinations, auditory hallucinations, disorganized behavior, and prodromal duration.

Results

We identified a distinct symptom profile in our Sarawak sample. Specifically, the Iban exhibit: low frequency of thought broadcast/insertion/withdrawal delusions, high frequency of auditory hallucinations and disorganized behavior, with a comparatively short prodrome when compared with Australian and Indian populations.

Discussion

Understanding between-site variation in symptom profile may complement future transethnic genetic studies, and provide important clues as to the nature of differing schizophrenia expression across ethnically distinct groups. A comprehensive approach to subtyping schizophrenia is warranted, utilizing comprehensively ascertained transethnic samples to inform both schizophrenia genetics and nosology.

Key words: psychotic disorders, schizophrenia, culture, diagnosis, population characteristics

Introduction

In the past, the syndrome of schizophrenia has been treated as a single entity diagnosed according to reliable, internationally accepted criteria consisting of symptoms, disability, duration, illness course, and exclusion of allied disorders (APA, 1994; WHO, 1992). However, there is now clear evidence that schizophrenia shares a genetic predisposition with bipolar disorder (ISC, 2009; Lichtenstein et al., 2009), which challenges the dichotomous view of functional psychosis (Craddock et al., 2009). There is currently little consensus on whether the latent structure of schizophrenia is best represented as a single (continuous) entity, with clinical variation represented as dimensions within a single class, or as two or more distinct, separate entities, with variation indicative of a number of distinct classes grouped under the label 'schizophrenia' (Fiedorowicz et al., 2008; Kendler et al., 1998; Linscott et al., 2009).

While the field has been mindful of within-group heterogeneity of schizophrenia, the between-group, transethnic differences in the phenotypes have received less scrutiny. Examination of transethnic schizophrenia samples provides an opportunity to elucidate differences in schizophrenia expression, which are important to a comprehensive understanding of this disorder (Kleinman, 1988).

Previous anthropological (Barrett, 2004) and psychiatric (Barrett et al., 2005) research on the Iban of Sarawak has proposed the following symptoms as characteristic of schizophrenia in that population: low rates of bizarre delusions, specifically thought broadcast, insertion and withdrawal delusions; and high rates of auditory hallucinations, disorganized behavior, restlessness and insomnia. Additionally, a comparatively short prodrome has been consistently noted in case review, particularly in comparison with other studied populations.

The Genetics Research group at the Queensland Centre for Mental Health Research (QCMHR) and our collaborators recruited three cohorts of individuals with psychosis for genetic analyses: European Australians (n=821); Tamil Brahmin and proximal caste groups from Tamil Nadu, India (n=520); and the Iban of Sarawak, Malaysia (n=298). In this paper, we examined nine variables previously associated with schizophrenia in the Iban, and compared the frequencies of these variables in the Iban sample with our Australian and Indian cohorts.

Our available Iban sample is an extension of the sample described in a previous publication (Barrett et al., 2005). Their sample included individuals with schizophrenia identified through an initial medical records screen (n=275). We recontacted and comprehensively assessed 122 of these individuals plus an additional 23 individuals who were primarily new cases diagnosed after the initial screen. Thus we increased both sample size (of included individuals with schizophrenia) and quality of clinical information available. We aimed to confirm the previous research proposing these characteristic symptoms, and explore the implications of differences across populations.

We hypothesized that (i) hallucinations (specifically auditory), disorganized behavior, sleep disturbance, and psychomotor changes would occur more frequently in the Iban than in samples derived from Australian or Indian populations; (ii) bizarre delusions (specifically broadcast, insertion and withdrawal delusions) would occur less frequently in the Iban than in Australia or India; and (iii) the prodrome would be shorter in the Iban than in Australia or India.

Methods

Sample details

Sample recruitment across sites and clinical ascertainment are detailed elsewhere (see McLean et al., 2012). Briefly, recruitment at each site involved: Australia – sibling pairs and unrelated individuals were recruited as part of a major US/Australian collaboration (Molecular Genetics of Schizophrenia [MGS] Consortium) from multiple sources, including local treatment facilities, physician referrals, community organizations, supported accommodation facilities and advertisements; India – sibling pairs, trios and unrelated individuals were identified and invited to participate through The Schizophrenia Research Foundation India (SCARF); and Sarawak – Iban individuals were identified through Malaysian census data, an initial medical records assessment was undertaken, then a subset of individuals and families were contacted for in-depth follow-up. We included all individuals with a Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (APA, 1994) diagnosis of schizophrenia or schizoaffective disorder who met the (self-reported) ethnicity inclusion criterion. Ethnicity was subsequently confirmed through genetic analysis (Australia: Shi et al., 2009; India and Sarawak: manuscripts in preparation). Exclusion criteria for individuals were: (i) inability to give informed consent; (ii) psychosis assessed as secondary to substance use or a neurological disorder; and (iii) severe intellectual disability. Informed consent was obtained across all sites, and local

Institutional Ethics Committee approval was obtained for each study. This research conforms to the provisions of the Declaration of Helsinki (as revised in Edinburgh 2000).

Clinical ascertainment

Clinical ascertainment included five elements.

(i) Trained clinicians used the semi-structured Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994) to obtain DSM-IV relevant diagnostic information.

(ii) A family informant, when possible, or the proband was interviewed about the family psychiatric history using the Family Interview for Genetic Studies (FIGS) (Gershon et al., 1988; Maxwell, 1992). The cultural equivalence of the DIGS and FIGS was extensively addressed by the chief investigators at the three sites, and each instrument was translated into Iban (Sarawak) and Tamil (India) with appropriate back-translation procedures.

(iii) All available medical records were retrieved for each participant and assessed by trained clinicians.

(iv) A trained clinician prepared a case summary based on all available information, which facilitated diagnostic review.

(v) DIGS interview, case summary, available medical records, and FIGS reports formed the basis for diagnostic review. Diagnoses were assigned using the Best Estimate Final Diagnosis (BEFD) procedure (Leckman et al., 1982), with two experienced psychiatrists independently reviewing all available information then conferring to assign a consensus diagnosis. Approximately half the Sarawak sample had diagnoses formulated by one experienced psychiatrist, with a BEFD generated in a random subset (20 cases).

Inter-rater reliability was assessed within the Australian/US sample (Shi et al., 2009; Suarez et al., 2006); within the Indian sample (Thara et al., 2009); within the Sarawak sample; between the Australian and Indian samples (disagreement in one of 20 cases; κ=0.886); and between the Australian and Sarawak samples (disagreement in one of 20 cases; κ=0.828). One psychiatrist (BM) was a Principal Investigator on all studies, and has reviewed all included cases.

Data analysis

We analyzed nine clinical variables identified in previous research: (i) lifetime delusions; (ii) bizarre delusions; (iii) delusions of thought broadcast, insertion or withdrawal; (iv) lifetime hallucinations; (v) auditory hallucinations; (vi) lifetime disorganized or catatonic motor

behavior; (vii) sleep disturbance; (viii) psychomotor changes; and (ix) length of prodromal period. We also included the following potentially confounding variables: (x) sex; (xi) age; and (xii) presence of lifetime major depressive episodes.

Prodromal duration was obtained from all available information (DIGS interview, case summary, medical records, FIGS reports), and was assessed as the period between when social and/or occupational decline was first observed and when definite psychotic symptoms were first recorded. It was coded as dichotomous: rapid=onset within 4 weeks; gradual=onset longer than 4 weeks. Two outcome variables (sleep disturbance and psychomotor changes) were dropped from the model due to a lack of statistical equivalence across sites, after the preliminary models exhibited unacceptable levels of overdispersion and failure to converge.

Sources of data were audited (both electronic and hard copy), and all potential cases were identified for whom comprehensive diagnostic information was available. Data were extracted from diagnostic interview databases, where possible, then responses were checked, corrected, and missing values retrieved from all available sources, including a detailed review of all narrative summaries.

Due to the potential confounding effect of including both related and unrelated individuals in our sample, we selected a conservative model. Individuals within families may be more similar with regard to demographic and symptom characteristics than unrelated individuals owing to shared socioeconomic and environmental circumstances. Given that between-site similarities and differences across these variables were a focus of this study, and the degree of inter-relatedness differed across sites, we included only unrelated individuals, with a single individual randomly selected from each of the 1124 families across the three sites.

Outcome variables were then assessed individually by logistic regression, fitting site, presence of lifetime depressive episode(s), age, and sex as explanatory variables, plus all second level effects (e.g. site-by-sex) for these variables. We performed model simplification based on AIC, with the least significant effect being removed from the model at each iteration, until all remaining effects were significant. The minimal adequate model is presented for each outcome variable. Statistical analyses used Proc Logistic in SAS

software, version 9.3 for Windows (SAS Institute Inc.). We used Bonferroni correction to account for multiple testing.

The present study was drawn from 1831 individuals from Australia (*n*=821), India (*n*=524) and Sarawak (*n*=486). We excluded 192 individuals because their DSM-IV diagnosis was a psychotic disorder other than schizophrenia or schizoaffective disorder (Australia, *n*=0; India, *n*=4; Sarawak, *n*=188). Of the resulting 1639 individuals we then excluded all individuals with missing data for any of the eleven variables (seven outcome, four explanatory) of interest (Australia, *n*=136; India, *n*=24; Sarawak, *n*=62), leaving 1417 individuals from 1124 independent families. One individual from each family was randomly selected to constitute the final sample of 1124 individuals (Australia, *n*=609; India, *n*=310; Sarawak, *n*=205). DIGS and FIGS data were available for over 90% of participants in Australia and India, and approximately 50% of participants in Sarawak. Case summaries were available for over 90% of participants in Australia and Sarawak, and for over 75% of participants in India. Best-estimate final diagnoses were available for all participants across the three sites (except as previously noted).

Results

A summary of symptom variable frequencies by site, including all outcome and explanatory variables, is provided in table 4-1.

Table 4-1: Demographic and symptom characteristics of affected individuals by site †

Variable	Australia	India	Sarawak	Total
N	609 (54.2%)	310 (27.6%)	205 (18.2%)	1124 (100%)
Demographic variables				
Age, Mean ± SD	38.95 ± 11.55	36.57 ± 11.37	47.19 ± 14.67	39.80 ± 12.66
Sex				
Female	173 (28.4%)	128 (41.3%)	85 (41.5%)	386 (34.3%)
Male	436 (71.6%)	182 (58.7%)	120 (58.5%)	738 (65.7%)
Symptom variables				
Diagnosis				
Schizoaffective, depressed	22 (3.6%)	1 (0.3%)	30 (14.6%)	53 (4.7%)
Schizoaffective, bipolar	26 (4.3%)	0 (0%)	16 (7.8%)	42 (3.7%)
Schizophrenia	561 (92.1%)	309 (99.7%)	159 (77.6%)	1029 (91.6%)
Onset type				
Rapid (4 weeks or less)	109 (17.9%)	70 (22.6%)	90 (43.9%)	269 (23.9%)
Gradual (longer than 4 weeks)	500 (82.1%)	240 (77.4%)	115 (56.1%)	855 (76.1%)
Presence of any delusions (lifetime)	599 (98.3%)	283 (91.3%)	164 (80.0%)	1046 (93.1%)
Presence of bizarre delusions (lifetime)	410 (67.3%)	113 (36.5%)	40 (19.5%)	563 (50.1%)
Presence of thought broadcast/insertion/withdrawal delusions (lifetime)	322 (52.9%)	44 (14.2%)	22 (10.7%)	388 (34.5%)
Presence of any hallucinations (lifetime)	566 (92.9%)	253 (81.6%)	194 (94.6%)	1013 (90.1%)
Presence of auditory hallucinations (lifetime)	551 (90.5%)	244 (78.7%)	192 (93.7%)	987 (87.8%)
Presence of disorganized behavior (lifetime)	464 (76.2%)	244 (78.7%)	177 (86.3%)	885 (78.7%)
Presence of major depressive episode(s) (lifetime)	261 (42.9%)	9 (2.9%)	44 (21.5%)	314 (27.9%)

† One affected family member randomly generated from each family included in the sample.

A summary of the logistic regression performed is provided in table 4-2, with associated odds ratios and 95% confidence intervals provided in table 4-3.

Table 4-2: Logistic regression showing predictors of the presence of identified characteristic Iban symptoms †

Outcome Variable	Explanatory Variables ‡	DF	Wald X^2	P-value §
Global Delusions				
	Intercept	**1**	**19.85**	**<0.0001*** **
	Site	**2**	**23.78**	**<0.0001*** **
	Age	1	0.84	0.36
	Major depressive episodes	1	7.59	0.006**
	Age by Site	2	4.62	0.10
Bizarre Delusions				
	Intercept	1	7.77	0.005**
	Site	**2**	**38.67**	**<0.0001*** **
	Age	**1**	**16.56**	**<0.0001*** **
	Sex	1	3.56	0.06
	Age by Site	2	9.63	0.008**
	Sex by Site	2	5.17	0.08
Broadcast/Insertion/Withdrawal Delusions				
	Intercept	**1**	**19.09**	**<0.0001*** **
	Site	**2**	**65.97**	**<0.0001*** **
	Age	1	10.57	0.001**
	Major depressive episodes	1	2.57	0.11
	Age by Site	2	6.38	0.041*
Global Hallucinations				
	Intercept	**1**	**51.18**	**<0.0001*** **
	Site	**2**	**24. 24**	**<0.0001*** **
	Age	1	4.82	0.028*
	Sex	1	5.68	0.017*
	Major depressive episodes	1	0.96	0.33
	Sex by Major depressive episodes	1	4.31	0.038*
Auditory Hallucinations				
	Intercept	**1**	**90.76**	**<0.0001*** **
	Site	**2**	**65.40**	**<0.0001*** **
	Age	1	4.89	0.027*
	Sex	1	0.16	0.69
	Sex by Site	2	9.39	0.009**
Disorganized Behavior				
	Intercept	**1**	**60.33**	**<0.0001*** **
	Site	2	6.38	0.041*
	Age	1	3.10	0.08
	Major depressive episodes	1	3.46	0.06
Rapid Onset Type				
	Intercept	1	2.52	0.11
	Site	**2**	**43.03**	**<0.0001*** **
	Age	1	10.56	0.001**
	Sex	1	6.90	0.009**
	Major depressive episodes	1	1.42	0.23
	Age by Site	2	5.18	0.08
	Sex by Site	2	5.96	0.05
	Age by Sex	1	8.06	0.005**
	Sex by Major depressive episodes	1	2.81	0.09

* p<0.05 ** p<0.01 *** p<0.001

† Iteration with best AIC (model fit) that passes overdispersion test shown for each outcome variable

‡ Odds ratios and 95% confidence intervals for relevant effect combinations presented as Table 3

§ Effects surpassing Bonferroni correction shown in bold

Table 4-3: Odds ratios and 95% confidence intervals for all variable combinations presented in Table 4-2

Outcome Variable	Explanatory Variable Combinations	Estimate (95% CI)
Global Delusions		
	Site (Australia vs. India) at mean age	5.06 (1.94 – 13.18)
	Site (Australia vs. Sarawak) at mean age	15.57 (6.17 – 39.32)
	Site (India vs. Sarawak) at mean age	3.08 (1.71 – 5.57)

	Age in Australia	0.21 (0.04 – 1.05)
	Age in India	0.22 (0.09 – 0.52)
	Age in Sarawak	0.70 (0.33 – 1.49)
	No major depressive episodes vs. one or more major depressive episodes	0.26 (0.10 – 0.68)
Bizarre Delusions		
	Site (Australia vs. India) at mean age, males	3.64 (2.40 – 5.54)
	Site (Australia vs. Sarawak) at mean age, males	11.91 (6.32 – 22.43)
	Site (India vs. Sarawak) at mean age, males	3.27 (1.64 – 6.51)
	Site (Australia vs. India) at mean age, females	4.40 (2.53 – 7.65)
	Site (Australia vs. Sarawak) at mean age, females	4.61 (2.31 – 9.18)
	Site (India vs. Sarawak) at mean age, females	1.05 (0.50 – 2.18)
	Age in Australia	0.73 (0.50 – 1.07)
	Age in India	0.49 (0.28 – 0.88)
	Age in Sarawak	0.17 (0.07 – 0.39)
	Sex (Male vs. Female) in Australia	1.15 (0.76 – 1.74)
	Sex (Male vs. Female) in India	1.39 (0.81 – 2.38)
	Sex (Male vs. Female) in Sarawak	0.44 (0.19 – 1.03)
Broadcast/ Insertion/ Withdrawal Delusions		
	Site (Australia vs. India) at mean age	6.29 (4.08 – 9.70)
	Site (Australia vs. Sarawak) at mean age	9.15 (5.09 – 16.44)
	Site (India vs. Sarawak) at mean age	1.45 (0.74 – 2.85)
	Age in Australia	0.65 (0.46 – 0.93)
	Age in India	0.79 (0.37 – 1.71)
	Age in Sarawak	0.15 (0.05 – 0.47)
	No major depressive episodes vs. one or more major depressive episodes	0.76 (0.54 – 1.06)
Global Hallucinations		
	Site (Australia vs. India)	3.58 (2.00 – 6.39)
	Site (Australia vs. Sarawak)	0.73 (0.32 – 1.66)
	Site (India vs. Sarawak)	0.20 (0.09 – 0.47)
	Age	0.58 (0.35 – 0.94)
	Sex (Male vs. Female), no major depressive episodes	0.46 (0.25 – 0.87)
	Sex (Male vs. Female) , one or more major depressive episodes	1.68 (0.59 – 4.74)
	Depressive episodes (none vs. one or more), males	0.66 (0.29 – 1.52)
	Depressive episodes (none vs. one or more), females	2.39 (0.89 – 6.40)
Auditory Hallucinations		
	Site (Australia vs. India), males	3.73 (2.61 – 5.34)
	Site (Australia vs. Sarawak), males	0.58 (0.31 – 1.10)
	Site (India vs. Sarawak), males	0.16 (0.08 – 0.30)
	Site (Australia vs. India), females	1.47 (0.86 – 2.50)
	Site (Australia vs. Sarawak), females	0.62 (0.30 – 1.30)
	Site (India vs. Sarawak), females	0.43 (0.20 – 0.90)
	Age	0.72 (0.54 – 0.96)
	Sex (Male vs. Female) in Australia	1.12 (0.72 – 1.76)
	Sex (Male vs. Female) in India	0.44 (0.28 – 0.70)
	Sex (Male vs. Female) in Sarawak	1.19 (0.50 – 2.83)
Disorganized Behavior		
	Site (Australia vs. India)	0.96 (0.67 – 1.38)
	Site (Australia vs. Sarawak)	0.57 (0.36 – 0.89)
	Site (India vs. Sarawak)	0.59 (0.36 – 0.97)
	Age	1.31 (0.97 – 1.76)
	Depressive episodes (none vs. one or more)	1.38 (0.98 – 1.94)
Rapid Onset Type		
	Site (Australia vs. India) at mean age, males	0.80 (0.50 – 1.29)
	Site (Australia vs. Sarawak) at mean age, males	0.20 (0.13 – 0.32)
	Site (India vs. Sarawak) at mean age, males	0.25 (0.15 – 0.43)
	Site (Australia vs. India) at mean age, females	0.34 (0.17 – 0.68)
	Site (Australia vs. Sarawak) at mean age, females	0.23 (0.12 – 0.43)
	Site (India vs. Sarawak) at mean age, females	0.66 (0.35 – 1.23)
	Age, males in Australia	0.66 (0.42 – 1.05)
	Age, males in India	0.88 (0.46 – 1.67)
	Age, males in Sarawak	0.36 (0.19 – 0.66)
	Age, females in Australia	1.62 (0.88 – 2.99)
	Age, females in India	2.15 (1.14 – 4.07)
	Age, females in Sarawak	0.87 (0.43 – 1.73)
	Sex (Male vs. Female) at mean age, no major depressive episodes in Australia	1.59 (0.83 – 3.04)
	Sex (Male vs. Female) at mean age, no major depressive episodes in India	0.68 (0.39 – 1.17)
	Sex (Male vs. Female) at mean age, no major depressive episodes in Sarawak	1.76 (0.95 – 3.25)

Sex (Male vs. Female) at mean age, one or more major depressive episodes in Australia	0.84 (0.48 – 1.47)
Sex (Male vs. Female) at mean age, one or more major depressive episodes in India	0. 36 (0.15 – 0.88)
Sex (Male vs. Female) at mean age, one or more major depressive episodes in Sarawak	0.93 (0.42 – 2.07)
Depressive episodes (none vs. one or more), males	0.77 (0.50 – 1.18)
Depressive episodes (none vs. one or more), females	0.41 (0.22 – 0.75)

Each of the seven outcome variables had significant site effects, while all outcome variables except global delusions and disorganized behavior had significant age effects. Both lifetime hallucinations and length of prodrome had significant sex effects, whereas only lifetime delusions had a significant depressive episode(s) effect.

Multiple testing correction

The site effect for six of the seven outcome variables remained significant using a Bonferroni corrected p-value=0.0007, with only the disorganized behavior effect (p=0.041) failing to reach this threshold. Age remained significant for bizarre delusions, with younger individuals having greater odds of reporting bizarre delusions. No other effects remained significant for any of the outcome variables.

Discussion

Consistent with previous reports (Barrett, 2004; Barrett et al., 2005), we found that individuals with schizophrenia from the Iban sample differed on key symptom variables. In addition, we identified a range of differences for these variables between the Iban, Australia and India.

Delusions

While the proportion of individuals reporting bizarre delusions and delusions of thought broadcast, insertion and withdrawal was lowest in the Iban, it is noteworthy that the frequencies in India were also low in contrast to Australia, and that India and Sarawak were similar in their reported frequencies of broadcast/insertion/withdrawal delusions (India 14.2%; Sarawak 10.7%). The difficulty of assessing bizarreness of beliefs is widely recognized (Kendler et al., 1983), particularly across cultures (APA, 1994). Moreover, the greater frequency of Schneiderian first-rank symptoms reported in Western populations has been attributed to bizarre experiences in Western cultures being considered normative in non-Western cultures (Barrett, 2004). However, several alternative explanations for these cross-cultural differences have also been proposed (for a summary see Barrett, 2004).

Younger individuals had significantly greater odds of experiencing lifetime bizarre delusions, after correction for multiple testing. This somewhat counter-intuitive result may reflect recall bias, with an under-reporting of bizarre delusions in older individuals, since age has been associated with decreased occurrence of delusions and hallucinations (Schultz et al., 1997).

