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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 is 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

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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.

Keywords

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 (WHO, 1992; APA, 1994). 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" (Kendler, et al., 1998; Fiedorowicz, et al., 2008; 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 (Kleinman, 1988; Alarcon, et al., 2009).

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 centres, 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%). Hebeephrenic 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. Gureje, et al., 1995; Arora, et al., 1997), 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. Fearon, et al., 2006; Cantor-Graae and Selten, 2005), 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; $\kappa=0.88$ for schizophrenia, $\kappa=0.89$ 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; $\kappa=0.886$); and between the Australian and Sarawak samples (disagreement in one of 20 cases; $\kappa=0.828$). 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 (Kakar, 1991; Corin, et al., 2004), 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 Chi-square 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 1.

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

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 3.

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 utilising 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 (Kakar, 1991; Barrett, 2004; Corin, et al., 2004). 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 disorganised 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 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 $\pm$ SD)		38.9 $\pm$ 11.73	37.9 $\pm$ 12.06	46.9 $\pm$ 14.86	39.93 $\pm$ 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%)

Table 2Criterion 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 Supplementary Table 1

Table 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
<i>Broadcast/Insertion/Withdrawal delusions</i>	368/776 (47.4%)	64/504 (12.7%)	27/259 (10.4%)	459/1539 (29.8%)	257.49	2	<0.0001
<i>Control delusions</i>	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
<i>Commentary/3rd person hallucinations</i>	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

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%).

[†] Schneiderian First Rank Symptoms are presented in italics

[‡] Chi-square analyses were conducted for each variable after 'unknown' responses were deleted (to remove any potential confounding effect).