Hallucinations

Auditory hallucinations were, as expected, reported most frequently in the Iban, although rates of both lifetime hallucinations and auditory hallucinations did not differ between Sarawak (lifetime 94.6%; auditory 93.7%) and Australia (lifetime 92.9%; auditory 90.5%), with Indian rates (lifetime 81.6%; auditory 78.7%) significantly lower. A 'striking resemblance' in the appearance of auditory hallucinations, between Australian and Iban samples with schizophrenia, has been noted (Barrett, 2004). This finding offers an interesting contrast to our delusion finding, in that any explanation relying on Western/non-Western cultural norms explaining site differences is not sufficient to explain the significant difference in rates of auditory hallucinations between the non-Western cultures of India and Sarawak.

Disorganized behavior

The frequency of disorganized behavior was marginally higher in the Iban (86.3%) than in Australia (76.2%) or India (78.7%), although this site difference was non-significant after correction for multiple testing.

Onset type

The clear site difference regarding greater frequency of rapid onset in Sarawak (43.9%) in contrast to Australia (17.9%) and India (22.6%) is of particular interest. A later age of onset (~6 years) finding in the Iban compared with Australia and India has been previously reported (McLean et al., 2012), yet the greater proportion of Iban individuals with rapid onset type is equally stark. Because the majority of Iban live with close family contact, and there is a societal propensity to seek early medical treatment (Barrett et al., 2005), early changes in behavior would likely be readily noted; thus, a longer reported prodrome may be expected, with social/occupational decline prior to psychosis onset identified more readily than in other populations. Clearly, the data do not support this. Alternatively, help-seeking behavior may prompt earlier diagnosis, truncating the period regarded as

prodromal, with definite psychosis detected earlier in the Iban, in contrast to other populations, where later detection may 'artificially' lengthen the period regarded as prodromal. Cultural considerations may also be fundamental to the identified site difference: e.g. the Iban may be more tolerant of aberrant behavior than other societies, and may not rate atypical behavior as 'prodromal' until immediately prior to recognition of definite psychosis.

Cultural considerations

Categorization of research participants by ethnicity and/or culture is problematic and highly contested (Egede, 2006; Ma et al., 2007). The fact that our cohorts are both ethnically homogeneous and geographically constrained enables assessment of cultural confounders because these two factors represent the best available proxy for culture (Azuonye, 1994). Our sample is large for a transethnic comparative schizophrenia study (*n*=1124), individuals were assessed using the same battery of instruments, and individuals were diagnosed using the best-estimate final diagnosis method, which offers consistently high diagnostic reliability and stability (Beckmann et al., 1996; Calkins et al., 2007), and is the benchmark method available with current methods of classifying schizophrenia (McLean et al., 2012). We assessed ethnicity by self-report, which is considered the research 'gold standard' in transcultural research (Ma et al., 2007). Furthermore, we ascertained birthplace for individuals' parents and grandparents, confirmed ethnic homogeneity genetically, and interviewed individuals in their home countries using local interviewers. These measures avoid many confounding factors frequently experienced in cross-cultural research, which can limit generalizability of findings (McKenzie and Crowcroft, 1996a, 1996b).

Methodological limitations

First, a lack of measurement equivalence was unavoidable. The samples were collected for specific genetic studies, thus there were differences in selection methods of included individuals. Both the Indian and Sarawak samples were chosen from ethnically homogeneous populations, whereas the Australian sample was not specifically recruited as such (although we did focus on Caucasian ethnicity). Furthermore, the Australian and Indian cohorts included sib-pairs as well as unrelated individuals recruited opportunistically, while only the Sarawak sample can be considered relatively epidemiologically sound (Barrett et al., 2005). As previously noted, we negated any effect of familial relatedness in our model by randomly selecting one individual per family for

analyses. The different recruitment methods also resulted in DIGS and FIGS data being unavailable for approximately half the Sarawak sample (see McLean et al., 2012).

Second, caution must always be exercised when using diagnostic instruments across cultures, since converting thoughts, feelings, and concepts such as bizarreness across languages can be difficult (Barrett, 2004). Consequently, we addressed cultural equivalence extensively in the preliminary planning for the studies (for a cultural equivalence framework see Herdman et al., 1998). We also employed state-of-the-art methods, translating and back-translating the DIGS, and using local interviewers who interviewed in the native language across the three sites, and recorded responses in Iban (Sarawak) and English (India and Australia). The reliability of the instrument (inter-rater reliability within and across the samples) was also tested across sites, although diagnostic inter-rater reliability was not assessed between India and Sarawak.

Third, the generalizability of our findings is limited, particularly given that both the Iban in Malaysia and the Tamil Brahmin and other geographically proximal castes in India are homogeneous groups within diverse societies. Furthermore, we did not specifically collect socioeconomic data across our samples, which further limits the generalizability of any findings attributed to ethnicity/culture, as socioeconomic position has been proposed as a stronger determinant of health outcomes than ethnicity (Egede, 2006).

Fourth, utilizing a sample of individuals meeting the DSM-IV criteria for either schizophrenia or schizoaffective disorder to study the nature of psychosis and/or schizophrenia itself may be problematic, in that we are not able to make comparisons with other DSM-IV diagnoses such as bipolar disorder, which would give a ‘broader perspective’. Furthermore, restricting the sample to those meeting DSM-IV schizophrenia criteria excludes cases with psychosis demonstrating the most clinical variation; these may be important to cultural understanding of psychosis (Kleinman, 1988).

Finally, because the samples were collected for specific genetic studies, there are limitations to the assumptions and generalizations we can make regarding difficult-to-quantify culturally-sensitive concepts such as length of prodrome, notwithstanding our extensive cross-cultural equivalence work and use of carefully ascertained ethnicity as our distinguishing factor between sites. In order to validate and interpret our finding of significantly shorter prodrome in Sarawak, further qualitative in-depth interviews

specifically addressing cultural interpretations of illness progression and associated concepts across sites should be undertaken. This follow-up research, while worthwhile, was beyond the scope of this study.

Conclusions

We have observed significant differences in the frequency of symptoms of schizophrenia across three ethnically different populations. A comprehensive search for clinical subtypes using ethnically distinct populations is warranted, as this may contribute to our understanding of between-group clinical variation, which may not only benefit future genetic studies, but also inform the ongoing nosological debate regarding schizophrenia.

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Declaration of Interest

No conflicts declared.

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Chapter 5. DSM-IV “criterion A” schizophrenia symptoms across ethnically different populations: evidence for differing psychotic symptom content or structural organization?

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Abstract

There is significant variation in the expression of schizophrenia across ethnically different populations, and the optimal structural and diagnostic representation of schizophrenia are contested. We contrasted both lifetime frequencies of DSM-IV criterion A (the core symptom criterion of the internationally recognized DSM classification system) symptoms and types/content of delusions and hallucinations in transethnic schizophrenia populations from Australia (n=776), India (n=504) and Sarawak, Malaysia (n=259), to elucidate clinical heterogeneity. Differences in both criterion A symptom composition and symptom content were apparent. Indian individuals with schizophrenia reported negative symptoms more frequently than other sites, whereas individuals from Sarawak reported disorganized symptoms more frequently. Delusions of control and thought broadcast, insertion or withdrawal were less frequent in Sarawak than Australia. Curiously, a subgroup of 20 Indian individuals with schizophrenia reported no lifetime delusions or hallucinations. These findings potentially challenge the long-held view in psychiatry that schizophrenia is fundamentally similar across cultural groups, with differences in only the content of psychotic symptoms, but equivalence in structural form.

Key words: psychotic disorders, culture, diagnosis, taxonomy

Introduction/Background

Schizophrenia is often treated as a discrete diagnostic entity based on widely-used and reliable criteria consisting of symptoms, duration, illness course, and exclusion of allied disorders (APA, 1994; WHO, 1992). However, schizophrenia shares a genetic predisposition with bipolar disorder (ISC, 2009; Lichtenstein, et al., 2009; Mowry and Gratten, 2013), which challenges the dichotomous view of functional psychosis (Craddock, et al., 2009). There is contention regarding the optimal representation of schizophrenia's structure: (1) a single (continuous) entity, with clinical variation represented as dimensions within a single class, or (2) two or more distinct, separate entities, with variation indicative of multiple classes grouped under the label "schizophrenia" (Fiedorowicz, et al., 2008; Kendler, et al., 1998; Linscott, et al., 2009).

Examination of the variation in schizophrenia expression across cultures may help clarify the complex nature of this disorder (Kleinman, 1988; Thakker and Ward, 1998). Whereas transethnic samples have been traditionally used to validate mainstream diagnostic criteria (Thakker and Ward, 1998), they provide an opportunity to examine differences in schizophrenia expression, as well as commonalities, both of which are important to a comprehensive nosological understanding (Alarcon et al., 2009; Kleinman, 1988).

While many transcultural psychiatry studies have sought to understand the expression of schizophrenia across cultures (e.g. the World Health Organization's groundbreaking Cross-Cultural Research Program (Jablensky et al., 1992)), they have implicitly favoured the prevailing view (Linscott et al., 2009) that schizophrenia is universal: it has similar manifestations in all cultures (Thakker and Ward, 1998). This view, consistent with the pathoplastic model favoured in Western psychiatry (Kulhara and Chakrabarti, 2001), contends that schizophrenia is fundamentally similar across cultural groups, with differences expressed only in the content (e.g. demons, government conspiracy) of symptoms, not the underlying cause and structure (Kleinman, 1988; Kulhara and Chakrabarti, 2001). The WHO International Pilot Study of Schizophrenia (IPSS) and the follow-up Determinants of Outcome of Severe Mental Disorder Project (DOSMeD) reported similar symptom profiles in all centers, although the DOSMeD noted important differences in the frequencies of traditional schizophrenia subtypes (utilizing ICD-9 (WHO, 1977)) across international sites. The acute subtype was reported almost twice as often (~40%) in developing countries as the paranoid subtype (~23%), in contrast with developed countries where the paranoid subtype (~34%) was diagnosed three times as

often as the acute subtype (~11%). Hebephrenic schizophrenia was more commonly diagnosed in developed counties (~13% developed vs. ~4% developing), whereas catatonic schizophrenia was more commonly diagnosed in developing countries (~1% developed vs. ~10% developing) (Sartorius et al., 1986). However, these studies widely reported similarities between sites, while differences received only a brief mention (Kleinman, 1988). Data indicating symptom differences deserve as much credence as data indicating broad similarities (Thakker and Ward, 1998).

A necessary (but not sufficient) diagnostic component of schizophrenia (and schizoaffective disorder) in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (APA, 1994) is criterion A, which comprises five symptom types: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms. Two or more of these are required for a diagnosis of schizophrenia (unless bizarre delusions or auditory hallucinations containing commentary or third person conversations are present, when one is sufficient) (for full details see APA, 1994).

The five criterion A symptoms align well with three well established dimensions (see Fiedorowicz et al., 2008): positive – delusions and hallucinations; negative – negative symptoms; and disorganized – disorganized speech and grossly disorganized or catatonic behavior. These dimensions form the basis for three corresponding syndromes within the schizophrenia diagnosis, which have been isolated using factor analysis in multiple cultures (e.g. Arora et al., 1997; Gureje et al., 1995), providing strong evidence for their cross-cultural robustness (Kulhara and Chakrabarti, 2001).

Similarities in the prevalence of different criterion A symptom types between groups would generally support schizophrenia having a continuous structure (similar organization of underlying symptoms). Significant differences in criterion A composition across sites, however, would potentially suggest multiple classes within the schizophrenia diagnosis (differences in underlying structural organization), given both genetic evidence for latent classes within the broad schizophrenia diagnosis evident in distinct ethnic groups (e.g. Holliday et al., 2009), and the current lack of biological confirmation of common etiology. Holliday et al. (2009) reported genomewide significant linkage of a deficit subtype (identified by latent class analysis), characterized by moderate to severe negative symptoms, prominent disorganization, and marked to severe functional impairment, in a

Han Chinese schizophrenia sample (n=606 affected sibling pair pedigrees; >1200 schizophrenia cases). This linked chromosomal region, previously implicated in schizophrenia pathogenesis, was not detected when the traditional DSM-IV schizophrenia diagnosis was used in the analysis.

The Genetics Research group at the Queensland Centre for Mental Health Research (QCMHR) and our collaborators recruited three cohorts of individuals with schizophrenia and related conditions for genetic analyses: European Australians (n=821); Tamil Brahmin and proximal caste groups from Tamil Nadu, India (n=520); and the Iban of Sarawak, Malaysia (n=298). We examined symptom organization and content in these three ethnically distinct populations in two ways: (1) we contrasted frequencies of the five DSM-IV criterion A schizophrenia symptoms by site, and (2) we contrasted frequencies of delusion and hallucination content by site, with a particular focus on Schneiderian First Rank Symptoms (FRS) (see Mellor, 1970), since the cross-cultural applicability of FRS has been questioned (Barrett, 2004), specifically in the Iban.

Much of the trans-ethnic schizophrenia research since the WHO's Cross-Cultural Research Program (Sartorius, 2007) has involved migrant groups within countries (e.g. Cantor-Graae and Selten, 2005; Fearon et al., 2006), with few recent studies contrasting core components of diagnostic classification across multiple international sites. Nuevo et al. (2012) conducted an analysis of psychotic symptoms in the general population with a large sample (n=256,445) comprising samples from 52 countries worldwide. They assessed the number of psychotic symptoms individuals experienced in the 12 months prior to interview and their impact on health status. They did report prevalence of diagnosed schizophrenia between countries, although this was not a focus of the study, their study design did not include institutionalized individuals, and their interview schedule only assessed four core symptoms: delusional mood, delusions of reference and persecution, delusions of control, and auditory or visual hallucinations. They found a very wide range in the prevalence of psychotic symptoms between countries; however significant differences in study goals and design with our study make drawing comparisons problematic.

Methods

Sample details

Sample recruitment across sites and clinical ascertainment are detailed elsewhere (see McLean et al., 2012). Briefly, recruitment at each site involved: Australia – sibling pairs and individuals were recruited as part of a major US/Australian collaboration (Molecular Genetics of Schizophrenia [MGS] Consortium) from a range of sources, including local treatment facilities, physician referrals, community organizations, supported accommodation facilities and advertisements; India – sibling pairs and individuals were identified and invited to participate through The Schizophrenia Research Foundation India's (SCARF's) well-established recruitment network of clinicians; and Sarawak – Iban individuals were identified through Malaysian census data, an initial medical records screen was undertaken, then a subset of individuals and families were contacted for in-depth follow-up. We included all individuals (probands and relatives) with a Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (APA, 1994) diagnosis of schizophrenia or schizoaffective disorder who met the (self-reported) ethnicity inclusion criterion: Australia – self-reported European Caucasian ancestry; India – membership of Brahmin caste from Tamil, Kerala, Karnataka, or Andhra Pradesh, or membership of geographically proximal caste groups from Tamil Nadu (Mudaliars, Chettiars, and Dalits) (for details see Thara et al., 2009); and Sarawak – self-reported Iban ethnicity. Ethnicity was subsequently confirmed through genetic analysis (Australia: Shi et al., 2009; India and Sarawak: manuscripts in preparation). Briefly, genomewide association analyses (GWAS) were undertaken for each sample; one quality control procedure involved conducting principal component analyses to confirm each individual's GWAS data against international control population GWAS data in order to exclude ancestral/ethnic outliers from further analyses. Clinical exclusion criteria for individuals were: (1) inability to give informed consent; (2) psychosis assessed as secondary to substance use or a neurological disorder; and (3) severe intellectual disability.

All participants in Australia and India gave written informed consent, and individuals in Sarawak who participated in the detailed screening follow-up gave verbal, videotaped informed consent (given that the Iban is traditionally a preliterate society). Individuals consented to an interview, a blood sample for DNA, and review of their psychiatric records. Local Institutional Review Board approval was obtained for each study.

Clinical ascertainment

Clinical ascertainment included five elements.

(1) Trained clinicians used the semi-structured Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994) to obtain DSM-IV relevant diagnostic information.
(2) A family informant, when possible, or the proband was interviewed about the family psychiatric history using the Family Interview for Genetic Studies (FIGS) (Gershon et al., 1988; Maxwell, 1992).
(3) All available medical records were retrieved for each participant and then assessed by trained clinicians.
(4) A trained clinician prepared a case summary based on all available information which facilitated diagnostic review.
(5) DIGS interview, case summary, available medical records, and FIGS reports formed the basis for diagnostic review. Diagnoses were assigned using the Best Estimate Final Diagnosis (BEFD) procedure (Leckman et al., 1982), with two experienced psychiatrists independently reviewing all available information then conferring to assign a consensus diagnosis. Approximately half the Sarawak sample had diagnoses formulated by one experienced psychiatrist, with a BEFD generated in a random subset (20 cases).

Inter-rater reliability was assessed within the Australian/US sample (50 cases; κ=0.88 for schizophrenia, κ=0.89 for schizoaffective disorder) (Suarez et al., 2006); within the Indian sample; within the Sarawak sample; between the Australian and Indian samples (disagreement in one of 20 cases; κ=0.886); and between the Australian and Sarawak samples (disagreement in one of 20 cases; κ=0.828). The robustness of inter-rater reliability within the unpublished assessments (India, Sarawak) is consistent with the other assessments presented here.

The cultural equivalence of the DIGS and FIGS was extensively addressed by the chief investigators at the three sites, with specific focus on conceptual equivalence, item equivalence, and functional equivalence (for details of a cultural equivalence framework see Herdman et al., 1998). Professor Barrett completed his PhD in Anthropology/Psychiatry, living for several years immersed in Iban culture, and pioneered modern schizophrenia research in the Iban; Dr. Thara has a long track record of schizophrenia research in India; and Professor Mowry oversaw diagnostic equivalence across all sites by reviewing every case. Both Professor Barrett, in Sarawak, and Dr. Thara, in India, have conducted qualitative research and written extensively on how culture mediates the experience of psychosis, and the implications for using standardized

diagnostic instruments and applying universal diagnostic criteria within these cultures (Barrett, 2004; Corin et al., 2004). An appreciation of the relational or interactional notion of 'self' in both Sarawak (Barrett, 2004) and India (Corin et al., 2004; Kakar, 1991), in contrast to individual uniqueness defining 'self' in post-Enlightenment Western cultures (Kakar, 1991) such as Australia, is central to establishing diagnostic equivalence across sites.

The DIGS and FIGS were translated into both Iban (Sarawak) and Tamil (India) with appropriate back-translation procedures. Interview schedules were translated into Tamil and Iban, affected individuals were interviewed by experienced bilingual research clinicians, and responses to questions were recorded and back-translated into English. This process was repeated several times until the research teams were sure that the final version accurately reflected clinical phenomenology.

Data analysis

We classified included individuals according to the lifetime-ever presence of DSM-IV criterion A symptoms that comprised their schizophrenia or schizoaffective diagnosis. Twenty-eight possible symptom combinations meet criterion A: two combinations where an included individual rates positive for only one of the five symptom types (i.e. bizarre delusions or third person auditory hallucinations); ten combinations with two symptoms (e.g. delusions and disorganized speech); ten combinations with three symptoms; five combinations with four symptoms; and one combination with all five symptoms.

These 28 categories were collapsed into six based on criterion A symptoms belonging to one of the three previously noted dimensions: positive – delusions and hallucinations; negative – negative symptoms; and disorganized – disorganized speech and grossly disorganized or catatonic behavior. Thus, the six discrete categories were: (1) positive only; (2) disorganized only; (3) positive and disorganized; (4) positive and negative; (5) disorganized and negative; and (6) positive, disorganized and negative. Site differences across these six groups were then explored.

We also examined the types of delusions and hallucinations experienced between sites, which were derived from categories assessed in the DIGS. The specific delusion categories include: bizarre; thought broadcast, insertion, or withdrawal; control; persecutory; referential; jealousy; guilt or sin; grandiose; religious; somatic; erotomanic;

and mind reading. The specific hallucination categories include: auditory; auditory with commentary or third person conversations; visual; olfactory or gustatory; and somatic or tactile. Three of these variables: delusions of thought broadcast, insertion, or withdrawal; control delusions; and auditory hallucinations with commentary or third person conversations were specifically included to capture Schneiderian First Rank Symptoms.

Statistical analyses used the χ^2 statistic in SAS software, version 9.3 for Windows (SAS Institute Inc.). Adequate statistical power for assessing the five dimension categories (no included individuals rated positively for the sixth category: disorganized dimension only) and nineteen symptom content variables utilizing three-way tests was confirmed using a Bonferroni correction (72 separate comparisons; adjusted p=0.0007).

Results

The present study was drawn from 1831 individuals from Australia (n=821), India (n=524) and Sarawak (n=486). We excluded 192 individuals with DSM-IV diagnoses other than schizophrenia or schizoaffective disorder (Australia, n=0; India, n=4; Sarawak, n=188). Of the resulting 1639 individuals we then excluded all individuals with missing data for any criterion A symptom variable (Australia, n=45; India, n=16; Sarawak, n=39). Therefore, the final sample comprised 1539 individuals (Australia, n=776; India, n=504; Sarawak, n=259). DIGS and FIGS data were available for over 90% of participants in Australia and India, and approximately 50% in Sarawak. Narrative summaries were available for over 90% of participants in Australia and Sarawak, and over 75% in India. Best-estimate final diagnoses were available for all participants across the three sites (except as previously noted).

A summary of demographic and diagnostic details of included individuals by site is provided in Table 5-1.

Table 5-1: Demographic and Diagnostic Characteristics of Included Individuals by Site

Symptom		Australia (N=776)	India (N=504)	Sarawak (N=259)	Total (N=1539)
Age in Years (Mean ± SD)		38.9 ± 11.73	37.9 ± 12.06	46.9 ± 14.86	39.93 ± 12.80
Sex	Male	547 (70.5%)	294 (58.3%)	152 (58.7%)	993 (64.5%)
	Female	229 (29.5%)	210 (41.7%)	107 (41.3%)	546 (35.5%)
Diagnosis	Schizophrenia	724 (93.3%)	502 (99.6%)	203 (78.4%)	1429 (92.9%)
	Schizoaffective Depressed	23 (3.0%)	1 (0.2%)	37 (14.3%)	61 (4.0%)
	Schizoaffective Bipolar	29 (3.7%)	1 (0.2%)	19 (7.3%)	49 (3.2%)

Symptoms/dimensions comprising schizophrenia criterion A for included individuals by site are provided as Table 5-2.

Table 5-2: Criterion A symptoms of schizophrenia – Dimensions with established lifetime ratings[†] by site

Criterion A Endorsed Dimensions[‡]	Australia		India		Sarawak		Total	
Positive Only	2	(0.3%)	4	(0.8%)	8	(3.1%)	14	(0.9%)
Positive + Disorganized	18	(2.3%)	7	(1.4%)	25	(9.7%)	50	(3.2%)
Positive + Negative	88	(11.3%)	89	(17.7%)	20	(7.7%)	197	(12.8%)
Disorganized + Negative	0	(0%)	20	(4.0%)	2	(0.8%)	22	(1.4%)
Positive + Disorganized + Negative	668	(86.1%)	384	(76.2%)	204	(78.8%)	1256	(81.6%)
Total	**776**	**(100%)**	**504**	**(100%)**	**259**	**(100%)**	**1539**	**(100%)**

[†] No included individuals rated positively for the disorganized dimension only
[‡] A detailed breakdown of specific criterion A symptom frequencies by site is provided as Table 5-4S

While the frequency of positive symptoms was high across each site (Australia 776/776: 100%; India 484/504: 96.0%; Sarawak 257/259: 99.2%), there were noticeably lower frequencies of negative symptoms in Sarawak (Australia 756/776: 97.4%; India 493/504: 97.8%; Sarawak 226/259: 87.3%), and disorganized symptoms in India (Australia 686/776: 88.4%; India 411/504: 81.5%; Sarawak 231/259: 89.2%).

There was a significant overall site difference using a Bonferroni-corrected p-value (p=0.0007) in the proportion of subjects who had each combination of endorsed symptom dimensions $\chi^2(8, N=1539) = 111.72$, $p < 0.0001$. The positive/disorganized/negative dimension category was reported most frequently in our Australian sample; the positive only and positive/disorganized dimension combinations were reported most frequently in our Sarawak sample; while the positive/negative and disorganized/negative dimension categories were reported most frequently in our Indian sample. Twenty (4.0%) individuals in India met the DSM-IV criteria for schizophrenia despite no lifetime delusions or hallucinations. Two individuals in Sarawak and no individuals in the Australian sample reported no positive symptoms.

Symptom content comparisons for included individuals by site are provided as Table 5-3.

Table 5-3: Symptom Content Comparison by Site

Symptom[†]	Australia	India	Sarawak	Total	$X^{2‡}$	DF	P
Global delusions	764/776 (98.5%)	465/504 (92.3%)	211/259 (81.5%)	1440/1539 (93.6%)	95.21	2	<0.0001
Bizarre delusions	497/776 (64.1%)	181/504 (35.9%)	51/259 (19.7%)	729/1539 (47.4%)	203.67	2	<0.0001
Broadcast/Insertion/Withdrawal delusions	*368/776 (47.4%)*	*64/504 (12.7%)*	*27/259 (10.4%)*	*459/1539 (29.8%)*	*257.49*	*2*	*<0.0001*
Control delusions	*213/776 (27.5%)*	*106/504 (21.0%)*	*22/259 (8.5%)*	*341/1539 (22.2%)*	*45.69*	*2*	*<0.0001*
Persecutory delusions	683/776 (88.0%)	402/504 (79.8%)	172/259 (66.4%)	1257/1539 (81.7%)	60.43	2	<0.0001
Referential delusions	585/776 (75.4%)	293/504 (58.1%)	72/259 (27.8%)	950/1539 (61.7%)	206.45	2	<0.0001
Jealousy delusions	81/776 (10.4%)	37/504 (7.3%)	28/259 (10.8%)	146/1539 (9.5%)	1.96	2	0.3756
Guilt/Sin delusions	122/776 (15.7%)	28/504 (5.6%)	8/259 (3.1%)	158/1539 (10.3%)	47.64	2	<0.0001
Grandiose delusions	419/776 (54.0%)	73/504 (14.5%)	36/259 (13.9%)	528/1539 (34.3%)	283.07	2	<0.0001
Religious delusions	279/776 (36.0%)	55/504 (10.9%)	58/259 (22.4%)	392/1539 (25.5%)	106.23	2	<0.0001
Somatic delusions	173/776 (22.3%)	65/504 (12.9%)	23/259 (8.9%)	261/1539 (17.0%)	35.42	2	<0.0001
Erotomanic delusions	85/776 (11.0%)	47/504 (9.3%)	16/259 (6.2%)	148/1539 (9.6%)	5.49	2	0.0644
Mind reading delusions	327/776 (42.1%)	63/504 (12.5%)	13/259 (5.0%)	403/1539 (26.2%)	204.01	2	<0.0001
Global hallucinations	721/776 (92.9%)	396/504 (78.6%)	245/259 (94.6%)	1362/1539 (88.5%)	73.11	2	<0.0001
Auditory hallucinations	692/776 (89.2%)	379/504 (75.2%)	241/259 (93.1%)	1312/1539 (85.3%)	69.61	2	<0.0001
Commentary/3rd person hallucinations	*331/776 (42.7%)*	*246/504 (48.8%)*	*108/259 (41.7%)*	*685/1539 (44.5%)*	*1.29*	*2*	*0.5248*
Visual hallucinations	390/776 (50.3%)	96/504 (19.1%)	133/259 (51.4%)	619/1539 (40.2%)	125.49	2	<0.0001
Olfactory/Gustatory hallucinations	170/776 (21.9%)	19/504 (3.8%)	57/259 (22.0%)	246/1539 (16.0%)	74.76	2	<0.0001
Somatic/Tactile hallucinations	200/776 (25.8%)	46/504 (9.1%)	44/259 (17.0%)	290/1539 (18.8%)	49.47	2	<0.0001

[†] Schneiderian First Rank Symptoms are presented in italics

[‡] χ^2 analyses were conducted for each variable after 'unknown' responses were deleted (to remove any potential confounding effect). The percentage of responses deleted varied between 0 (0%) and 202 (13.1%), with only Commentary/3rd person hallucinations having greater than 6.7% of responses deleted. The average number of 'unknown' responses deleted for each variable was 59 (3.8%).

Frequencies differed significantly by site for sixteen of the nineteen delusion and hallucination categories after using a Bonferroni correction. Bizarre delusions, delusions of reference, and mind reading delusions were most frequently reported in Australia and least frequently reported in Sarawak, with the magnitude of site differences noticeably more pronounced than for global delusions. Both visual hallucinations and olfactory/gustatory hallucinations were comparatively rare in India compared with the other sites, whereas grandiose delusions were reported less frequently in both India and Sarawak than Australia.

Of the three symptom variables that primarily capture Schneiderian First Rank Symptoms (FRS) (see Mellor, 1970), the frequency of auditory hallucinations with commentary or 3rd person conversations (Australia 42.7%, India 48.8%, Sarawak 41.7%) was similar (non-significant) between sites; the frequency of control delusions (Australia 27.5%, India 21.0%, Sarawak 8.5%) was lower in Sarawak; and frequency of thought broadcast/insertion/withdrawal delusions (Australia 47.4%, India, 12.7%, Sarawak 10.4%) was markedly lower in both India and Sarawak.

Discussion

As in previous transcultural studies (e.g. Jablensky et al., 1992) we identified broad symptom profile similarities across sites, and also notable differences. Variation was clearly demonstrated in the frequencies of both the DSM-IV criterion A symptoms of schizophrenia (broadly identifiable as core components of well established dimensions (Fiedorowicz et al., 2008)), and in the content of most delusions and hallucinations across our three ethnically distinct samples. Indian individuals reported negative symptoms more frequently than other sites, whereas individuals from Sarawak reported disorganized symptoms more frequently. These differences in schizophrenia expression across populations suggest potential differences in structural organization as well as symptom expression.

Inconsistent findings from genetic linkage and association studies using the diagnostic category “schizophrenia” as a single phenotype suggest that the current concept of schizophrenia is not a single disease entity (Jablensky, 2006). Furthermore, there is increasing evidence that individual differences in clinical presentation are in part due to differences in genetic etiology (Fanous and Kendler, 2008). Breaking schizophrenia into clinical subtypes utilizing ethnically distinct populations may yield more meaningful results

(e.g. Holliday et al., 2009). Therefore, distinct population “groupings” of individual differences in clinical presentations of schizophrenia (as in the current study) suggest possible etiological differences, and by extension differences relevant to diagnostic classification, across populations.

Readily identifiable clinical sub-populations within the three samples, such as the twenty Indian individuals (4.0%) with no positive symptoms – a symptom profile somewhat resembling the traditional concept “simple schizophrenia” (APA, 1994), further support the hypothesis that schizophrenia is not a single, continuous entity. This symptom pattern was rare in the Iban (n=2, 0.8%), and absent in our Australian sample.

Interestingly, nine individuals from this Indian subgroup (1.8% of our entire Indian cohort) would no longer meet the criteria for schizophrenia when classified using the new DSM-5 diagnostic criteria (APA, 2013), since they were diagnosed based on the presence of disorganized behaviour and negative symptoms; there was no evidence of any of the three “core” symptoms: delusions, hallucinations, or disorganized speech. One individual from Sarawak met the DSM-IV criteria for schizophrenia based on presence of bizarre delusions only, and would also no longer be diagnosed with schizophrenia in DSM-5.

We identified both similarities and differences in the content of delusions and hallucinations across sites. The contrasting site frequencies for FRS are interesting. Significant cross-cultural variation in the frequency of FRS has been noted across many countries (Barrett, 2004), although Barrett found striking qualitative similarities in the appearance and frequency of auditory hallucinations between Australian (n=50) and Iban (n=50) schizophrenia cohorts, whereas subjective thought disorder (e.g. delusions of control and thought broadcast, insertion or withdrawal) was extremely rare in the Iban sample. Barrett (2004) had previously done extensive work translating the Present State Examination (Wing et al.,1974) into Iban, in close collaboration with both an experienced Iban mental health professional, an Iban educationalist, and an Iban language tutor. Despite exploring and testing a range of cultural idioms, Barrett was unable to arrive at a satisfactory translation of the questions specifically relating to subjective thought disorder, due primarily to differing concepts of personhood between Western cultures and Iban culture. He postulates that some components of the clinical definition of schizophrenia (e.g. subjective thought disorder) may be tied to the cultural and intellectual history of Western psychiatry more than others (e.g. auditory hallucinations with commentary or 3rd

person conversations), and therefore be culturally contingent rather than cross-culturally robust.

The pattern of relevant FRS symptoms between our Australian and Iban samples mirrors the contrast reported by Barrett: frequency of auditory hallucinations with commentary or 3rd person conversations was similar between sites, while the frequency of control delusions and thought broadcast/insertion/withdrawal delusions was markedly lower in Sarawak.

The effect of cultural contingency, which we have explored as an important consideration for our Iban sample, also requires elucidation in our Indian sample. One illustrative domain is major mood symptoms. The differential importance of symptoms in diagnosing depression versus somatoform disorders in India is well documented (e.g. Weiss et al., 1995). Moreover, within India itself there is significant cultural variation in the content of somatic complaints (Gautam and Jain, 2010). Extremely low frequencies of schizoaffective disorder have been previously reported in our Indian sample, potentially due to differential weighting given to mood symptoms by local diagnosticians or sample participants (McLean et al., 2012). This exemplifies almost inevitable, culturally mediated, imperfect conceptual equivalence in isolated domains across sites, even when an instrument is robustly equivalent overall.

The potential impact of cultural contingency on FRS symptoms in our Indian sample is interesting. Curiously, India had the highest frequency of auditory hallucinations with commentary or 3rd person conversations (not significantly different from other sites) despite having the lowest frequency of auditory hallucinations overall. Our Indian population also reported fewer thought broadcast/insertion/withdrawal delusions than control delusions, unlike Australia and Sarawak; such between-site variability further supports the assertion that subjective thought disorder may be culturally contingent, while auditory hallucinations with commentary or 3rd person conversations may be culturally robust.

Although questions relating to subjective thought disorder were problematic when translating their meaning into Iban (Barrett, 2004), highlighting imperfect conceptual equivalence, no significant issues were reported when translating questions relating to delusions generally, in either India or Sarawak. For example, the questions assessing

delusions of persecution and reference were similar across sites, and were assessed as having sound conceptual equivalence – does the questionnaire have the same relationship to the underlying concepts at each site?; item equivalence – do items estimate the same parameters on the latent traits being measured at each site?; and functional equivalence – does the instrument achieve its purpose equally well at each site (see Herdman et al., 1998)? It is interesting, therefore, that most measured delusion categories had significant site differences. For most categories, Australia had the highest frequency, then India, then Sarawak, although the relative magnitude of differences between sites varied greatly by symptom. The two exceptions were delusions of jealousy, for which the frequency was highest in Sarawak, then Australia, then India; and religious delusions, for which the frequency was highest in Australia, then Sarawak, then India.

Given general acceptance in both anthropology and psychiatry that culture plays an integral role in the content of psychotic symptoms, any attempt to identify and characterize clinical subtypes within the broader schizophrenia diagnosis should incorporate both symptom content and organizational structure.

Further cultural considerations

We acknowledge that categorization of research participants by ethnicity and/or culture is problematic and highly contested (Egede, 2006; Ma et al., 2007). Despite this, our sample is large for a transethnic comparative schizophrenia study (n=1539), individuals were assessed using the same battery of instruments, and individuals were diagnosed using the best-estimate final diagnosis method, which offers consistently high diagnostic reliability and stability (Beckmann et al., 1996; Calkins et al., 2007), and is the benchmark method available with current methods of classifying schizophrenia (McLean et al., 2012). We assessed ethnicity by self-report, which is considered the research “gold standard” in transcultural research (Ma, et al., 2007). Furthermore, we ascertained birthplace for individuals’ parents and grandparents, confirmed ethnic homogeneity genetically via principal component analyses of GWAS data, and interviewed individuals in their home countries using local interviewers. These measures avoid many confounding factors frequently experienced in cross-cultural research, which can limit generalizability of findings (McKenzie and Crowcroft, 1996a, 1996b).

Transethnic schizophrenia samples can inform debate at every level of the diagnostic spectrum: (1) broad theoretical (universalist vs. relativist); (2) diagnostic (nosological vs.

dimensional); (3) structure of psychosis generally; and (4) structure of schizophrenia specifically. However, while multiple, distinct transethnic samples have been used (primarily from an anthropological perspective) to challenge DSM-IV at the two broader levels, less work has been undertaken at the more specific levels. If we generally acknowledge that DSM-IV may not accurately represent the structure of schizophrenia, then the variation consistently demonstrated across cultural groups (Kleinman, 1988) supports the view that examining transethnic samples at all levels of the diagnostic process is worthwhile, even accepting the pervasive, complex interaction between biological and social processes at all levels.

Neither the “tightening” of the inclusion criteria for schizophrenia, nor the removal of schizophrenia subtypes in DSM-5 lessen the importance of transethnic samples in the diagnostic debate; rather, these classification changes elevate their status. Categorical classification systems, by definition, refine groupings through simplifying common membership characteristics (Möller, 2008), whereas transethnic samples force us to acknowledge the complex reality of real-world cases, providing sound evidence for clinical variation. The complex mix of culturally contingent and culturally robust symptoms between transethnic samples reminds us that culture is critical in nearly every aspect of the experience of schizophrenia (Jenkins and Barrett, 2004); even when an individual breaks away from accepted social norms, as in psychosis, those cultural norms and rituals still shape the illness (Kakar, 2012).

The ‘Emerging Measures and Models’ section of the DSM-5 attempts to address variation in a clinically meaningful way, specifically through the ‘Clinician-Rated Dimensions of Psychosis Symptom Severity’ scales, and the ‘Cultural Formulation Interview’ (APA, 2013), although a categorical classification system will inevitably inadequately incorporate real world complexity, as it is not designed for that purpose (Fiedorowicz et al., 2008; Möller, 2008). Therefore, cultural impact is still peripheral to the DSM-5 (relegated to Section III, separated from the diagnostic criteria), a criticism that has carried over from its predecessor, the DSM-IV (Kleinman, 1997). It could be argued that embracing a dimensional approach to characterizing the expression of schizophrenia, without strict qualifications regarding applicability, would be incompatible with the very diagnostic foundation of the DSM.

Methodological limitations

First, imperfect sampling equivalence was unavoidable. Our samples were collected for specific genetic studies, thus there were differences in selection methods of included individuals. Both the Indian and Sarawak samples were chosen from ethnically homogeneous populations, whereas the Australian sample was not specifically recruited as such (although we targeted European Caucasian ethnicity). Furthermore, the Australian and Indian cohorts included sibling-pairs plus unrelated individuals recruited opportunistically, while only the Sarawak sample can be considered relatively epidemiologically sound. Differing recruitment methods also resulted in DIGS and FIGS data being unavailable for approximately half the Sarawak sample (i.e. those from the initial medical records screen). While these identified site differences may complicate attributing findings to culture, the strength of our study design: rigorously recruiting cohorts that are (1) ethnically homogeneous, and (2) geographically constrained, outweighs these shortcomings, as these two factors, taken together, form a valid, important variable in medical research for assessing culture (Azuonye, 1994).

Second, limited precision or validity of diagnostic criteria may be problematic. Caution is required when using instruments across cultures, as converting thoughts and feelings across languages is difficult (Barrett, 2004), and language is central to understanding individuals' subjective experience of schizophrenia (Jenkins and Barrett, 2004). To address this issue the chief investigators at each site undertook extensive cultural equivalence work in the planning stages of each study. We further employed state-of-the-art methods, translating and back-translating the DIGS, and using local interviewers who interviewed in the native language across the three sites, and recorded responses in Iban (Sarawak) and English (India and Australia). The reliability of the instrument (inter-rater reliability within and across the samples) was also tested to establish reliability across sites, although diagnostic inter-rater reliability was not assessed between India and Sarawak, nor was inter-rater reliability assessed on individual diagnostic components other than the DIGS.

Third, generalizability of our findings is limited, given that (1) the Iban in Malaysia and the Brahmin in India are homogeneous groups within diverse societies; and (2) we did not specifically collect socioeconomic data across our samples, and socioeconomic position has been proposed as a stronger determinant of health outcomes than ethnicity (Egede, 2006).

Fourth, utilizing a sample of individuals meeting the DSM-IV criteria for either schizophrenia or schizoaffective disorder to potentially hypothesize about the latent structure of psychosis and/or schizophrenia itself may be problematic, in that we are not able to make comparisons with other DSM-IV diagnoses such as bipolar disorder, which would potentially give a “wider perspective” on the clustering of symptoms of psychosis. Additionally, using a homogeneous schizophrenia sample to examine clinical variation is not ideal as it excludes individuals with psychoses who do not meet the DSM-IV criteria, but are of particular cultural interest (Kleinman, 1988). The release of DSM-5 highlights the effect of this limitation: had this sample been recruited using the new criteria for schizophrenia, nine of the most interesting cases from a cultural perspective would not have been included.

Fifth, while we used the same battery of diagnostic instruments across sites, significant variation was unavoidable, both due to the varying quality and quantity of medical records we could access, and also due to the reliance on retrospective assessment of lifetime symptoms. Therefore, it is possible bias may be introduced – for example through under-reporting of criterion A symptoms in India where there have been fewer hospitalisations, or in Sarawak, where detailed records could not be accessed for many individuals. Under-reporting of symptoms due to recall failure is a recognized, but difficult to quantify shortcoming of using a retrospective survey method to obtain symptom information (Moffitt et al., 2010); this effect is magnified in cases where medical records are unavailable for corroboration.

Finally, while the use of transethnic samples to inform the debate on the structure of schizophrenia is a worthwhile pursuit, the well-known difficulties regarding operationalizing the role of culture introduces an additional confounder that makes isolating the source of non-cultural variation more difficult. For example, the content of one’s delusions can, in practice, only be accessed through language – asking them the content of their thoughts (Barrett, 2004). Yet, any attempt to understand the role of culture in this thought variation is obfuscated by the powerful cultural impact on language – the very concept we are attempting to understand integrally mediates the only method of assessment available to us. We acknowledge therefore, that the process of establishing cultural equivalence, while important, rigorously addressed in our study, and worthwhile, is necessarily imperfect. Thus, it is difficult to make assertions regarding the cultural underpinnings of our identified site differences in frequencies of measured delusion content categories, beyond

acknowledging well-established cultural differences in notions of self across our samples (Barrett, 2004; Corin et al., 2004; Kakar, 1991). Ethno-cultural exploration of our site differences in delusion content, while beyond the scope of this study, is warranted.

Conclusions

There is enough variation in both the frequency and the content of DSM-IV criterion A symptoms of schizophrenia across our three sites to make a comprehensive exploration of symptom profiles across the three samples worthwhile. While content-only symptom differences could be explained within the pathoplastic model favoured by Western psychiatry, the additional 'weight' provided by statistically-significant differences in the frequencies of the core diagnostically-significant symptom types across sites, illustrated by the greater frequency of disorganized symptoms in Sarawak and negative symptoms in India, cannot as easily be dismissed. The possibility of isolating and characterizing distinct clinical sub-groups within these populations, such as the individuals in India with no lifetime delusions or hallucinations, further strengthens this case.

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Declaration of Interest

No conflicts declared.

Chapter 5 Supplemental Tables

Supplementary Table 5-4S: Criterion A symptoms of schizophrenia – Frequencies of positive ratings by site

Criterion A positive ratings[†]	**Dimensions**	**Australia**		**India**		**Sarawak**		**Total**	
Any unknown values (Exclude)	*N/A*	*45 (5.5%)*		*16 (3.1%)*		*39 (13.1%)*		*100 (6.1%)*	
All Combinations (Total Included)	***N/A***	***776***		***504***		***259***		***1539***	
1. Bizarre Delusions Only	Pos	0	(0%)	0	(0%)	1	(0.4%)	1	(0.1%)
2. Third Person/Commentary Hallucinations Only	Pos	0	(0%)	0	(0%)	0	(0%)	0	(0%)
3. Delusions + Hallucinations	Pos	2	(0.3%)	4	(0.8%)	7	(2.7%)	13	(0.8%)
4. Delusions + Disorganized Speech	Pos, Dis	0	(0%)	0	(0%)	0	(0%)	0	(0%)
5. Delusions + Disorganized Behaviour	Pos, Dis	1	(0.1%)	1	(0.2%)	1	(0.4%)	3	(0.2%)
6. Delusions + Negative Symptoms	Pos, Neg	7	(1.0%)	14	(2.8%)	1	(0.4%)	22	(1.4%)
7. Hallucinations + Disorganized Speech	Pos, Dis	0	(0%)	0	(0%)	0	(0%)	0	(0%)
8. Hallucinations + Disorganized Behaviour	Pos, Dis	0	(0%)	0	(0%)	3	(1.2%)	3	(0.2%)
9. Hallucinations + Negative Symptoms	Pos, Neg	1	(0.1%)	3	(0.6%)	2	(0.8%)	6	(0.4%)
10. Disorganized Speech + Disorganized Behaviour	Dis	0	(0%)	0	(0%)	0	(0%)	0	(0%)
11. Disorganized Speech + Negative Symptoms	Dis, Neg	0	(0%)	3	(0.6%)	0	(0%)	3	(0.2%)
12. Disorganized Behaviour + Negative Symptoms	Dis, Neg	0	(0%)	9	(1.8%)	0	(0%)	9	(0.6%)
13. Delusions + Hallucinations + Disorganized Speech	Pos, Dis	1	(0.1%)	1	(0.2%)	1	(0.4%)	3	(0.2%)
14. Delusions + Hallucinations + Disorganized Behaviour	Pos, Dis	6	(0.8%)	3	(0.6%)	9	(3.5%)	18	(1.2%)
15. Delusions + Hallucinations + Negative Symptoms	Pos, Neg	80	(10.3%)	72	(14.3%)	17	(6.6%)	169	(11.0%)
16. Delusions + Disorganized Speech + Disorganized Behaviour	Pos, Dis	0	(0%)	1	(0.2%)	2	(0.8%)	3	(0.2%)
17. Delusions + Disorganized Speech + Negative Symptoms	Pos, Dis, Neg	7	(1.0%)	2	(0.4%)	2	(0.8%)	11	(0.7%)
18. Delusions + Disorganized Behaviour + Negative Symptoms	Pos, Dis, Neg	15	(1.9%)	43	(8.5%)	1	(0.4%)	59	(3.8%)
19. Hallucinations + Disorganized Speech + Disorganized Behaviour	Pos, Dis	0	(0%)	0	(0%)	4	(1.5%)	4	(0.3%)
20. Hallucinations + Disorganized Speech + Negative Symptoms	Pos, Dis, Neg	1	(0.1%)	1	(0.2%)	4	(1.5%)	6	(0.4%)
21. Hallucinations + Disorganized Behaviour + Negative Symptoms	Pos, Dis, Neg	5	(0.6%)	8	(1.6%)	7	(2.7%)	20	(1.3%)
22. Disorganized Speech + Disorganized Behaviour + Negative Symptoms	Dis, Neg	0	(0%)	8	(1.6%)	2	(0.8%)	10	(0.6%)
23. Delusions + Hallucinations + Disorganized Speech + Disorganized Behaviour	Pos, Dis	10	(1.3%)	1	(0.2%)	5	(1.9%)	16	(1.0%)
24. Delusions + Hallucinations + Disorganized Speech + Negative Symptoms	Pos, Dis, Neg	106	(13.7%)	16	(3.2%)	5	(1.9%)	127	(8.3%)
25. Delusions + Hallucinations + Disorganized Behaviour + Negative Symptoms	Pos, Dis, Neg	91	(11.7%)	180	(35.7%)	25	(9.7%)	296	(19.2%)
26. Delusions + Disorganized Speech + Disorganized Behaviour + Negative Symptoms	Pos, Dis, Neg	25	(3.2%)	27	(5.4%)	4	(1.5%)	56	(3.6%)
27. Hallucinations + Disorganized Speech + Disorganized Behaviour + Negative Symptoms	Pos, Dis, Neg	5	(0.6%)	7	(1.4%)	26	(10.0%)	38	(2.5%)
28. Delusions + Hallucinations + Disorganized Speech + Disorganized Behaviour + Negative Symptoms	Pos, Dis, Neg	413	(53.2%)	100	(19.8%)	130	(50.2%)	643	(41.8%)

[†] Criterion A symptoms were dichotomized Yes/No (with observations having unknown values in any of the 5 symptoms deleted)

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Chapter 6. Is 'Deficit schizophrenia' a distinct class within the syndrome of schizophrenia? Evidence from factor mixture modeling in three ethnically distinct population

McLean D, Linscott R, Barrett R, McGrath J, Thara R and Mowry B. Is 'Deficit schizophrenia' a distinct, universal class within the syndrome of schizophrenia? Evidence from factor mixture modeling in three ethnically distinct populations. Submitted to *Australian and New Zealand Journal of Psychiatry*.

Abstract

Schizophrenia's expression varies across ethnically-different populations, and its optimal structural and diagnostic representation remains unclear. The deficit subtype has been proposed as a discrete entity within schizophrenia with potential to elucidate genetic and clinical heterogeneity.

We tested the underlying statistical demarcation of deficit schizophrenia (DS) among those with DSM-IV schizophrenia in three ethnically-distinct populations from Australia (n=812), India (n=474), and Sarawak, Malaysia (n=145). We analyzed twelve characteristic DS variables by exploratory factor analysis, latent class analysis, and factor mixture modeling in each population, to determine models with the best fit and utility. Results were corroborated using taxometric analyses: MAXCOV, MAXEIG and LMODE.

Both single and multi-class models had good overall fit, with three models: one class/two factors, one class/three factors, and two classes/one factor in the four best-fitting models for each site. Broadly, variation within the single-class models was explained by one 'negative symptom' dimension and one 'dysfunction' dimension, whereas the two-class models seemingly differentiated DS from non-DS more clearly in India and Sarawak than Australia. Taxometric findings favored a two-class distribution in each sample, distinguishing a relatively large deficit class.

Our findings tentatively support the hypothesis that DS has a hybrid categorical/dimensional latent structure. Broad similarities in the structural appearance of DS variables in three ethnically-distinct schizophrenia populations, and taxometric confirmation of a two-class distribution in the data are suggestive of the universality of DS

across these populations, although between-site variability was also evident within the best-fitting models.

Key Words: Psychotic disorders, Culture, Diagnosis, Taxonomy

Introduction

Schizophrenia is often treated as a discrete diagnostic entity based on widely-used, reliable criteria consisting of symptoms, duration, illness course, and exclusion of allied disorders (APA, 2013a; WHO, 1992). However, the optimal representation of schizophrenia's structure is unclear: (1) a continuous entity, with clinical variation represented as dimensions within a single class, or (2) two or more distinct entities, with variation indicative of multiple classes labelled *schizophrenia* (Fiedorowicz et al., 2008; Kendler et al., 1998; Linscott et al., 2009).

Schizophrenia subtypes have long been proposed to aid understanding of phenotypic variability and genetic heterogeneity within schizophrenia (Jablensky, 2006), although they have historically lacked usefulness in both clinical and research settings (Fiedorowicz et al., 2008). For example, the traditional DSM-IV subtypes (paranoid, disorganized, catatonic, undifferentiated, residual) were dropped from DSM-5 due to their limited diagnostic stability, low reliability, and poor validity (APA, 2013b). In contrast, evidence concerning *deficit schizophrenia* (DS) suggests this may be a distinct illness subtype, holding promise for understanding heterogeneity in schizophrenia (Ahmed et al., 2015; Cohen et al., 2010; Kirkpatrick et al., 2001).

DS is characterized by primary, enduring negative symptoms (Carpenter et al., 1988). Key symptoms identified as supporting the construct validity (forming an indirect measure of the criterion (Cronbach and Meehl, 1955)) of DS include: greater anhedonia, less depression, less suicidal ideation, and less severe delusions with exclusively social content (Kirkpatrick et al., 2001). Other symptoms identified in DS include: greater flat affect and alogia (Holliday et al., 2009), fewer suicide attempts (Holliday et al., 2009) and completed suicides (Fenton and McGlashan, 1994), and greater disorganized speech and behavior (Fenton and McGlashan, 1994; Holliday et al., 2009). A meta-analysis of DS symptomatology (Cohen et al., 2010) showed that patients with DS did not differ in positive or overall psychiatric symptoms from non-DS patients, but had less severe overall mood symptoms, more severe overall negative symptoms, and slightly more severe overall disorganization symptoms.

Furthermore, regarding illness course, those with DS have poorer premorbid functioning (Buchanan et al., 1990), poorer social and occupational function (Holliday et al., 2009; Kirkpatrick et al., 2001; Tiryaki et al., 2003), and are more likely to have had an insidious

(gradual) onset (Fenton and McGlashan, 1994; Kirkpatrick et al., 2001) and a continuous illness course (Fenton and McGlashan, 1994) than those with non-DS.

Examining variation in expression across ethnic groups may help clarify schizophrenia's complex nature (Kleinman, 1988; Thakker and Ward, 1998). Evidence from genetic studies investigating specific ethnic groups suggests that DS may be a genetically-significant, identifiable entity. Holliday et al. (2009) reported genomewide significant linkage to chromosome 1q23-25 of a subtype resembling DS (identified by latent class analysis), characterized by moderate-severe negative symptoms, prominent disorganization, and marked-severe functional impairment, in a Han Chinese schizophrenia sample. This linked chromosomal region, previously implicated in schizophrenia pathogenesis, was not detected when the traditional DSM-IV schizophrenia diagnosis was analyzed as the clinical phenotype. Bakker et al. (2007) reported that two genes, PIP5K2A and RGS4, were differentially associated with DS and non-DS in an ethnically-homogeneous Dutch schizophrenia sample. Rethelyi et al. (2010) partially replicated the Dutch study in a homogeneous Hungarian sample.

Mixture modeling and taxometric methods were recently used to detect and validate the structure of negative symptoms within a US sample of individuals with psychoses (Ahmed et al., 2015), and taxometric methods had previously been used to examine negative symptoms in schizophrenia (Blanchard et al., 2005). These methods have yet to be applied to DS in multiple ethnically-distinct populations, to test the transethnic applicability of the subtype.

The Genetics Research group at the Queensland Centre for Mental Health Research (QCMHR) and our collaborators recruited three ethnically-distinct cohorts of individuals with schizophrenia and related conditions for genetic analyses. These included: European Australians (n=821); Tamil Brahmin and geographically proximal caste groups from Tamil Nadu, India (n=520); and the Iban of Sarawak, Malaysia (n=298). Importantly, these samples allowed us to statistically model the symptom profile in each to determine if DS could be identified using factor mixture modeling with taxometric confirmation. We hypothesized that we would find a distinct 'class' resembling DS within each of our broad DSM-IV schizophrenia diagnosed samples. This would provide evidence both for the existence of a distinct subtype, and for the stability/universality of this class. We previously contrasted demographic and clinical characteristics (McLean et al., 2012), distinctive

symptom profiles (McLean et al., 2015), and variation within DSM-IV diagnostic criteria (McLean et al., 2014) between these samples.

Methods

Sample details

Sample recruitment and clinical ascertainment are detailed elsewhere (McLean et al., 2012). Briefly, recruitment involved: Australia – sibling-pairs and individuals were recruited for a major US/Australian collaboration (Molecular Genetics of Schizophrenia Consortium) from multiple sources, including treatment facilities, physician referrals, community organizations, supported accommodation facilities and advertisements; India – sibling-pairs and individuals were identified/invited to participate through The Schizophrenia Research Foundation India's (SCARF's) well-established recruitment network of clinicians; and Sarawak – Iban individuals were identified through Malaysian census data, an initial medical records screen was undertaken, then a subset of individuals and families were contacted for in-depth follow-up. We included all individuals (probands and relatives) with a Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (APA, 1994) diagnosis of schizophrenia or schizoaffective disorder who met the ethnicity inclusion criterion: Australia – self-reported European Caucasian ancestry; India – membership of Brahmin caste from Tamil, Kerala, Karnataka, or Andhra Pradesh, or membership of geographically proximal caste groups from Tamil Nadu (for details see Thara, et al., 2009); and Sarawak – self-reported Iban ethnicity. Ethnicity was subsequently confirmed through genetic analysis (Australia: Shi et al., 2009; India and Sarawak: manuscripts in preparation), and ancestral/ethnic outliers were excluded from further analyses. Clinical exclusion criteria included: (1) inability to give informed consent; (2) psychosis assessed as secondary to substance use or a neurological disorder; and (3) severe intellectual disability.

All Australian and Indian participants gave written informed consent, and individuals in Sarawak who participated in the detailed screening follow-up gave verbal, videotaped informed consent (given the Iban is traditionally a preliterate society). Individuals consented to an interview, a blood sample for genetic analyses and review of their psychiatric records. Local institutional review board approval was obtained for each study.

Clinical ascertainment

Clinical ascertainment included five elements.

(1) Trained clinicians used the semi-structured Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994) to obtain DSM-IV diagnostic information.
(2) A family informant, when possible, or the proband was interviewed about the family psychiatric history using the Family Interview for Genetic Studies (FIGS) (Gershon et al., 1988; Maxwell, 1992).
(3) Available medical records were retrieved and assessed by trained clinicians.
(4) A trained clinician prepared a case summary based on all available information.
(5) Diagnoses were assigned using the Best Estimate Final Diagnosis (BEFD) procedure (Leckman et al., 1982), with two experienced psychiatrists independently reviewing all available information outlined above then conferring to assign a consensus diagnosis. Approximately half the Sarawak sample had diagnoses formulated by one experienced psychiatrist, with a BEFD generated in a random subset (20 cases).

DIGS data, FIGS data, and case summaries were available for over 96% of participants at all sites, except narrative summaries in India (84% available). BEFD were available for all participants. Inter-rater reliability was assessed within the full Australian/US sample (Suarez et al., 2006); within the Indian sample; within the Sarawak sample; between the Australian and Indian samples (disagreement in one of 20 cases; κ=0.89); and between the Australian and Sarawak samples (disagreement in one of 20 cases; κ=0.83).

Cultural equivalence of the DIGS and FIGS was extensively addressed by the chief investigators at each site (see McLean et al., 2014). The DIGS and FIGS were translated into both Iban (Sarawak) and Tamil (India) with appropriate back-translation procedures. Affected individuals were interviewed by experienced bilingual research clinicians, and responses to questions were recorded and back-translated into English. This process was repeated until the research teams were sure that the final version accurately reflected clinical phenomenology.

Data analysis

We analyzed 13 symptom and illness course variables: 11 identified as important in either establishing the construct validity of DS, or differentiating the illness course of DS from non-DS (see Kirkpatrick et al., 2001); and two (disorganized speech, disorganized behavior) identified in previous studies of DS (Fenton and McGlashan 1994; Holliday et al., 2009), which have been identified as important in schizophrenia expression in the Iban (McLean et al., 2014; McLean et al., 2015). These included: (i) affective flattening (past 30

days); (ii) alogia (past 30 days); (iii) avolition/apathy (past 30 days); (iv) anhedonia (past 30 days); (v) disorganized speech (lifetime); (vi) disorganized behavior (lifetime); (vii) global dysfunction (past 30 days); (viii) social/occupational dysfunction (past 5 years); (ix) deterioration (over course of illness); (x) delusions with an exclusively social content; (xi) episodes of major depression (lifetime); (xii) one or more suicide attempts (lifetime); and (xiii) speed of psychosis onset.

Affective flattening, alogia, avolition/apathy, and anhedonia were obtained from the SANS assessment (Andreasen, 1983) within the DIGS, and were dichotomized as 1=present, 0=not present. Disorganized speech and disorganized behavior were dichotomized as 1=present, 0=not present. Global dysfunction was obtained from the current GAF score (Endicott et al., 1976) within the DIGS, and was dichotomized as 1=1-60 (moderate-severe dysfunction), 0=61-100 (no-mild dysfunction). Social/occupational dysfunction was dichotomized as 1=severe dysfunction, 0=less than severe dysfunction. Deterioration was dichotomized as 1=severe deterioration, 0=less than severe deterioration. Delusions with an exclusively social content was a composite variable incorporating lifetime presence of grandiose delusions, guilt or sin delusions, erotomanic delusions, and jealousy delusions. It was dichotomized as 1=no social delusions present, 0=at least one social delusion present. Lifetime episodes of major depression was dichotomized as 1=no episodes, 0=one or more episodes. Suicide attempts was dichotomized as 1=no attempts, 0=one or more attempts. Psychosis onset was dichotomized as 1=insidious onset (at least one month), 0=onset within one month.

Included individuals were drawn from: Australia (n=821), India (n=520) and Sarawak (n=298). We only included individuals from Sarawak who participated in the detailed follow-up assessment (n=145), due to the detailed dysfunction and illness course data requirements. We excluded 55 individuals: Australia n=9 (1%); India n=46 (9%) with missing values for any of the three dysfunction/deterioration variables.

We explored model fit in increasingly complex models using three statistical methods designed for modeling latent variables: exploratory factor analysis (EFA; all models with a single class and one or more factors explaining variation within that class); latent class analysis (LCA; all models with multiple discrete classes and no factors explaining variation within these classes); and factor mixture modeling (FMM; all models with multiple discrete

classes and at least one factor explaining variation within these classes). Analyses were conducted using Mplus, version 7.11 (Muthen and Muthen, 2013).

Conceptually, FMM effectively performs EFA and LCA simultaneously. Whereas EFA only ever identifies dimensions in (continuous) data, and LCA only ever finds (categorical) classes (Linscott et al., 2009), FMM are latent variable models with categorical and continuous latent variables (Lubke and Neale, 2008). Thus, unlike EFA and LCA, FMM are unbiased and can provide evidence for either continuous or class hypotheses (Muthen and Asparouhov, 2006). We utilized all three modeling methods, and applied parameters for model fit aided by confirmation from observable data based on clinical experience (since these methods are not intelligent systems (Linscott et al., 2009)). Thus we contrasted the explanatory power of all likely combinations of factors and classes in the attempt to identify DS.

We used taxometric analyses to further explore data structure at each site. Distinct from latent variable modeling, taxometric procedures distinguish continuous latent (one-class) distributions from two-class categorical distributions. Most taxometric procedures share an underlying principle: if a two-class structure exists and there is conditional independence, manipulating the presence and prevalence of class members within subsets of a population sample will lead to systematic changes in statistical parameters (e.g., difference score, covariance, eigenvalue) derived from those subsets. The primary taxometric method used was maximum covariance (MAXCOV), with results confirmed using maximum eigenvalue (MAXEIG) and latent mode (LMODE) methods.

Variables were dichotomized to maximize their utility for analysis. In FMM, the loss of information when dichotomizing variables does not result in deterioration of results – the smaller number of estimated parameters compensates for the relatively ‘crude’ categorization (Lubke and Neale, 2008).

The 13 DS variables were used to test 15 pure and hybrid models: one to four factors within a single class (EFA); one to five classes with no factors (LCA); and combinations of two classes with one to three factors, three classes with one or two factors, and four classes with one factor (FMM). All models used maximum likelihood estimation with robust standard errors.

One variable, suicide attempts, was dropped from the analyses, as it was consistently non-significant across factors and classes in the initial models for each site. The analyses were re-run with the remaining twelve variables. The results of the twelve variable modeling are presented here.

Item screening for taxometric analyses was undertaken using the Australian sample because it was the largest cohort. Subsequently, the same variables were used in taxometric analyses for India and Sarawak. In item screening, tetrachoric correlations among the 12 binary variables in the Australian sample were used to determine that variables were monotonically related. Subsequently, MAXCOV was applied iteratively using all possible triplets of variables, with slab n≥20, to identify variables with flat covariance curves. Flatness was judged on the basis of visual appearance and variances of raw and loess-smoothed covariances.

When the final set of variables was identified with MAXCOV, MAXEIG and LMODE analyses were used to corroborate the MAXCOV findings. MAXEIG was applied using the inchworm consistency approach, starting with 5 windows overlapping by 90%. The number of windows was increased in steps to the point where windows were n≥~5 per variable (i.e., n=~60). Thus, for the Australian (n=812), Indian (n=474), and Sarawak (n=145) cohorts, the maximum number of windows were 125, 70, and 15, respectively. The taxon base rates obtained using MAXEIG were used as initial estimates of the factor score modes used in LMODE analyses. As LMODE does not require variables to be monotonically related, LMODE was applied to both the final variable set and to the initial 12-item set. Taxometric analyses were undertaken in R (R Core Team, 3.1.2 Pumpkin Helmet ed., 2014) using MAXCOV, MAXEIG, and LMODE packages adapted from Grove (2003; 2004) and Waller and Meehl (1998).

Results

Fifteen statistical models were tested and ranked, as outlined in the data analysis section. Three of these models, both single-class with factors explaining variation within that class: (1) one class/two factors, (2) one class/three factors; and also multi-class with factors explaining variation within the classes: (3) two classes/one factor, showed good overall model fit. These three models were within the four best-fitting models (weighting the three well-established fit statistics equally) for each site. Demographic and diagnostic information for the final included sample, and fit statistics for these models are included as

Table 6-1. Fit indices for all fifteen models (each of the above models for all sites) are included as Table 6-6S. Details of the three above models for each site are provided as tables 6-7S – 6-15S.

Table 6-1: Demographic, diagnostic, and best model fit information by site

		Australia (*n* = 812)	India (*n* = 474)	Sarawak (*n* = 145)
Sex	Male	573 (70.6%)	273 (57.6%)	89 (61.4%)
	Female	239 (29.4%)	201 (42.4%)	56 (38.6%)
Mean Age (SD)		39.01 years (11.82)	38.31 years (12.06)	43.05 years (12.91)
DSM-IV Diagnosis	Schizophrenia	756 (93.1%)	472 (99.6%)	101 (69.7%)
	Schizoaffective, Depressed	24 (3.0%)	1 (0.2%)	32 (22.1%)
	Schizoaffective, Bipolar	32 (3.9%)	1 (0.2%)	12 (8.3%)
1 Class/2 Factors	AIC	10753.9	5434.3	1596.6
	BIC	10918.4	5579.9	1700.8
	SSA-BIC	10807.3	5468.8	1590.0
	Total (Rank)	32479.6 (2^{nd})	16483.0 (2^{nd})	4887.4 (1^{st})
1 Class/3 Factors	AIC	10718.6	5430.5	1598.8
	BIC	10930.1	5617.7	1732.8
	SSA-BIC	10787.2	5474.9	1590.4
	Total (Rank)	32435.8 (1^{st})	16523.1 (3^{rd})	4922.0 (2^{nd})
2 Classes/1 Factor	AIC	10758.2	5426.7	1604.4
	BIC	10941.5	5589.0	1720.5
	SSA-BIC	10817.6	5465.2	1597.1
	Total (Rank)	32517.3 (4^{th})	16480.8 (1^{st})	4922.0 (3^{rd})

AIC: Akaike information criterion
BIC: Bayesian information criterion
SSA-BIC: Sample size adjusted Bayesian information criterion

Explanatory usefulness of FMM models

Both the one class/two factors, and the one class/three factors model in Australia differentiated one factor where intra-class variation was broadly explained by the four core negative symptom variables, and a second factor where variation was explained by the dysfunction and deterioration variables, along with major depression, onset and social delusions. The third factor in the three factor model differentiated from the other factors based on disorganized speech and behavior.

One class in the two classes/one factor model in Australia contained individuals with significant affective flattening and deterioration, while the other contained individuals who did not have significant anhedonia, nor deterioration. Although all three dysfunction variables (30 day-, five year-, and deterioration) had high loadings on the factor, no variables were significant. Overall, the two classes/one factor model did not differentiate DS from non-DS within the Australian sample particularly well.

The one class/two factors model in India differentiated one factor broadly on the negative symptom variables (except avolition), plus disorganized speech and social delusions. The second factor was differentiated by avolition, anhedonia, disorganized behavior, and the dysfunction variables. The one class/three factors model was less informative; no variables significantly loaded on one of the factors, only alogia and disorganized speech loaded on a second, and only deterioration loaded on the third.

The two classes/one factor model in India appeared to differentiate a DS class more clearly than in Australia. One class displayed low thresholds for 9 of the 12 variables, with 4 of these (affective flattening, avolition, anhedonia, and major depression) lower than -2, all highly significant ($p<0.001$). The other class was notable for its high threshold for alogia (11.04, $p=0.04$). The factor in this model did not have any variables with high loadings.

The one class/two factors model in Sarawak clearly differentiated factors: one based on the negative symptom variables (except anhedonia), with disorganized behavior, major depression and social delusions; the other based on avolition, anhedonia, both disorganized symptoms, all dysfunction variables, and onset. As with India, the one class/three factors model was less informative, as no variables significantly loaded on one of the factors, the second was based on the dysfunction variables, and the third on affective flattening, alogia and major depression.

The two classes/one factor model in Sarawak also broadly identified a DS class with low thresholds for nine of the twelve variables, with four of these (avolition, disorganized speech, disorganized behavior, and major depression) lower than -2, all highly significant ($p<0.001$), except avolition (fixed – no p-value). Interestingly, the factor had three variables with very high loadings (>28): avolition ($p<0.001$), 5 year dysfunction (fixed – no value), and deterioration (ns).

Taxometric confirmation

In the Australian cohort, six (9%) tetrachoric *rho* coefficients were negative, indicating that the assumption of monotonicity was not met in the 12-variable distribution. To correct this, two variables (disorganized speech and disorganized behavior) were removed from the variable set. In the first two MAXCOV analysis iterations, covariance curves for affective flattening and anhedonia, respectively, were flat and these variables were removed. The final MAXCOV iteration was of eight variables and yielded a peaked covariance curve (Figure 6-3), a base rate of *M*=.76 (*SD*=.08), variable validity (*K*) of *M*=1.25 (*SD*=0.17), and a j-shaped distribution of Bayesian posterior class membership probabilities consistent with a large prevalence class (Table 6-2). Classification based on posterior probabilities placed n=735 (.91) in the DS class. The inchworm consistency test results from the Australian cohort corroborated a class structure: The MAXEIG curve developed a clear peak that remained as the number of windows increased (Figure 6-4). The observed base rate with 95 windows was .78 (*SD*=.15) and with 125 windows, .91 (*SD*=.08). Similarly, LMODE results from the 8- and 12-item variable sets provided evidence of bimodality in the factor score density functions (Figure 6-5) with base rate estimates of .76 and .75, respectively, and n=640 and n=633 in the class, respectively.

Results obtained for the Indian and Sarawak cohorts were similarly taxonic across the three taxometric methods (Figures 6-3 to 6-5). In each case, the MAXCOV curves were peaked, the inchworm consistency curves remained peaked, and the factor scores were bimodal.

Table 6-2: Parameter estimates obtained from the taxometric methods for the three cohorts

Test	Statistic	Australia (*n* = 812)	India (*n* = 474)	Sarawak (*n* = 145)

MAXCOV	Base rate estimate (*p*)	.76	.68	.63
	Class size (*n*)	735	384	106
	Variable validity (*K*)	1.25	1.22	1.36
MAXEIG	Base rate estimate	.91	.69	.57
LMODE	Base rate estimate	.76	.76	.67
	Class size (*n*)	640	368	98

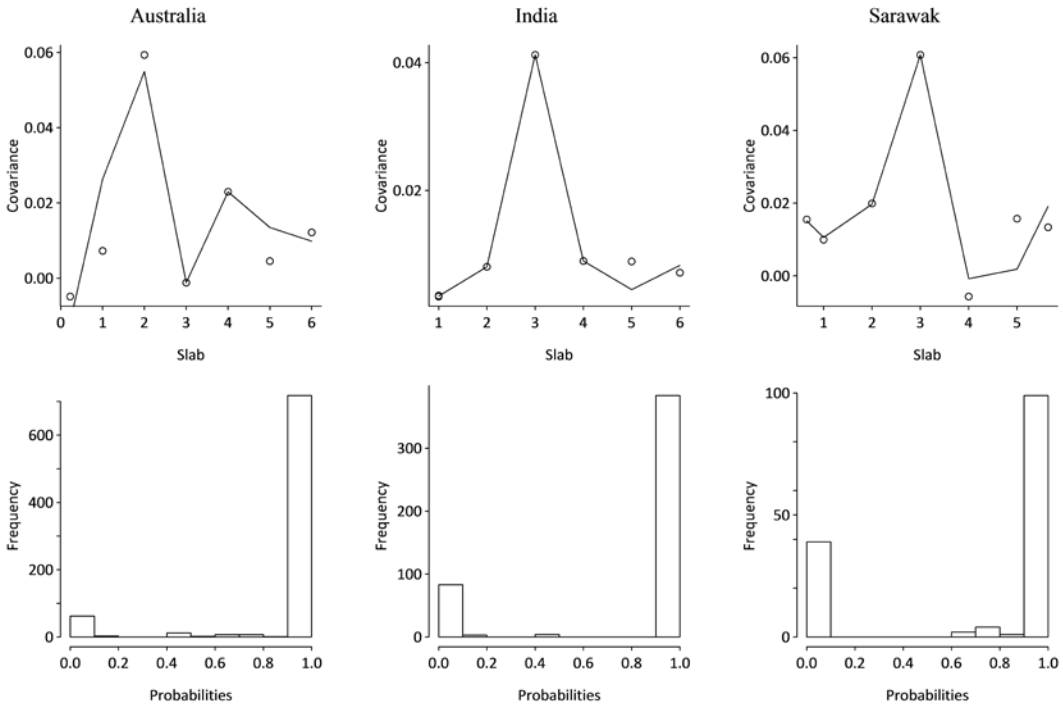

Figure 6-3. **Upper panel**: MAXCOV covariance plot obtained using 8 variables for the Australian (*n*=812), Indian (*n*=474) and Sarawak (*n*=145) cohorts. The circles indicate mean covariance estimates, and the solid line the loess-smoothed covariance. **Lower panel:** Frequency histogram of the Bayesian posterior membership probabilities for class membership for each cohort.

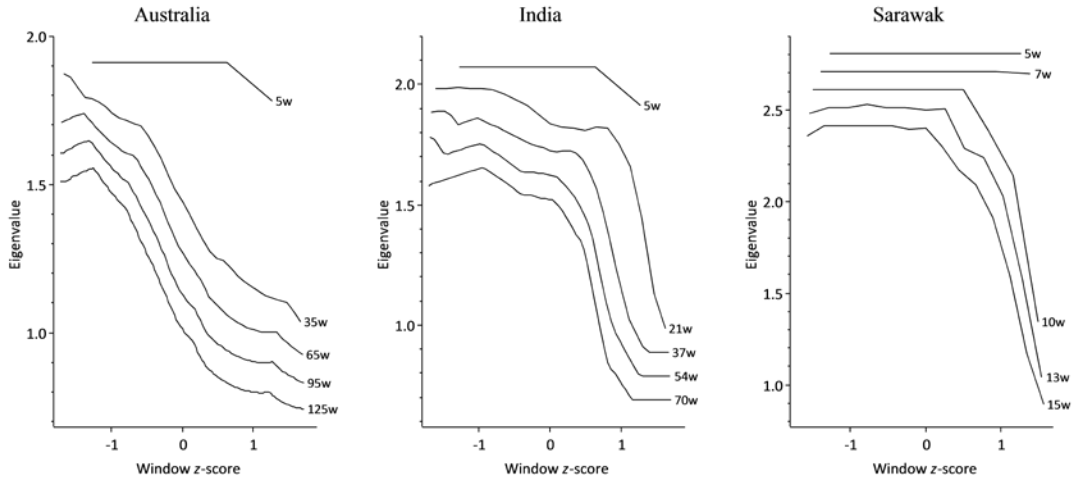

Figure 6-4. MAXEIG inchworm consistency test results for the Australian (*n*=812), Indian (*n*=474), and Sarawak (*n*=145) cohorts. Curves are loess-smoothed eigenvalues obtained using the number of windows (w) shown. The *y*-axis λ-values are true for the curves with most windows, and curves with fewer windows are offset on the *y*-axis using steps of λ=+0.1. Consequently, the 5w curves are offset by +0.4 on the *y*-axis, the 35w, 21w, and 10w curves by +0.3, etc.

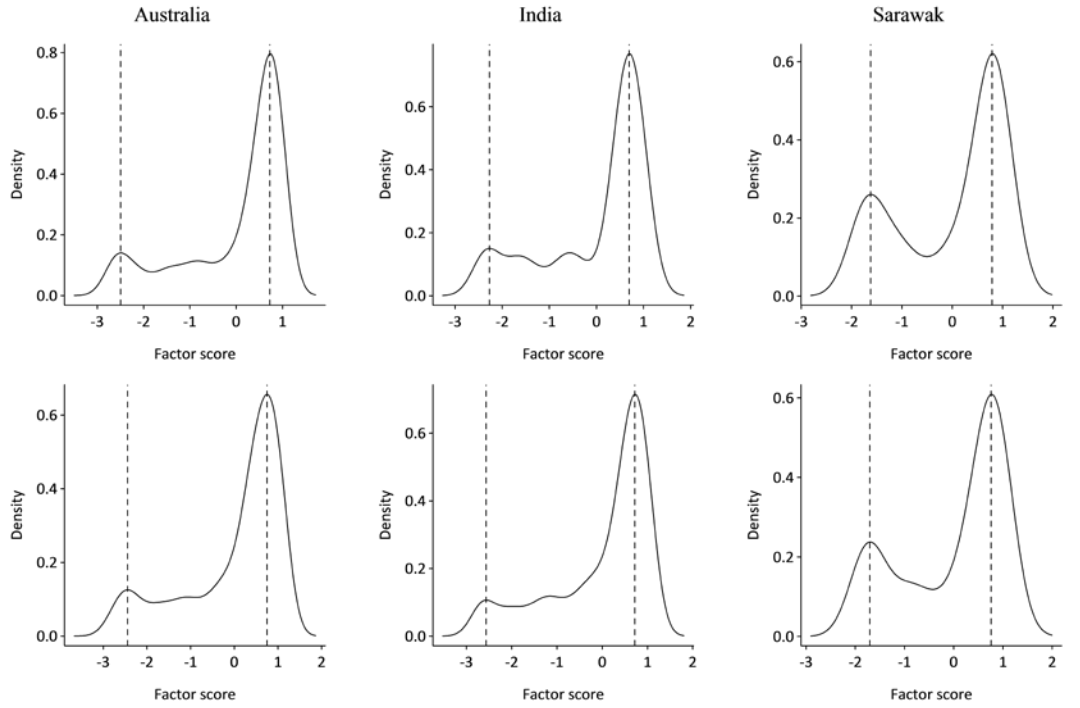

Figure 6-5. **Upper panel**: Factor-score density plots for the Australian (*n*=812), Indian (*n*=474), and Sarawak (*n*=145) cohorts from LMODE analysis of the 8 variables, with modes indicated by vertical dashed lines. **Lower panel**: The corresponding plot obtained with 12 variables.

Discussion

Broad structural similarity in model fit was evident across each of our three ethnically-distinct schizophrenia populations. This data distribution concordance across sites is potentially indicative of the universality of DS across certain ethnically-distinct populations although there were subtle but important variations between sites. Comparability between single-class and hybrid multi-class models in FMM fit statistics across the three sites tentatively supports the assertion of Ahmed and colleagues (2015) that DS may have a hybrid categorical/dimensional structure.

The single class models across all sites, particularly the one class/two factors model, broadly differentiated one factor explaining within-class variation based on core negative symptoms, and a second factor based on dysfunction variables. Overall, the two classes/one factor model in India and Sarawak differentiated DS from non-DS more clearly than in Australia. The size of the FMM deficit class across the sites: Australia, n=303 (37.3%); India, n=345 (72.8%); Sarawak, n=109 (75.2%) was broadly congruent with the taxometric analyses, in that the deficit class was larger, in India and Sarawak, but incongruent in Australia. This potentially confirms that the Australian two classes/one factor model lacks explanatory usefulness for defining DS, as neither class closely resembled the subtype.

Tantalizingly, there was a striking similarity in the taxometric two-class appearance of the data distribution of DS variables across sites, as has been identified previously (Blanchard et al., 2005). Analyses of the Australian sample suggest a large DS class, comprising 75% to 90% of the sample. Similar DS classes were identified in the Indian and Sarawak cohorts although the relative class sizes appear slightly smaller. Importantly, flat affect and anhedonia appeared to reduce the clarity of findings, suggesting that these components of DS may not have the same population structure as other components. This makes sense clinically, as these two symptoms can be characteristic in depression co-occurring in non-DS as well as representing core symptoms in DS. Overall, however, the taxometric analyses appear to support the existence of a distinct DS class, although this class (between 57% and 91% across sites) is larger than previously identified in general schizophrenia populations (between 15% and 30% (Kirkpatrick et al., 2001)).

Methodological limitations

First, our cohorts were recruited for specific genetic studies and thus were not representative schizophrenia samples. In particular they did not represent the entire chronicity spectrum, which may, at least partially, explain our larger-than-expected DS classes. Chronic, long-term cases were over-represented, particularly in the Australian and Indian samples, since these cohorts were recruited opportunistically. In contrast, the Sarawak sample can be considered relatively epidemiologically sound.

Second, the study protocol did not include a standardized instrument for diagnosis of DS. Therefore, we can only demarcate a proxy for the diagnostic entity identified by Kirkpatrick and colleagues (2001). Some variation in results has been identified between studies that assess DS using the Schedule for the Deficit Syndrome (SDS) (Kirkpatrick et al., 1989), and other validated self-report and interview-based instruments (Cohen et al., 2010).

Third, several potentially significant attributes of DS were not ascertained, e.g. suspiciousness, suicidal ideation (Kirkpatrick et al., 1989), marital status prior to onset, and completed suicides (Fenton and McGlashan 1994). Hence, the inability of our cross-sectional assessment to differentiate between *primary* negative symptoms in DS, and a broader category of *persistent* negative symptoms (see Ahmed et al., 2015), may contribute to our identified DS taxometric class being significantly larger than expected.

Conclusions

The broad similarities in the structural appearance of key DS variables in our three ethnically-distinct schizophrenia populations from Australia, India and Sarawak provide tentative support for the universality of DS across these populations. Furthermore, both single-class and multi-class models exhibited good fit statistics, which supports the hypothesis that DS has a hybrid categorical/dimensional latent structure.

Ethnically-distinct schizophrenia populations are important in elucidating the underlying distribution and heterogeneity of schizophrenia. Not only could we attempt to identify DS in other ethnically-distinct populations, but homogeneous populations can also be used to test the universality/stability of other schizophrenia subtypes identified either clinically or genetically.

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Declaration of Interest

No conflicts declared.

Chapter 6 Supplemental Tables

Table 6-6S: Fit indices for all included models by site

Model	Type	Australia			India			Sarawak		
		AIC	BIC	SSA-BIC	AIC	BIC	SSA-BIC	AIC	BIC	SSA-BIC
1 class 0 factor	LCA	11543.67	11600.07	11561.96	6248.18	6298.11	6260.03	2032.02	2067.74	2029.77
1 class 1 factor	EFA	10844.12	10956.91	10880.70	5486.84	5586.71	5510.54	1638.25	1709.69	1633.74
1 class 2 factors	EFA	10753.94	**10918.42**	10807.28	5434.28	**5579.92**	5468.84	1596.58	**1700.76**	1590.01
1 class 3 factors	EFA	10718.59	10930.07	**10787.17**	5430.48	5617.73	5474.91	1598.82	1732.78	1590.38
1 class 4 factors	EFA	****	****	****	5427.67	5652.37	5480.98	1597.27	1758.01	1587.14
2 classes 0 factors	LCA	10921.64	11039.12	10959.73	5580.75	5684.78	5605.44	1701.47	1775.89	1696.78
2 classes 1 factor	FMM	10758.20	10941.48	10817.63	5426.68	5588.97	**5465.19**	1604.41	1720.50	1597.09
2 classes 2 factors	FMM	10724.43	10978.20	10806.72	5431.46	5656.17	5484.78	1604.82	1765.56	1594.68
2 classes	FMM	10703.31	11032.28	10809.98	5426.79	5718.08	5495.91	****	****	****

3 factors										
3 classes	LCA	10801.21	10979.79	10859.12	5500.43	5658.56	5537.95	1652.77	1765.88	1645.64
0 factors										
3 classes	FMM	10733.16	10986.93	10815.45	****	****	****	1595.14	1755.88	1585.01
1 factor										
3 classes	FMM	**10699.61**	11033.28	10807.81	5429.25	5724.69	5499.35	1612.02	1823.37	1598.70
2 factors										
4 classes	LCA	10763.71	11003.38	10841.43	5456.89	5669.11	5507.24	1628.01	1779.83	1618.45
0 factors										
4 classes	FMM	10714.53	11038.80	10819.68	**5414.81**	5701.93	5482.93	**1595.07**	1800.46	**1582.12**
1 factor										
5 classes	LCA	10747.45	11048.21	10844.98	5446.87	5713.19	5510.06	1624.67	1815.18	1612.66
0 factors										

AIC: Akaike information criterion
BIC: Bayesian information criterion
SSA-BIC: Sample size adjusted Bayesian information criterion
EFA: Exploratory factor analysis
LCA: Latent class analysis
FMM: Factor mixture model

Bolded data reflect the best/optimal scores for each criterion at each site
**** No data available due to model failure

Table 6-7S: One class/two factors model in Australia

Model Type	Exploratory Factor Analysis (EFA)	
Fit Statistics (Rank)[a]	Akaike information criterion (AIC)	10753.94 (8/15)
	BIC: Bayesian information criterion (BIC)	10918.42 (1/15)
	SSA-BIC: Sample size adjusted Bayesian information criterion (SSA-BIC)	10807.28 (3/15)
	Total	32479.65 (2/15)
Factor Loadings[b]	**Factor 1**	**Factor 2**
Affective flattening	0.52*	-0.05
Alogia	0.41*	0.19*
Avolition	0.65*	0.23*
Anhedonia	0.85*	-0.08*
Disorganized speech	-0.08	0.25*
Disorganized behavior	-0.08	0.09
Dysfunction (5 year)	-0.03	0.72*
Dysfunction (30 day)	0.01	0.94*
Deterioration	0.04	0.72*
Major depression	-0.05	0.35*
Onset	0.03	0.32*
Social delusions	0.12	0.20*

a Rank (lowest to highest) out of all fifteen models for each fit statistic
b Quartimin Rotated Loadings
* $p < 0.05$

Table 6-8S: One class/two factors model in India

Model Type	Exploratory Factor Analysis (EFA)	
Fit Statistics (Rank)[a]	Akaike information criterion (AIC)	5434.28 (8/15)
	BIC: Bayesian information criterion (BIC)	5579.92 (1/15)
	SSA-BIC: Sample size adjusted Bayesian information criterion (SSA-BIC)	5468.84 (2/15)
	Total	16483.04 (2/15)
Factor Loadings[b]	**Factor 1**	**Factor 2**
Affective flattening	0.77*	0.14
Alogia	0.93*	-0.04
Avolition	0.12	0.82*
Anhedonia	0.37*	0.52*
Disorganized speech	0.29*	0.05
Disorganized behavior	-0.09	0.36*
Dysfunction (5 year)	-0.04	0.81*
Dysfunction (30 day)	0.05	0.84*
Deterioration	-0.08	0.96*
Major depression	0.34	-0.27
Onset	0.17	0.09
Social delusions	0.29*	-0.12

a Rank (lowest to highest) out of all fifteen models for each fit statistic
b Quartimin Rotated Loadings
* $p < 0.05$

Table 6-9S: One class/two factors model in Sarawak

Model Type	Exploratory Factor Analysis (EFA)	
Fit Statistics (Rank)[a]	Akaike information criterion (AIC)	1596.58 (3/15)
	BIC: Bayesian information criterion (BIC)	1700.76 (1/15)
	SSA-BIC: Sample size adjusted Bayesian information criterion (SSA-BIC)	1590.01 (4/15)
	Total	4887.35 (1/15)
Factor Loadings[b]	**Factor 1**	**Factor 2**
Affective flattening	0.77*	0.24
Alogia	0.72*	0.27
Avolition	0.25*	0.87*
Anhedonia	0.24	0.67*
Disorganized speech	-0.32	0.46*
Disorganized behavior	-0.54*	0.60*
Dysfunction (5 year)	-0.05	0.97*
Dysfunction (30 day)	0.02	0.93*
Deterioration	0.04	0.97*
Major depression	0.61*	0.02
Onset	-0.14	0.30*
Social delusions	0.47*	-0.08

a Rank (lowest to highest) out of all fifteen models for each fit statistic
b Quartimin Rotated Loadings
* $p < 0.05$

Table 6-10S: One class/three factors model in Australia

Model Type	Exploratory Factor Analysis (EFA)		
Fit Statistics (Rank)[a]	Akaike information criterion (AIC)	10718.59 (4/15)	
	BIC: Bayesian information criterion (BIC)	10930.07 (2/15)	
	SSA-BIC: Sample size adjusted Bayesian information criterion (SSA-BIC)	10787.17 (1/15)	
	Total	32435.83 (1/15)	
Factor Loadings[b]	**Factor 1**	**Factor 2**	**Factor 3**
Affective flattening	0.51*	-0.04	-0.00
Alogia	0.43*	0.15	0.12*
Avolition	0.64*	0.26*	-0.07
Anhedonia	0.86*	-0.09*	0.03
Disorganized speech	0.01	0.01	0.96*
Disorganized behavior	-0.03	-0.03	0.33*
Dysfunction (5 year)	-0.03	0.71*	0.02
Dysfunction (30 day)	0.01	0.94*	0.04
Deterioration	0.03	0.76*	-0.06
Major depression	-0.02	0.28*	0.19*
Onset	0.03	0.32*	0.01
Social delusions	0.11	0.24*	-0.11

a Rank (lowest to highest) out of all fifteen models for each fit statistic
b Quartimin Rotated Loadings
* $p < 0.05$

Table 6-11S: One class/three factors model in India

Model Type	Exploratory Factor Analysis (EFA)		
Fit Statistics (Rank)[a]	Akaike information criterion (AIC)	5430.48 (6/15)	
	BIC: Bayesian information criterion (BIC)	5617.73 (4/15)	
	SSA-BIC: Sample size adjusted Bayesian information criterion (SSA-BIC)	5474.91 (3/15)	
	Total	16523.12 (3/15)	
Factor Loadings[b]	**Factor 1**	**Factor 2**	**Factor 3**
Affective flattening	0.80	0.08	0.05
Alogia	0.95*	-0.06	-0.04
Avolition	0.18	0.60	0.37
Anhedonia	0.47	0.43	0.14
Disorganized speech	0.35*	-0.44	0.29
Disorganized behavior	-0.06	-0.09	0.42
Dysfunction (5 year)	0.08	0.09	0.66
Dysfunction (30 day)	0.14	0.33	0.56
Deterioration	-0.03	-0.04	1.03*
Major depression	0.30	-0.34	-0.02
Onset	0.20	0.20	-0.08
Social delusions	0.25	0.18	-0.21

a Rank (lowest to highest) out of all fifteen models for each fit statistic
b Quartimin Rotated Loadings
* $p < 0.05$

Table 6-12S: One class/three factors model in Sarawak

Model Type	Exploratory Factor Analysis (EFA)		
Fit Statistics (Rank)[a]	Akaike information criterion (AIC)	1598.82 (5/15)	
	BIC: Bayesian information criterion (BIC)	1732.78 (4/15)	
	SSA-BIC: Sample size adjusted Bayesian information criterion (SSA-BIC)	1590.38 (5/15)	
	Total	4921.98 (2/15)	
Factor Loadings[b]	**Factor 1**	**Factor 2**	**Factor 3**
Affective flattening	0.75*	0.25	-0.27
Alogia	0.72*	0.23	-0.08
Avolition	0.38	0.64	0.25
Anhedonia	0.44	0.41	0.39
Disorganized speech	-0.02	0.09	0.59
Disorganized behavior	-0.14	0.12	0.65
Dysfunction (5 year)	-0.07	0.99*	-0.00
Dysfunction (30 day)	0.01	0.96*	-0.02
Deterioration	0.03	0.96*	0.04
Major depression	0.81*	-0.24	0.13
Onset	0.04	0.08	0.39
Social delusions	0.34	0.11	-0.43

a Rank (lowest to highest) out of all fifteen models for each fit statistic
b Quartimin Rotated Loadings
* $p < 0.05$

Table 6-13S: Two classes/one factor model in Australia

Model Type	Factor Mixture Model (FMM)			
Fit Statistics (Rank)[a]	Akaike information criterion (AIC)	10758.20 (9/15)		
	BIC: Bayesian information criterion (BIC)	10941.48 (3/15)		
	SSA-BIC: Sample size adjusted Bayesian information criterion (SSA-BIC)	10817.63 (7/15)		
	Total	32517.32 (4/15)		
Model Results	**Estimate**	**S.E.**	**Est./S.E.**	**Two-Tailed P-Value**
Factor 1 By				
Affective flattening	1.00	0.00	999.00	999.00
Alogia	2.66	1.41	1.89	0.06
Avolition	4.59	2.54	1.81	0.07
Anhedonia	1.35	1.60	0.85	0.40
Disorganized speech	1.84	1.26	1.46	0.14
Disorganized behavior	0.52	0.67	0.77	0.44
Dysfunction (5 year)	7.43	4.95	1.50	0.13
Dysfunction (30 day)	25.94	17.08	1.52	0.13
Deterioration	8.09	5.53	1.46	0.14
Major depression	2.65	1.81	1.46	0.14
Onset	2.68	1.82	1.47	0.14
Social delusions	1.73	1.04	1.66	0.10
Class 1 (n = 303)				
Means Factor 1	0.56	0.33	1.70	0.09

Class 1 Thresholds	**Estimate**	**S.E.**	**Est./S.E.**	**Two-Tailed P-Value**
Affective flattening	-3.00	0.71	-4.21	<0.01**
Alogia	0.40	0.57	0.70	0.48
Avolition	-0.78	1.66	-0.47	0.64
Anhedonia	-0.50	1.24	-0.40	0.69
Disorganized speech	0.03	0.56	0.05	0.96
Disorganized behavior	-0.55	0.40	-1.39	0.17
Dysfunction (5 year)	2.05	1.53	1.34	0.18
Dysfunction (30 day)	7.86	6.62	1.19	0.24
Deterioration	5.15	1.94	2.66	0.01*
Major depression	0.94	0.59	1.60	0.11
Onset	-0.49	0.63	-0.79	0.43
Social delusions	1.21	0.00	999.00	999.00
Variances Factor 1	0.05	0.07	0.67	0.50
Class 2 (n = 509)				
Means Factor 1	0.00	0.00	999.00	999.00
Class 2 Thresholds	**Estimate**	**S.E.**	**Est./S.E.**	**Two-Tailed P-Value**
Affective flattening	-1.40	0.16	-8.90	<0.01**
Alogia	0.71	0.16	4.35	<0.01**
Avolition	0.50	0.22	2.26	0.02*
Anhedonia	2.17	0.37	5.95	<0.01**
Disorganized speech	-1.01	0.17	-6.05	<0.01**
Disorganized behavior	-0.99	0.13	-7.54	<0.01**
Dysfunction (5 year)	-1.11	0.23	-4.79	<0.01**

Dysfunction (30 day)	-3.19	1.68	-1.90	0.06
Deterioration	2.09	0.34	6.15	<0.01**
Major depression	-0.29	0.14	-2.09	0.04*
Onset	-1.50	0.15	-9.77	<0.01**
Social delusions	0.98	0.12	7.97	<0.01**
Variances Factor 1	0.05	0.06	0.81	0.42

a Rank (lowest to highest) out of all fifteen models for each fit statistic
* $p < 0.05$
** $p < 0.01$

Table 6-14S: Two classes/one factor model in India

Model Type	Factor Mixture Model (FMM)			
Fit Statistics (Rank)[a]	Akaike information criterion (AIC)	5426.68 (2/15)		
	BIC: Bayesian information criterion (BIC)	5588.97 (3/15)		
	SSA-BIC: Sample size adjusted Bayesian information criterion (SSA-BIC)	5465.19 (1/15)		
	Total	16480.85 (1/15)		
Model Results	**Estimate**	**S.E.**	**Est./S.E.**	**Two-Tailed P-Value**
Factor 1 By				
Affective flattening	1.00	0.00	999.00	999.00
Alogia	1.43	0.66	2.17	0.03*
Avolition	0.97	0.25	3.96	<0.01**
Anhedonia	0.81	0.19	4.19	<0.01**
Disorganized speech	0.19	0.06	3.42	<0.01**
Disorganized behavior	0.16	0.05	3.08	<0.01**
Dysfunction (5 year)	0.78	0.18	4.27	<0.01**
Dysfunction (30 day)	0.95	0.22	4.29	<0.01**
Deterioration	1.32	0.40	3.28	<0.01**
Major depression	0.05	0.08	0.56	0.57
Onset	0.14	0.05	2.79	0.01*
Social delusions	0.08	0.04	1.95	0.05
Class 1 (n = 129)				
Means Factor 1	0.70	2.68	0.26	0.79

Class 1 Thresholds	**Estimate**	**S.E.**	**Est./S.E.**	**Two-Tailed P-Value**
Affective flattening	-0.09	2.64	-0.04	0.97
Alogia	11.04	5.33	2.07	0.04*
Avolition	-29.59	0.00	999.00	999.00
Anhedonia	-2.81	2.15	-1.30	0.19
Disorganized speech	1.49	0.58	2.55	0.01*
Disorganized behavior	-1.55	0.52	-3.00	<0.01**
Dysfunction (5 year)	0.41	2.27	0.18	0.86
Dysfunction (30 day)	-3.11	3.17	-0.98	0.33
Deterioration	0.02	3.77	0.01	1.00
Major depression	-2.68	0.37	-7.18	<0.01**
Onset	-1.00	0.39	-2.59	0.01*
Social delusions	-0.37	0.00	999.00	999.00
Variances Factor 1	2.89	1.63	1.78	0.08
Class 2 (n = 345)				
Means Factor 1	0.00	0.00	999.00	999.00
Class 2 Thresholds	**Estimate**	**S.E.**	**Est./S.E.**	**Two-Tailed P-Value**
Affective flattening	-2.70	0.49	-5.45	<0.01**
Alogia	-0.61	0.69	-0.88	0.38
Avolition	-2.64	0.50	-5.34	<0.01**
Anhedonia	-2.93	0.47	-6.21	<0.01**
Disorganized speech	0.59	0.14	4.32	<0.01**
Disorganized behavior	-1.13	0.16	-7.25	<0.01**
Dysfunction (5 year)	1.21	0.27	4.55	<0.01**

Dysfunction (30 day)	-1.17	0.28	-4.17	<0.01**
Deterioration	1.80	0.55	3.26	<0.01**
Major depression	-4.30	0.52	-8.32	<0.01**
Onset	-1.00	0.14	-7.23	<0.01**
Social delusions	-0.99	0.13	-7.58	<0.01**
Variances Factor 1	10.57	3.62	2.92	<0.01**

a Rank (lowest to highest) out of all fifteen models for each fit statistic
* $p < 0.05$
** $p < 0.01$

Table 6-15S: Two classes/one factor model in Sarawak

Model Type	Factor Mixture Model (FMM)			
Fit Statistics (Rank)[a]	Akaike information criterion (AIC)	1604.41 (6/15)		
	BIC: Bayesian information criterion (BIC)	1720.50 (3/15)		
	SSA-BIC: Sample size adjusted Bayesian information criterion (SSA-BIC)	1597.09 (7/15)		
	Total	4922 (3/15)		
Model Results	**Estimate**	**S.E.**	**Est./S.E.**	**Two-Tailed P-Value**
Factor 1 By				
Affective flattening	1.00	0.00	999.00	999.00
Alogia	0.92	0.23	4.03	<0.01**
Avolition	32.70	7.70	4.25	<0.01**
Anhedonia	1.41	0.46	3.04	<0.01**
Disorganized speech	0.28	0.18	1.55	0.12
Disorganized behavior	0.33	0.26	1.29	0.20
Dysfunction (5 year)	30.06	0.00	999.00	999.00
Dysfunction (30 day)	3.04	1.04	2.92	<0.01**
Deterioration	28.45	129.73	0.22	0.83
Major depression	0.51	0.25	2.04	0.04*
Onset	0.22	0.15	1.49	0.14
Social delusions	0.17	0.11	1.49	0.14
Class 1 (n = 36)				
Means Factor 1	0.68	3.10	0.22	0.83

Class 1 Thresholds	**Estimate**	**S.E.**	**Est./S.E.**	**Two-Tailed P-Value**
Affective flattening	1.42	2.98	0.48	0.63
Alogia	2.53	2.98	0.85	0.40
Avolition	19.90	101.07	0.20	0.84
Anhedonia	1.51	4.48	0.34	0.74
Disorganized speech	-2.17	1.09	-2.00	0.05
Disorganized behavior	-27.63	0.00	999.00	999.00
Dysfunction (5 year)	-5.09	0.00	999.00	999.00
Dysfunction (30 day)	-0.69	9.33	-0.07	0.94
Deterioration	20.17	0.00	999.00	999.00
Major depression	1.95	1.32	1.47	0.14
Onset	1.08	0.93	1.16	0.25
Social delusions	0.56	0.00	999.00	999.00
Variances Factor 1	3.75	2.66	1.41	0.16
Class 2 (n = 109)				
Means Factor 1	0.00	0.00	999.00	999.00
Class 2 Thresholds	**Estimate**	**S.E.**	**Est./S.E.**	**Two-Tailed P-Value**
Affective flattening	-1.94	0.42	-4.58	<0.01**
Alogia	-0.85	0.35	-2.42	0.02*
Avolition	-43.73	0.00	999.00	999.00
Anhedonia	-1.722	0.518	-3.325	<0.01**
Disorganized speech	-2.05	0.33	-6.31	<0.01**
Disorganized behavior	-3.01	0.48	-6.31	<0.01**
Dysfunction (5 year)	0.14	0.42	0.34	0.74

Dysfunction (30 day)	-1.15	0.49	-2.36	0.02*
Deterioration	1.24	0.63	1.96	0.05
Major depression	-2.41	0.46	-5.22	<0.01**
Onset	1.22	0.26	4.72	<0.01**
Social delusions	-0.90	0.23	-3.96	<0.01**
Variances Factor 1	3.25	1.58	2.06	0.04*

a Rank (lowest to highest) out of all fifteen models for each fit statistic
* $p < 0.05$
** $p < 0.01$

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Chapter 7. Summary and General Discussion

Overview: Defining the scope of the project

This thesis aimed to: (1) compare and contrast the way 'schizophrenia' is experienced by three ethnically different populations, (2) to identify significant demographic, clinical and symptom differences in these populations, (3) to examine these differences in the context of their relevance to the structure of schizophrenia, and (4) to identify dimensions and/or clusters based on these differences, both within and across these populations, which may contribute to the discourse on the diagnostic classification of schizophrenia.

While the impact of culture on the expression and experience of schizophrenia was centrally important in the conceptualisation, operationalisation, and interpretation of the project, it was not possible to meaningfully elucidate the role of culture on schizophrenia in ethnically-distinct populations – this was clearly beyond the scope of this thesis. Rather, the impact of culture was acknowledged in the methodology, cultural equivalence was prioritised in the ascertainment of the samples, and a 'cultural lens' was applied to the interpretation of the analyses undertaken in Chapters Three, Four, Five and Six. While this thesis approached the expression of schizophrenia from a psychiatric (universalist) perspective, this was judged by the candidate to be a necessary concession to the anthropological (relativist) perspective, acknowledging that culture is critical in nearly every aspect of schizophrenic illness experience (Jenkins and Barrett, 2004).

The three transethnic schizophrenia samples were contrasted using increasingly broad criteria. First, site differences in individual demographic and clinical characteristics were investigated (Chapter Three); next, characteristic symptom profiles were sought (Chapter Four); and then, the core schizophrenia diagnostic criteria widely used in psychiatry were examined in relation to the differential schizophrenia expression identified across sites (Chapter Five).

For the final analyses (Chapter Six), the scope of enquiry was narrowed, and the lessons learned in previous chapters were used to guide the search for a deficit schizophrenia subtype in each of the three ethnically-distinct populations. Deficit schizophrenia was chosen as the target subtype because: (a) the candidate's group had previously published on a subtype resembling DS (Holliday et al., 2009); (b) the subtype is of current interest in the literature against the backdrop of subtypes being dropped from DSM-5 (APA, 2013b); (c) the available ethnically-distinct samples provided a unique opportunity to seek DS in

multiple ethnicities using similar statistical methods to those utilised in contemporary, single population studies (see Ahmed et al., 2015); and (d) the candidate's group had compiled anecdotal evidence that the Indian sample appeared generally 'more unwell', with a high frequency of negative symptoms in their diagnostic symptomatology. While this may be considered a modest goal in isolation (necessarily so for the scope of this thesis), the methodology used for these analyses can be applied to other schizophrenia subtypes and other ethnically-distinct populations, and potentially to other complex disorders.

Contributions to the literature

The thesis makes a significant independent and original contribution to the academic discourse on the expression of schizophrenia in ethnically different populations across each of the aims outlined above.

Compare and contrast the experience of 'schizophrenia' in three ethnically different populations

A significant contribution of this thesis has been the consistent, successful application of a transcultural/transethnic lens to a theoretical debate that has generally been conducted in single, often 'Western' populations. The decisions to: (1) meaningfully engage with the anthropological literature (best exemplified by Chapter Five) in order to enrich the transcultural understanding generated from this work; (2) use well-ascertained and confirmed ethnicity as a proxy to explore cultural impact on illness experience; and (3) contrast three unique schizophrenia populations, have resulted in a greater depth of enquiry than would otherwise be possible when approaching this topic from a universalist, psychiatric perspective.

These studies have shown that the complex, multi-dimensional role of culture is not necessarily an impediment to isolating candidates for genetic studies (Chapter Three). Rather, examining ethnically-distinct populations can potentially uncover candidates due to their differing expression across samples (Chapter Five).

Identify significant demographic, clinical and symptom differences in these populations

At every level of enquiry, significant differences in these populations were identified and explored. Whereas Chapter Three identified site differences across individual *variables*, Chapter Four identified differences in symptom *profiles*, using previously reported Iban

characteristic symptoms as a framework for enquiry and comparison, and Chapter Five identified significant differences in the frequencies of core *diagnostic criteria* across sites, and also the content of delusions and hallucinations.

The older AAO finding in the Iban (Chapter Three) is worthy of further genetic interrogation, since the reported mean age was older than both the figure for LAMI countries (Large et al., 2008), and that reported for indigenous groups in Malaysia (Chee et al., 2010), and AAO heritability has been reported (Hare et al., 2010), with AAO-associated genetic variants having been uncovered (Renou et al., 2007).

As with any stark result, particularly one that can be considered counter-intuitive, caution is needed in interpreting and generalising this finding. While it is certainly possible that the reported AAO result identifies a population-specific illness characteristic, it is also possible the finding may be confounded by other characteristics or by differences in the overarching social determinants (economic and social conditions that influence health status) between sites (see limitations below for more detail). For example, duration of untreated psychosis (DUP) in the Sarawak sample was significantly shorter than for the other sites, age at assessment was significantly older in Sarawak, as was age at first treatment, and frequency of rapid psychosis onset was higher in the Iban. It is logical that this group of age and onset related symptoms may be related, and may be acted upon by a common confounding variable or variables.

Examine these differences in the context of their relevance to the structure of schizophrenia

Chapters Four, Five and Six have each made a modest novel contribution either to our understanding of the structure of the entity we call ‘schizophrenia’, or by generating avenues for future research.

This thesis has confirmed the value of searching for specific symptom profiles, both within ethnically distinct populations (e.g. the Iban of Sarawak – Chapter Four), and between them (e.g. deficit schizophrenia – Chapter Six). Chapter Four also provides confirmation of a characteristic Iban symptom profile proposed by Professor Barrett (Barrett, 2004; Barrett et al., 2005) in an extended, more comprehensively ascertained sample. While small scale replication is certainly not a ground-breaking contribution, it is an important scientific undertaking.

The Indian sub-group with no positive schizophrenia symptoms (Chapter Five) is of particular interest because this expression somewhat resembled “simple schizophrenia” (APA, 1994), a profile that was absent in the largest ethnically-distinct (Australian) cohort. Thus, this may not only be an attractive candidate for genetic interrogation, but it also supports the hypothesis that schizophrenia is not a single, continuous entity.

The identification of the simple schizophrenia subtype has widely been attributed to Bleuler in 1911 (Black and Boffeli, 1989), although Diem described the first few cases as early as 1903 (Martinez Serrano et al., 2012). The diagnosis has always been controversial (Black and Boffeli, 1989; Martinez Serrano et al., 2012), with only two of eight reported symptom complexes, avolition and deteriorating course, accepted as core components in all major diagnostic texts (Black and Boffeli, 1989). The subtype was first included in ICD-6 in 1948, and DSM-I in 1952 (Black and Boffeli, 1989). Although it has remained in each subsequent iteration of the International Classification of Diseases, up to and including ICD-10, simple schizophrenia was dropped from DSM-III and DSM-IIIR, brought back (as simple deteriorative disorder) in the Appendices of DSM-IV and DSM-IV-TR as a “Criteria Set Provided for Further Study” (APA, 1994, 2000), and then dropped again from DSM-5.

Importantly for transcultural/transethnic research, simple schizophrenia was recognised as a diagnostic category for both the IPSS and DOSMed, although it was consistently applied rarely across sites. In a subtype analysis conducted on the IPSS sample, Carpenter et al. (1976) reported that simple schizophrenia was diagnosed in only 31 cases out of 811 (3.8%), and there were never more than seven cases at any site, making comparisons problematic. The DOSMed reported a similar trend, “Diagnoses of simple schizophrenia, latent schizophrenia and residual schizophrenia were rarely made in either type [developed or developing] of setting” (Sartorius et al., 1986: 920). Thus, the WHO studies were unable to identify significant differences in the rates of simple schizophrenia diagnosis across sites.

A contemporary literature review by Martinez Serrano et al. (2012), found that, although the literature on the disorder remains scant, many (>26) of the articles published on simple schizophrenia were in languages other than English or Spanish, which is certainly of interest from a transcultural perspective. The authors propose several explanations for the low rate of diagnosis that may disguise its true prevalence: (1) the less dramatic clinical

presentation may reduce the likelihood of individuals affected by simple schizophrenia to seek psychiatric assistance in contrast to other subtypes; (2) the loss of insight and initiative that are characteristic of simple schizophrenia may reduce the likelihood of individuals seeking assistance; and (3) the general lack of interest in the subtype from clinicians may lead to the under-diagnosis of simple schizophrenia, as individuals receive other diagnoses when they present for assistance (Martinez Serrano et al., 2012).

Certainly, the Indian subgroup identified in Chapter Five is interesting, as the factors identified above would likely lead to the under-reporting of simple schizophrenia in India, given that the sample was recruited opportunistically from a primarily clinical cohort. Thus, the true proportion of those with simple schizophrenia in the Tamil Brahmin and geographically proximal caste groups in Chennai, may be greater than the reported 4%. Given that the opportunistic Australian sample recruited in this thesis would be expected to have similar 'classification biases' to the Indian sample, the finding of a difference in the presence/absence of a subtype resembling simple schizophrenia appears robust. Furthermore, Carpenter et al. (1976) noted that, whereas most subtypes of schizophrenia were indistinguishable from each other in the IPSS sample based on 27 psycho-pathologic signs and symptoms, both the simple and catatonic subtypes were modest exceptions (i.e. they were distinguishable from other subtypes). Thus, simple schizophrenia may offer promise as a discrete entity, despite its controversial history.

Identify dimensions and/or clusters based on these differences, both within and across these populations, which may contribute to the discourse on the diagnostic classification of schizophrenia

The analyses presented in Chapter Six are extremely topical, given the current interest in deficit schizophrenia (Cohen et al., 2010), and the growing use and acceptance of Factor Mixture Modeling methods in the schizophrenia field (e.g. Ahmed et al., 2014; Linscott et al., 2009). The thesis has made a small, but important novel contribution, both directly to testing the deficit schizophrenia construct using FMM through the interrogation of multiple relevant schizophrenia samples, but also indirectly through proposing directions for future enquiry (see below).

In relation to testing the DS construct, the structural similarity of DS variables across populations (Chapter Six) is important in a syndrome where there does appear to be structural variation (Chapter Five). Both single class and multi-class models exhibited good

model fit, although a degree of interpretability is common in analysing FMM results. It is particularly noteworthy that taxometric analyses strongly indicate a two class structure in all three populations, irrespective of symptom and illness course variation across sites. While these results offer tentative support to previous studies examining negative symptoms in schizophrenia (see Ahmed et al., 2014; Blanchard et al., 2005), it is noteworthy that the identified 'deficit' class is significantly larger than previous studies, possibly due to the analyses in Chapter Six identifying a larger class of general, persistent negative symptoms (rather than primary, idiopathic negative symptoms), and possibly related to the characteristics of included individuals (see limitations below). Given that this result was somewhat unexpected, it will be important to explore how accurately the identified deficit class truly represents deficit schizophrenia. Until more work is undertaken, this finding should be interpreted with caution.

In assessing the novel contribution of these DS findings, it is worthwhile viewing these results as two separate entities: (1) structural similarity across the three sites, and (2) potential identification of a deficit class. The former finding is noteworthy, regardless of what construct the latter is truly demarcating. Despite the differences in expression identified in Chapter Three and Chapter Four, and the diagnostic differences identified in Chapter Five, there was broad similarity in the appearance of the data distribution across sites when structure was assessed on the presence or absence of the twelve variables selected (based on prior research) in Chapter Six. Furthermore, the broad similarity was apparent utilising two different statistical methods, factor mixture modelling and taxometric analyses. Thus, against a background of identified contrasts in the expression and experience of schizophrenia between ethnically distinct groups, it is apparent that some aspects and symptom groupings are similar and consistent. This finding has overarching importance when interpreted with previous chapters in that it places the true construct of what we currently call schizophrenia somewhere on the continuum between universalism and relativism. On a more specific diagnostic level, it adds weight to the notion that schizophrenia is not a single, homogeneous entity.

The second finding is also important, independent of whether it can truly be ascribed to deficit schizophrenia as defined by Carpenter et al. (1988). A clear, categorical (two-class) distribution was identified by multiple taxometric methods, and this finding was not contradicted by factor mixture modelling. Therefore, there is an entity worthy of further

investigation, incorporating the twelve variables examined, regardless of what that entity represents clinically.

The thesis has also confirmed the usefulness of FMM and taxometric analyses in interrogating complex disorders such as schizophrenia, building on past (Blanchard et al., 2005; Linscott et al., 2009) and contemporary (Ahmed et al., 2015) studies in the field. This thesis is a partial replication of the methods utilised by Ahmed et al. (2015), the research group that pioneered the concept of a deficit schizophrenia subtype (Carpenter et al., 1988). Whereas their group interrogated a single cohort of mixed-ethnicity schizophrenia patients in the United States, this thesis was able to extend this work to contrasting three ethnically-different populations. These methods are valuable in exploratory endeavours specifically because they are unintelligent systems that make fewer assumptions about data distribution than other commonly used statistical methods. These methods are relatively new in this field, so replication of the method in three distinct populations is methodologically worthwhile, regardless of the results.

Important strengths and limitations

There are many noteworthy strengths of the body of work undertaken in this thesis. The candidate had access to three unique schizophrenia samples recruited and ascertained by Professor Mowry and his collaborators that are relatively large for transethnic studies (Australia, n=821; India, n=520; Sarawak, n=298). Two of these samples are from genetically isolated groups – the Tamil Brahmin in India and the Iban of Sarawak, and the Iban sample in particular was logistically difficult to obtain. Thus, the three samples for comparison are truly unique, and the expression of schizophrenia in similar samples has never previously been contrasted.

The psychiatric and anthropological groundwork undertaken collaboratively by the experienced site coordinators resulted in a high degree of cultural equivalence in the ascertainment of the samples, combined with genetic confirmation of their ethnic distinctness. In summary, this confirmation involved undertaking genomewide association analyses (GWAS) for each sample. One quality control procedure involved conducting principal component analyses to confirm each individual's GWAS data – typically the first three principal component scores for each subject using single nucleotide polymorphisms (SNPs) from the particular study population that are in common with SNPs from international HapMap or 1000 Genome populations in order to exclude ancestral/ethnic

outliers from further analyses. Thus, all included individuals at each site were closely 'grouped' genetically, consistent with externally-generated control populations for each ethnicity. These procedures are routinely conducted in genetic analyses. This rigour in study design either negated or minimised the impact of many criticisms of cross-cultural research.

The samples were collected primarily for genetic studies, thus the quality of demographic, clinical, symptom and illness course data required was relatively high. Since the effect sizes in schizophrenia genetic studies tend to be relatively small, it is particularly important to minimise phenotypic heterogeneity. As a result, these studies used the BEFD method, which is the benchmark method available with current methods of classifying schizophrenia (McLean et al., 2012a). The data available were therefore both rich and comprehensive.

The extensive data cataloguing, extraction, formatting and checking strategy (outlined in Appendix C) resulted in a clean, easy to interrogate data set. This allowed the candidate to have a high degree of confidence in the results obtained from the analyses undertaken.

Finally, although this thesis was not able to 'unravel' the complex impact of culture (which was beyond the scope of this work), the analyses contained herein were able to control for many conditions that are often 'possibly' attributable to cultural confounding.

There are many significant limitations that also must be acknowledged across five major areas: (1) data collection issues, (2) population characteristics, (3) directly culture-based issues, (4) limitations of diagnostic methods and scope of study, and (5) overarching confounders in the data.

(1) Data collection issues: There was an unavoidable lack of measurement equivalence across samples, due to differing recruitment methods and the fact that these samples were primarily collected for genetic studies. Notably, there was a potential confounding effect of including both related and unrelated individuals in analyses. Consequently, conservative models were selected for analyses that were likely confounded by a lack of complete independence; specifically, only unrelated individuals were included in the logistic regressions undertaken in Chapter Four.

Additionally, there were differences in the quality of clinical and diagnostic data (e.g. differing comprehensiveness of available medical records) obtained across sites. The lack of measurement equivalence across sites certainly introduces the potential for significant selection bias, as the coverage of the treatment 'spectrum' at each site differs. For example, many of the included individuals accessed through initial comprehensive medical records screen in the Sarawak sample would not be identified using the opportunistic recruitment methods from primarily clinical settings that were utilised in both Australia and India. This necessarily limits the generalisability of any findings to 'schizophrenia' as a general population-wide category at each site.

Regardless of the rigour of the methodology used for establishing cultural equivalence across sites, there will inevitably be limited precision and uncertainties regarding the validity of diagnostic instruments used across different cultural groups.

(2) Population characteristics: There is limited generalisability of findings due to the Iban and Tamil Brahmin being distinct, unique subgroups within larger societies. Certainly, while findings of equivalence across the three samples in this thesis can, to a degree, be generalised more widely to these specific schizophrenia populations, there is no assertion that these findings may imply universality across 'schizophrenia'.

(3) Directly culture-based issues: While the robustly ascertained and genetically confirmed ethnicity of the three schizophrenia populations is certainly a strength of the thesis, it must be acknowledged that although working with ethnically homogeneous and geographically constrained samples enables assessment of cultural confounders because these two factors represent the best available proxy for culture (Azuonye, 1994), ethnicity is still a proxy. Therefore, consistent with the summary provided in Chapter One, it is not possible to elucidate the complexities of cultural impact on psychoses (e.g. cultural variation within the European Caucasian Australian sample and differences between the included castes in India), and this was certainly beyond the scope of the thesis.

The confounding role of culture will also necessarily be problematic due to the importance of language (a culture-bound construct) in diagnosing the syndrome of schizophrenia. Furthermore, using a sample diagnosed with DSM-IV schizophrenia or schizoaffective disorder to interrogate the classification of schizophrenia itself is problematic, from both cultural and validity standpoints.

(4) Limitations of diagnostic methods and scope of study: Excluding cases of Bipolar Affective Disorder (BPAD) prevents the possibility of meaningfully examining the interplay between mood and psychotic symptoms, whereas excluding cases of psychosis that do not meet DSM-IV schizophrenia or schizoaffective disorder criteria ignores cases that may be of the most transcultural interest. A related, general limitation of using DSM-IV to assess psychosis in diverse, often non-clinical settings, results from the DSM system primarily relying on clinical observations made by mental health professionals to generate a diagnosis. Thus, a significant proportion of people with mental disorders world-wide will never be assessable, and will be missed in studies such as the work undertaken in this thesis.

The samples ascertained in this thesis are necessarily cross-sectional, with no opportunity to revisit included individuals at a later time point. As a result, there are significant limitations in determining temporal relationships between certain symptoms, and establishing detailed illness course variables. This limitation is particularly relevant to the analyses in Chapter Six, making it difficult to distinguish between primary negative symptoms in DS, and a broader category of persistent negative symptoms.

Finally, there are limitations imposed from using genetic samples to explore non-genetic constructs and culturally-sensitive variables. The researchers did not ask follow-up questions that may have been able to clarify ambiguities, and there were limited qualitative data recorded. The problematic ascertainment of deficit schizophrenia without using the Schedule for the Deficit Syndrome exemplifies this issue.

(5) Overarching confounders in the data: Significant differences in some clinical phenotype variables between sites results in the potential for these to confound all other explanations of psychopathology. For example, the speed of psychosis onset (rapid onset being significantly more frequent in Sarawak) may confound any results showing associations with positive symptoms. The importance of speed of onset as a crucial variable in understanding site differences is certainly acknowledged in Chapter Four and Chapter Six, although it is unrealistic in an exploratory research design to control for all potential confounding variables. Instead, the thesis highlights many candidates for future interrogation, and speed of psychosis onset is certainly an illness characteristic deserving of future examination.

A related overarching confounder that must be acknowledged is the global effect of social determinants such as gender and socio-economic deprivation on illness expression. As has been acknowledged throughout the thesis, socioeconomic position is a strong determinant of health outcomes (Egede, 2006), as it is crucial to many aspects of the illness experience. The differential sex effects by site (Table 3-2S and Table 3-3S) show the importance of sex as a mediating variable. Other examples of important factors in illness experience are caste in India and differential access to health care by site (as noted in the introduction of Chapter Three).

Translation of research into other applications (e.g. genetics)

The analyses undertaken in this thesis derive from samples recruited specifically for genetic studies. Certainly, there are opportunities for the findings generated herein to aid genetic exploration within the complex syndrome of schizophrenia. Specific directions for future enquiry are detailed below.

Moreover, the demarcation of three relatively large, ethnically distinct, equivalently ascertained schizophrenia samples has applications beyond just the field of schizophrenia genetics. The candidate and his collaborators have already published on the drug and alcohol variables in the Australian sample (McLean et al., 2012b). Multiple peer-reviewed papers have been accepted for publication in the vocational rehabilitation field in Australia, based on variables from the Australian dataset (Westcott et al., in press(a); Westcott et al., in press(b)). Variables from the Australian dataset have also been used in multiple publications on neuroimaging in schizophrenia (Martin et al., 2014a; Martin et al., 2014b), in addition to the genetics of schizophrenia (Martin and Mowry, in press; Martin et al., 2015; Martin et al., 2014c).

Having access to these samples also allows researchers to begin to test the universality of findings regarding schizophrenia generated in single samples, both within and outside the genetics field.

Directions for future enquiry

The general methodology laid out in this thesis has potential to guide future genetic enquiries, both generating and testing candidates that will assist in ‘unravelling’ the complex clinical phenotype of schizophrenia. Variation in *individual variables* can be

identified in ethnically-distinct populations, such as the older AAO finding in Sarawak (Chapter Three) that may be novel targets for genetic analyses. Characteristics that have been identified as heritable in other ethnic populations can be tested in multiple, ethnically-distinct samples, whereas other characteristics may be initially targeted due to their distinctive clinical phenotype in one or more ethnically-distinct cohorts. Between-group clinical variation can be identified and interrogated through examination of *distinct symptom profiles* (Chapter Four). Where observable between-site differences are present, variation can be quantified and tested by either *clusters of cases*, such as the Indian subgroup with no positive symptoms (Chapter Five), or by *clusters of symptoms*, such as attempting to demarcate deficit schizophrenia (Chapter Six).

These search strategies and statistical methods could certainly be transferred to genetically-complex disorders other than schizophrenia. Of more direct relevance to this thesis however, this general design can be used to test proposed subtypes of schizophrenia other than DS in the Australian, Indian, and Sarawak samples. Additionally, these specific ethnically-distinct schizophrenia samples can be used to clinically interrogate additional novel genetic findings identified in the future, which may be important given the promising results being generated currently.

The specific findings presented in this thesis can potentially be tested and/or replicated in other, single ethnically-distinct populations, without needing to specifically recruit multiple samples. Increasing recognition of the need to pool large schizophrenia samples to produce meaningful genetic results (see Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) has resulted in researchers world-wide having greater access to well-ascertained samples of diverse ethnicities.

Alternatively, given that many transcultural studies in the health field focus on ethnic migrant groups, each of the samples ascertained in this thesis potentially has a role in providing contrast to migrant studies. Do these populations (i.e. European Caucasian Australians, Tamil Brahmin and geographically proximal caste groups from Chennai, and the Iban of Sarawak) retain the same demographic, clinical, and symptom characteristics when they migrate to other countries, and does their taxonic profile remain stable in a new setting? Recruiting migrant schizophrenia populations would certainly be problematic due to the Iban and Tamil Brahmin being distinct, unique subgroups, although such a sample may be achievable in expatriate Australians.

The three samples ascertained in this thesis will continue to be interrogated and widely reported, due to (1) the high quality, uniqueness and equivalence of the data, (2) the responsibility of the candidate and his collaborators to maximise the research impact of these cohorts, and (3) the currency and open-endedness of several of the study ethics approvals. There are multiple variables (e.g. treatment resistance) that were painstakingly extracted in all three populations, but have yet to be comprehensively analysed (see Appendix B). Given the importance of schizophrenia treatment resistance as a variable both clinically and genetically, there is certainly scope to test further hypotheses in these samples.

On reflection, there are characteristics of the samples that could be improved should major transethnic schizophrenia cohorts be recruited in the future. Ideally, once target populations and/or sites are identified, standardised, epidemiologically-sound sampling methods should be used at all included sites, incorporating a longitudinal design capturing illness onset. An explicit framework for establishing cultural equivalence, such as that presented by Herdman et al. (1998) would be useful, as this would make explicit both the steps taken in establishing equivalence, and also the theoretical underpinning of the study. Furthermore, the standardised diagnostic instruments used would be subjected to this rigorous testing prior to the commencement of the study.

Recruiting ethnically-distinct cohorts specifically for comparing and contrasting schizophrenia expression would allow key qualitative questions to be included in the assessment battery, and could incorporate a longitudinal study design. This would allow for in-depth examination of the complex relationship between cultural identity, national identity, and self-assigned ethnicity, which would enhance the potential for generalisability of results where equivalence can be reasonably established. Furthermore, broad populations that are not genetic isolates could be targeted to enhance wider applicability.

A target set of variables for extraction could be identified in the study design that would address specific research questions. For example, a more comprehensive assessment of illness course would have greatly enhanced this thesis, as it would have allowed the candidate to better elucidate the temporal relationships between variables. This enables researchers to test the stability of characteristics and profiles over time, and would greatly facilitate the assessment of subtypes such as DS. Also, known and expected cultural-

confounding variables could be purposefully collected, along with crucial variables in transcultural research, such as socio-economic status.

However, recruiting samples such as those included in this thesis is a prodigious task that is both time consuming and expensive. Therefore, it is unrealistic to expect large ethnically-distinct schizophrenia cohorts to be collected primarily for these purposes. Certainly, the immediate future for the field is likely to rely upon existing genetic and epidemiological collaborations to provide samples for analysis.

Conclusions

Overall, there is support for schizophrenia not being a discrete, homogeneous condition. Some elements of expression (individual variables, symptom profiles, diagnostic demarcations) differ between the three ethnically-distinct populations presented here, whereas other elements of expression (e.g. tentative evidence for deficit schizophrenia) appear stable across these samples. There is also evidence that some expressions are population-specific, for example the subgroup in India (n=20) with no positive symptoms.

Transcultural schizophrenia samples can have an important role in unravelling and understanding clinical complexity, assisting genetic enquiry, and informing diagnostic classification, particularly when samples are equivalent and viewed through a culturally sensitive lens.

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Appendix A

Holliday EG, **McLean DE**, Nyholt DR and Mowry BJ (2009) Susceptibility locus on chromosome 1q23-25 for a schizophrenia subtype resembling deficit schizophrenia identified by latent class analysis. *Archives of General Psychiatry* 66(10): 1058-1067.

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Appendix B: Data Dictionary

Variable	Type	Format	Characteristic	Definition	Range	Coding Decisions/Implications
PrimID	Char	$12.	Primary ID number	Primary ID number	1639 unique code numbers	Different formats retained across sites/studies: Australia/MGS1: 41-XXXX-XXX; Australia/MGS2: 141-XXXX-XXX; India: XXXX-XXX; Sarawak XXX.
SecID	Char	$7.	Secondary ID number	ID number for Sarawak detailed pedigree subset	Australia: NA India: NA Sarawak: 1-001 – 203-001	Only relevant for Sarawak pedigree subset (n=145)
Country	Char	$3.	Site	Australia, India, Sarawak	AUS; IND; SWK	
Diagnosis	Char	$8.	Diagnosis	DSMIV Diagnosis	SAD; SAM; SZ	SAD = Schizoaffective, depressed SAM = Schizoaffective, bipolar SZ = Schizophrenia
SEX	Char	$1.	Sex	Sex: Male or Female	M; F	M = Male; F = Female
AGE	Char	$3.	Age at Assessment	Age at Assessment (Current age)	14-100; UU	UU = Unknown
OnsetAge	Char	$3.	Onset Age	Age at onset of psychosis	3-81; UU	UU = Unknown
IllDur	Char	$3.	Illness Duration	Illness duration (onset to current) in years	0-62; 16+; 20+; UU	16+ = at least 16 years 20+ = at least 20 years UU = Unknown When changing 'n+' values to numeric, each becomes 'n'. '0' encompasses all individuals with illness duration <1 year (at assessment).
FirstTr	Char	$3.	Age at First Treatment	Age at which psychiatric treatment first accessed	12-81; N/A; UU	N/A = Not applicable/never treated UU = Unknown
DUP	Char	$3.	Duration of Untreated Psychosis	Period between onset and first treatment (in years)	0-57; 16+; 20+; UU	16+ = at least 16 years 20+ = at least 20 years UU = Unknown When changing 'n+' values to numeric, each becomes 'n'. '0' encompasses all individuals with DUP <1 year.
Marital	Char	$8.	Marital Status	Current marital status (at time of assessment)	married; nevmar; sepdiv; widowed; unknown	married = married nevmar = single, never married sepdiv = separated or divorced widowed = widowed, not remarried unknown = unknown How the widowed category is grouped is dependent on the hypothesis being tested
LivArr	Char	$8.	Living Arrangements	Who the individual currently resides with (at time of assessment)	alone; facility; family; others; unknown	alone = lives alone (including hostel) facility = lives in a psychiatric treatment facility family = lives with biological family members and/or spouse others = lives with people who are not family (e.g. friends, housemates) unknown = unknown
Hos_YN	Char	$4.	Hospitalised (Yes/No)	Whether the individual has ever been hospitalised for psychiatric reasons	No; Yes; Unk	Unk = Unknown
Hospital	Char	$4.	Number of hospitalisations	Number of psychiatric hospitalisations (lifetime)	0-104; >10; >12; >14; >2; >20; >25; >3; >5; Unk	Unk = Unknown When changing '>n' values to numeric, each becomes 'n+1'.
YrsSchl	Char	$4.	Years of Formal Schooling	Years of formal schooling	0-22; Unk	Unk = Unknown

						Tertiary study years as defined by the DIGS: 1 year college or any amount technical school (TAFE) = 13 2,3,4 years college = 14,15,16 Masters = 18 PhD = 20+
CurrEmp	Char	$12.	Current Employment Status	Employment status (at time of assessment)	disabled; homemaker; never worked; student; unemployed; working; unknown	disabled = formerly worked, no longer able homemaker = homemaker primary role never worked = never worked at least 30% of time student = full-time student unemployed = not disabled but not working working = working at least 30% of time
EmpHist	Char	$2.	Employment History	Level of occupational disability over the past 5 years	1; 2; 3; 4; 5; U	1 = Always worked 2 = Periods of unemployment not related to illness 3 = Minor occupational dysfunction 4 = Moderate occupational dysfunction 5 = Severe occupational dysfunction U = Unknown
Thyroid	Char	$4.	Thyroid	Definite evidence of clinically significant thyroid problems	No; Yes; Unk	Unk = Unknown
Epilepsy	Char	$4.	Epilepsy	Definite evidence of epilepsy or clinically significant seizures	No; Yes; Unk	Unk = Unknown
HeadInj	Char	$4.	Head Injury	Definite evidence of a significant head injury (i.e. serious enough to involve loss of consciousness) (lifetime)	No; Yes; Unk	Unk = Unknown
AbnoBED	Char	$4.	Abnormal Birth or Early Development	Definite evidence of clinically significant birth complications during individual's birth, or definite delayed developmental milestones	No; Yes; Unk	Unk = Unknown
IntDis	Char	$4.	Intellectual Disability	Intellectual disability: IQ assessed <75	No; Yes; Unk	Unk = Unknown
Alcohol	Char	$4.	Alcohol Use Disorder	DSMIV lifetime alcohol abuse and/or dependence	No; Yes; Unk	Unk = Unknown
Cannabis	Char	$4.	Cannabis Use Disorder	DSMIV lifetime cannabis abuse and/or dependence	No; Yes; Unk	Unk = Unknown
OthDrug	Char	$4.	Other Drug Use Disorder	DSMIV lifetime other illicit drug abuse and/or dependence	No; Yes; Unk	Unk = Unknown
DrugType	Char	$60.	Illicit Drug Use Disorder Type	Types of illicit drugs for which the individual meets the DSMIV criteria for lifetime abuse and/or dependence	Text field	Blank for all individuals where OthDrug is not 'Yes'
Suicide	Char	$4.	Suicide Attempts	Whether the individual has ever attempted suicide	No; Yes; Unk	Unk = Unknown
SerInt	Char	$4.	Serious Suicidal Intent	Whether the individual's most serious/severe suicide attempt involved serious intent to die	No; Yes; Unk; N/A	Unk = Unknown N/A = Not applicable, no suicide attempts
FinDel	Char	$4.	Final Delusions	Definite (lifetime) presence of delusions	No; Yes; Unk	Unk = Unknown
SevCuDel	Char	$8.	Severity of Current Delusions	Severity of current delusions (past 30 days)	None; Question; Mild; Moderate; Marked; Severe; Unknown	'Question' category usually grouped with 'Unknown' category for analyses

BizDel	Char	$4.	Bizarre Delusions	Presence (lifetime) of definitely bizarre delusions	No; Yes; Unk	Unk = Unknown
BIWDel	Char	$4.	Broadcast/Insertion/Withdrawal Delusions	Presence (lifetime) of thought broadcast/insertion/withdrawal delusions	No; Yes; Unk	Unk = Unknown
ContDel	Char	$4.	Control Delusions	Presence (lifetime) of delusions of control of thought or actions	No; Yes; Unk	Unk = Unknown
PersDel	Char	$4.	Persecutory Delusions	Presence (lifetime) of persecutory delusions	No; Yes; Unk	Unk = Unknown
RefDel	Char	$4.	Referential delusions	Presence (lifetime) of delusions of reference	No; Yes; Unk	Unk = Unknown
JealDel	Char	$4.	Jealousy Delusions	Presence (lifetime) of delusions of jealousy	No; Yes; Unk	Unk = Unknown
GuSinDel	Char	$4.	Guilt/Sin Delusions	Presence (lifetime) of guilt or sin delusions	No; Yes; Unk	Unk = Unknown
GrandDel	Char	$4.	Grandiose delusions	Presence (lifetime) of grandiose delusions	No; Yes; Unk	Unk = Unknown
ReligDel	Char	$4.	Religious/Magic Delusions	Presence (lifetime) of religious delusions or delusions of magic	No; Cul; Yes; Unk	Cul = Culturally acceptable (non-delusional) beliefs Unk = Unknown
SomatDel	Char	$4.	Somatic Delusions	Presence (lifetime) of somatic delusions	No; Yes; Unk	Unk = Unknown
ErotoDel	Char	$4.	Erotomanic Delusions	Presence (lifetime) of erotomanic delusions	No; Yes; Unk	Unk = Unknown
MindRDel	Char	$4.	Mind Reading Delusions	Presence (lifetime) of delusions of mind reading (of individual's mind by others)	No; Yes; Unk	Unk = Unknown
FinHal	Char	$4.	Final Hallucinations	Definite (lifetime) presence of hallucinations	No; Yes; Unk	Unk = Unknown
SevCuHal	Char	$8.	Severity of Current Hallucinations	Severity of current hallucinations (past 30 days)	None; Question; Mild; Moderate; Marked; Severe; Unknown	'Question' category usually grouped with 'Unknown' category for analyses
AuditHal	Char	$4.	Auditory hallucinations	Presence (lifetime) of auditory hallucinations	No; Yes; Unk	Unk = Unknown
ComTPHal	Char	$4.	Commentary/3rd Person Auditory Hallucinations	Presence (lifetime) of auditory hallucinations involving commentary or third person conversations between voices	No; Yes; Unk	Unk = Unknown
VisHal	Char	$4.	Visual Hallucinations	Presence (lifetime) of visual hallucinations	No; Yes; Unk	Unk = Unknown
OlGusHal	Char	$4.	Olfactory/Gustatory Hallucinations	Presence (lifetime) of olfactory or gustatory hallucinations	No; Yes; Unk	Unk = Unknown
SomatHal	Char	$4.	Somatic/Tactile Hallucinations	Presence (lifetime) of somatic/tactile hallucinations	No; Yes; Unk	Unk = Unknown
DisorgSp	Char	$4.	Disorganised Speech	Definite (lifetime) presence of disorganised speech/positive formal thought disorder	No; Yes; Unk	Unk = Unknown
SevCuDS	Char	$8.	Severity of Current Disorganised Speech	Severity of current disorganised speech/positive formal thought disorder (past 30 days)	None; Question; Mild; Moderate; Marked; Severe; Unknown	'Question' category usually grouped with 'Unknown' category for analyses
DisorgBe	Char	$4.	Disorganised/Catatonic Behaviour	Definite (lifetime) presence of disorganised/catatonic behaviour	No; Yes; Unk	Unk = Unknown
SevCuDB	Char	$8.	Severity of Current	Severity of current disorganised/catatonic	None; Question; Mild;	'Question' category usually grouped with 'Unknown' category for analyses

			Disorganised Behaviour	behaviour (past 30 days)	Moderate; Marked; Severe; Unknown	
NegatSym	Char	$4.	Negative Symptoms	Definite (lifetime) presence of negative symptoms	No; Yes; Unk	Unk = Unknown
AffFlat	Char	$8.	Affective Flattening	Severity of current affective flattening/inappropriate affect (past 30 days)	None; Question; Mild; Moderate; Marked; Severe; Unknown	'Question' category usually grouped with 'Unknown' category for analyses
Alogia	Char	$8.	Alogia	Severity of current alogia/negative thought disorder (past 30 days)	None; Question; Mild; Moderate; Marked; Severe; Unknown	'Question' category usually grouped with 'Unknown' category for analyses
Avolit	Char	$8.	Avolition/Apathy	Severity of current avolition/apathy (past 30 days)	None; Question; Mild; Moderate; Marked; Severe; Unknown	'Question' category usually grouped with 'Unknown' category for analyses
Anhed	Char	$8.	Anhedonia/Asociality	Severity of current anhedonia/asociality (past 30 days)	None; Question; Mild; Moderate; Marked; Severe; Unknown	'Question' category usually grouped with 'Unknown' category for analyses
WLGAF	Char	$8.	Worst Lifetime Global Assessment of Function	Lowest (lifetime) rating on the Global Assessment of Function Scale	Mild; Moderate; Severe; Unknown	Mild = 61-80 Moderate = 31-60 Severe = 1-30
CurrGAF	Char	$8.	Current Global Assessment of Function	Current (past 30 days) rating on the Global Assessment of Function Scale	None; Mild; Moderate; Severe; Unknown	None = 81-100 Mild = 61-80 Moderate = 31-60 Severe = 1-30
IllCour	Char	$4.	Illness Course	Categorical illness course, as defined in the DIGS	1; 2; 3; 4; 5; 6	1 = Episodic with interepisode residual symptoms 2 = Episodic with no interepisode residual symptoms 3 = Continuous 4 = Single episode in partial remission 5 = Single episode in full remission 6 = Other, unspecified, unknown course
SymptPat	Char	$4.	Symptom Pattern	Relationship between positive and negative symptoms throughout the course of the illness, as defined in the DIGS	1; 2; 3; 5; U	1 = Continuously positive 2 = Predominantly negative 3 = Positive converting to negative 4 = Negative converting to positive (0 observations coded '4') 5 = Continuous mixture of positive and negative symptoms U = Unknown
SevPat	Char	$4.	Severity Pattern	Pattern of severity of decline in functioning over the course of the illness, as defined in the DIGS	1; 2; 3; 4; U	1 = Episodic shift (no deterioration when not actively unwell) 2 = Mild deterioration 3 = Moderate deterioration 4 = Severe deterioration U = Unknown
Onset	Char	$8.	Onset of Psychosis	Rapidity of prodromal period (between noticeable social/occupational decline and definite onset of psychosis)	Abrupt; Acute; ModAcute; Gradual; Unknown	Abrupt = within a day Acute = within a week ModAcute = within a month Gradual = Longer than one month
FinDEP	Char	$4.	Final Depression	Definite (lifetime) presence of at least one DSMIV major depressive episode	No; Yes; Unk	Unk = Unknown
DepMood	Char	$4.	Depressed Mood	Persistent depressed mood for 2+ weeks	No; Yes; Unk	Unk = Unknown

				(DSMIV depression symptom – either depressed mood or anhedonia must be present for a major depressive episode)		
DepAnh	Char	$4.	Anhedonia (Depression)	Persistent anhedonia for 2+ weeks (DSMIV depression symptom – either depressed mood or anhedonia must be present for a major depressive episode)	No; Yes; Unk	Unk = Unknown
AWChange	Char	$4.	Appetite/Weight Change	Significant appetite and/or weight change during depression (DSMIV depression symptom)	No; Yes; Unk	Unk = Unknown
SleepDis	Char	$4.	Sleep Disturbance	Significant sleep pattern disturbance – either trouble sleeping or sleeping too much during depression (DSMIV depression symptom)	No; Yes; Unk	Unk = Unknown
PsyChang	Char	$4.	Psychomotor Change	Psychomotor agitation or retardation during depression (DSMIV depression symptom)	No; Yes; Unk	Unk = Unknown
FatLosEn	Char	$4.	Fatigue/Energy Loss	Fatigue or loss of energy during depression (DSMIV depression symptom)	No; Yes; Unk	Unk = Unknown
WorGuilt	Char	$4.	Worthlessness/Guilt	Persistent feelings of worthlessness or guilt during depression (DSMIV depression symptom)	No; Yes; Unk	Unk = Unknown
DecConc	Char	$4.	Decreased Concentration	Decreased concentration during depression (DSMIV depression symptom)	No; Yes; Unk	Unk = Unknown
DeathSui	Char	$4.	Thoughts of Death/Suicide	Persistent thoughts of death or suicide during depression (DSMIV depression symptom)	No; Yes; Unk	Unk = Unknown
DepCount	Char	$4.	Count of Depressive Symptoms	Count of DSMIV depressive symptoms used to establish the presence/absence of an episode (0-9)	0-9	Symptoms are operationalised to correspond with the DSMIV diagnostic criteria. 5+ required, one of which must be depressed mood or anhedonia (although presence of symptoms concurrently does not guarantee a positive rating for an episode due to time criterion).
FinMania	Char	$4.	Final mania	Definite (lifetime) presence of at least one DSMIV manic episode	No; Yes; Unk	Unk = Unknown
ElevMood	Char	$4.	Elevated/Elated mood	Elated mood for 1+ week (or any duration if hospitalised) (either elated or irritable mood must be present for a DSMIV manic episode)	No; Yes; Unk	Unk = Unknown
IrriMood	Char	$4.	Irritable mood	Irritable mood for 1+ week (or any duration if hospitalised) (either elated or irritable mood must be present for a DSMIV manic episode)	No; Yes; Unk	Unk = Unknown
Grandios	Char	$4.	Grandiosity	Grandiosity/inflated self-esteem (DSMIV manic symptom)	No; Yes; Unk	Unk = Unknown
DecSleep	Char	$4.	Decreased Need for Sleep	Decreased need for sleep – feels rested on little or no sleep (DSMIV manic symptom)	No; Yes; Unk	Unk = Unknown
PrSpeech	Char	$4.	Pressured Speech	More talkative or pressured speech	No; Yes; Unk	Unk = Unknown

				(DSMIV manic symptom)		
RacingTh	Char	$4.	Racing Thoughts/Flight of Ideas	Flight of ideas or subjective racing thoughts (DSMIV manic symptom)	No; Yes; Unk	Unk = Unknown
Distract	Char	$4.	Distractibility	Distractibility (DSMIV manic symptom)	No; Yes; Unk	Unk = Unknown
PsychAgi	Char	$4.	Psychomotor Agitation	Increased goal-oriented activity or psychomotor agitation (DSMIV manic symptom)	No; Yes; Unk	Unk = Unknown
RiskyBe	Char	$4.	Risky Behaviour	Excessive risky pleasurable behaviour (DSMIV manic symptom)	No; Yes; Unk	Unk = Unknown
ManCount	Char	$4.	Count of Manic Symptoms	Count of DSMIV manic symptoms used to establish the presence/absence of an episode (0-7)	0-7	Symptoms are operationalised to correspond with the DSMIV diagnostic criteria. 3+ required (if elevated mood is present), 4+ required (if only irritable mood is present). One of elevated or irritable mood is essential for a manic episode (note: the presence of symptoms concurrently does not guarantee a positive rating for an episode due to time criterion).
CuAntMed	Char	$4.	Current Antipsychotic medication	Whether the individual is definitely taking antipsychotic medication at the time of assessment	No; Yes; Unk	Unk = Unknown
Clozstat	Char	$3.	Clozapine Status	Whether the individual is definitely taking clozapine at the time of assessment	No; Yes	Only rated yes if there was clear evidence for current clozapine prescription and compliance, otherwise rated no.
TreatRes	Char	$4.	Treatment Resistant	Whether the individual meets strictly defined criteria for treatment resistance	No; Yes	Criteria for treatment resistance were formulated in consultation with the treatment resistance literature. The binary coding favoured negative ratings; we acknowledge that some treatment resistant individuals will be rated 'no', but we are confident that all individuals who rate 'yes' are definitely treatment resistant. Criterion 1: Two of Delusions, Hallucinations, Disorganisation, and Negative Symptoms must rate positive. Criterion 2: CurrGAF must be 'Moderate' or 'Severe' Criterion 3: IllCour must be '3' (continuous) Criterion 4: SevPat must be 3 (moderate) or 4 (severe) Criterion 5: CuAntMed must be 'Yes' To rate positive, each dimension in criterion 1 must rate as follows: Delusions: SevCuDel must be 'Moderate', 'Marked', or 'Severe' Hallucinations: SevCuHal must be 'Moderate', 'Marked', or 'Severe' Disorganisation: Either SevCuDS or SevCuDB must be 'Moderate', 'Marked', or 'Severe' Negative Symptoms: Two of AffFlat, Alogia, Avolit, and Anhedonia must be 'Moderate', 'Marked', or 'Severe'

Appendix C: Establishing and Confirming Data Source and Formatting Equivalence

Establishing data source equivalence was a nine step process.

DE-1. Set inclusion criteria

Preliminary inclusion criteria and the framework for a comprehensive data search were set based on the candidate's prior knowledge of existing datasets, and in consultation with Professor Mowry, who reviewed all cases across the three sites. Broadly, individuals with a confirmed DSM-IV diagnosis of schizophrenia or schizoaffective disorder would be the target of the search, since all included individuals in the two Molecular Genetics of Schizophrenia studies in Australia (MGS1, MGS2) had these diagnoses, all included probands in the Indian sample had these diagnoses, and approximately 83% of Iban individuals included in the detailed pedigree subset had these diagnoses. These samples would form the basis for the three ethnically distinct samples compared in this thesis.

DE-2. Identify all available individuals and map data sources

The candidate searched all available sources (electronic and paper) and compiled a list of every individual ID/code number. At this stage, all individuals were retained, and potential errors, inconsistencies and duplicates were flagged for follow up. Concurrently, as the ID list was being compiled, a map of all data sources where demographic, clinical, symptom, illness course, and (crucially) diagnostic information was available was also compiled. This *data map* was continually updated, and formed the 'backbone' of the search strategy.

At this stage, the sample included 819 Australian individuals (167 from MGS1 and 652 individuals from MGS2), 524 Indian individuals, and 486 Iban individuals (comprising all those included in the general screening sample – of which the 192 detailed pedigree group was a subset). Two additional individuals from MGS 1 in Australia were later also included who had been excluded from the genetic study due to a problem with their DNA samples but for whom all data needed for this thesis were available.

DE-3. Catalogue data source availability for each individual

Availability of each of the six major data types (DIGS interview, FIGS interview, medical records, narrative summary, consensus diagnosis, and Lifetime Dimensions of Psychosis Scale (LDPS)) was catalogued (initially in Microsoft Excel) for each ID number. Availability categories were set as: 0=No; 1=Yes (electronic); 2=Yes (hard copy only); 3=Yes (proof of

existence but unable to locate); 9=Unknown. This *complete data set* complemented, and was used in conjunction with the *data map* created in step two.

DE-4. Quarantine all 'potentially useful' electronic files

All electronic files identified in the *data map* (step two) were copied and 'quarantined' by the candidate. From this point forward, all work relating to the thesis was undertaken on these files only. This ensured that there was consistency in the data used, and that later changes to files available to individuals other than the candidate would not cause problems in data cleaning and future analyses. Twenty six electronic files were mapped and quarantined, with all included tables and worksheets catalogued.

DE-5. Confirm accuracy of all ID numbers

The candidate consulted all data sources (both electronic and hard copy) to confirm the accuracy of all ID numbers, resolving all conflicts identified in step two, and (conservatively) dropping all IDs from the dataset that could not be confirmed or were ambiguous.

DE-6. Confirm DSM-IV diagnoses for all ID numbers

The candidate checked the DSM-IV diagnoses for all included ID numbers and excluded all individuals whose schizophrenia/schizoaffective diagnosis could not be confirmed. This step included reading all narrative summaries and consensus diagnosis sheets across the three sites.

After this step, the available sample consisted of 821 Australian individuals, 520 Indian individuals, and 298 individuals from Sarawak (total n=1639).

DE-7. Identify target variables

The candidate next defined an initial set of demographic, clinical and symptom variables in consultation with Professor Mowry that were both useful and feasible to extract based on available data sources. This process relied heavily on multiple DIGs interview variable indexes (data dictionaries) that had previously been compiled by the candidate for both the Australian and Indian samples. This guided variable extraction for Chapter Three; although the final master file eventually contained 89 distinct variables (see Appendix B).

DE-8. Create SAS master file

The candidate created a dataset (master file) in SAS with 1639 unique IDs, comprising all included individuals confirmed in step six. While the above steps were completed (a protracted process), the candidate had learned SAS coding, as this package was determined to be the most appropriate for the planned analyses, given the expertise available within Professor Mowry's team, the format of other analyses utilising these samples, and the licenses available to the candidate.

DE-9. Confirm data source availability for each included individual

Prior to the commencement of data extraction, the candidate rechecked data source availability for each final ID number (repeating step 3). This additionally served as an 'error check' of previous steps.

Once all available data for all included individuals had been identified and located, the extraction, cleaning and formatting of variables was systematically undertaken as a nine step process.

CF-1. Set SAS rules and coding conventions

The candidate, in consultation with Professor Mowry, Professor McGrath, and Dr. McLean, devised a 'set' of SAS rules, coding conventions and real-time error checking steps to ensure systematic cleaning, importing, and merging of variables.

All SAS files (datasets) were divided, saved, and interrogated in three general categories: raw files – datasets as extracted from quarantined files (e.g. from Excel workbooks, Access tables); intermediate files – datasets that had been worked on in SAS but were not cleaned or merged into a final form; and merged files – datasets that had been cleaned and merged in SAS. All analyses for Chapters Three to Six were conducted only on merged datasets.

The general strategy (detailed below) involved the following steps: 1. Extract given variable in Australia (MGS1); 2. Extract given variable in Australia (MGS2); 3. Extract given variable in India; 4. Extract given variable in Sarawak (General screen); 5. Extract given variable in Sarawak (pedigree subset); 6. Merge the five subsets into a single variable set; and 7. Append the variable onto the master set.

CF-2. Convert relevant quarantined data files into SAS datasets

Potentially important tables and worksheets were previously identified and catalogued when all relevant files were quarantined (see above). Each table and worksheet was imported into SAS as an individual dataset, and stored as a ‘raw’ file.

CF-3. Extract each variable

Eighty-nine variables (eighty-six excluding ID numbers and site) were extracted, one at a time, for each unique individual (ID) in Australia, then India, then Sarawak. Data were imported from available electronic sources first, then manually extracted from hard copy/paper sources. No coding decisions were made at this stage.

CF-4. Clean each variable

All unknown values, missing values, and outliers were then interrogated (using logic checks in SAS built into the rules and coding conventions). All available sources were consulted to extract previously missing values and resolve conflicts. Generally, in cases where there was any doubt over the veracity of a given value, that data point was rated either down, absent or unknown (as appropriate for the variable). Details of cleaning modifications were meticulously recorded in SAS code notes.

CF-5. Recode each variable as required

Variable value sets were set to those of the ‘least detailed’ site, and ‘scoring’ of data points was modified as necessary to ensure that the same variable represented the same concept across the three datasets/sites. In practice, that meant that some detail was necessarily lost, particularly at the Australian site. For example, where a severity rating for a symptom variable was available in Australia and India, but only the lifetime presence of that symptom was available in Sarawak, the Australian and Indian datasets were recoded to present/absent for the purposes of site comparisons. Details of recoding modifications were meticulously recorded in SAS code notes.

CF-6. Merge each variable across sites

Once coding was consistent across sites, all observations for each of the five data subsets (Australia MGS1, Australia MGS2, India, Sarawak general screen, and Sarawak detailed pedigree subset) were appended into a single variable data set. The two Australian subsets were appended to each other, the two Sarawak subsets were appended to each other, and then the Indian set was appended to the Australian set, and the Sarawak set was appended to the Australian/Indian set. Checks were then conducted to ensure that

each of the 1639 unique IDs had a valid value for the variable, and random records were checked with source data (e.g. narrative summaries, consensus sheets) to ensure the correct value was recorded for the given variable.

CF-7. Append each variable to master dataset

Once a given variable was ‘cleaned’, ‘checked’, and all sites were merged into a single ‘column’, the variable was appended (by unique ID) onto the latest iteration of a master dataset in SAS. The file was then interrogated for any missing values, as a check that the merge had executed correctly.

CF-8. Build master dataset

Steps three to seven were repeated for each variable requiring extraction.

CF-9. Record audits

Random audits of records were undertaken during each iteration of the SAS master file. This ensured that any unintended coding anomalies (as opposed to coding errors that were routinely picked up by the SAS software itself) were identified and rectified at the earliest opportunity. For example, it is possible in SAS to merge datasets without correctly sorting/specifying the variable to merge ‘by’, without triggering a SAS error. The result is a ‘decoupling’ of IDs and associated data points. Record audits ensured that errors such as these were not perpetuated through the master file.

Appendix D

McLean D, John S, Barrett R, McGrath J, Loa P, Thara R and Mowry B (2012) Refining clinical phenotypes by contrasting ethnically different populations with schizophrenia from Australia, India and Sarawak. *Psychiatry Research* 196(2-3): 194-200.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22401968

Appendix E

McLean D, Barrett R, Loa P, Thara R, John S, McGrath J, Gratten J and Mowry B (2015) Comparing schizophrenia symptoms in the Iban of Sarawak with other populations to elucidate clinical heterogeneity. *Asia-Pacific Psychiatry* 7(1): 36-44.

http://www.ncbi.nlm.nih.gov/pubmed/24038814

Appendix F

McLean D, Thara R, John S, Barrett R, Loa P, McGrath J and Mowry B (2014) DSM-IV "criterion A" schizophrenia symptoms across ethnically different populations: evidence for differing psychotic symptom content or structural organization? *Culture, Medicine and Psychiatry* 38(3): 408-426.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24981830