Limiting clinical heterogeneity in schizophrenia: can affected Xhosa sib pairs provide valid subtypes?

Daniel Jan Hendrik Niehaus

Promoter:

Prof. R. A. Emsley

Department of Psychiatry

University of Stellenbosch

Co-promoter

Dr. E. Jordaan

Biostatistics Unit

Medical Research Council of South Africa

Bellville

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Declaration:

I, the undersigned, hereby declare that the work contained in this dissertation is my own original work and that I have not previously in its entirety or in part submitted it at any university for a degree.

Signature:_____ Date:_____

ABSTRACT

BACKGROUND

Schizophrenia is a heterogeneous disorder, which has been shown to have both environmental and genetic risk factors. Since family history (genetic loading) of psychosis appears to be one of the strongest risk factors for the development of schizophrenia, the investigation of affected sib pairs can be used to explore shared familial factors. The Xhosa-speaking inhabitants in the Western, Eastern and Southern Cape provinces, an African population of relatively homogeneous ethnicity, provided a sample of the first large clinical phenotype of schizophrenia.

AIM

The main aim of this study was to identify shared symptoms or symptom clusters in a sample of Xhosa-speaking sib pairs, with the aid of structured assessment tools.

METHODS

PARTICIPANTS

Xhosa participants with schizophrenia were recruited from in- and outpatient hospital services and community clinics throughout the Western, Southern

and Eastern Cape Provinces of South Africa. The participants were affected individuals without an affected sib (n=299) and sib pairs (104 sibships [100 pairs, 2 trios, 2 fours]). For the purpose of this study the sib pairs were extracted for analysis.

ASSESSMENT

The patients were assessed by means of the Diagnostic Interview for Genetic Studies (DIGS 2.0) which includes the Schedule for the Assessment of Negative Symptoms (SANS) and the Schedule for the Assessment of Positive Symptoms (SAPS).

DATA ANALYSIS

Exploratory factor analyses (one in which factors with eigenvalues > 1 were retained, and a forced 5 factor analysis) were performed on the nine global ratings and on the individual items of the SANS and SAPS in both the sib pair and non-sib pair groups, to identify factors unique to the sib group. The factor solution was then rotated using the varimax procedure. Sib pairs selected for the factor analysis were used for concordance analysis to determine the degree of agreement between siblings on SAPS and SANS items.

RESULTS

Factor analysis yielded a two-factor solution (a positive and a negative factor) when eigenvalues < 1 were discarded. The forced five-factor analysis generated results similar to those previously reported in non-sib pair samples and produced positive, negative and disorganised factors. Several individual and global items of the SANS and SAPS showed higher than expected concordance between sib pairs. Stratification of the sib pair group into gender groups (male-male versus mixed gender group) reduced the items with a higher than expected concordance. Subsequent investigation of the associations between possible confounding factors and concordance between sib pairs, using only the items that had shown higher than expected concordance, revealed that the items most likely to be linked to shared familial factors were eye contact, auditory hallucinations, the global hallucination score and delusions of control.

CONCLUSIONS

Factor analysis failed to reveal any significant phenomenological differences between the " more strongly familial" sib pair group and the " non related" non-sib pair group. Eye contact, auditory hallucinations, the global hallucination score and delusions of control had higher than expected

concordance. The item, delusions of control was considered the most promising candidate for further genetic linkage studies.

ABSTRAK

AGTERGROND

Skisofrenie is ‘ n multifaktoriale siekte met beide omgewings- en genetiese risikofaktore. Aangesien familiegeskiedenis (genetiese lading) van psigose een van die sterkste risikofaktore vir die ontwikkeling van skisofrenie blyk te wees, kan sibpare gebruik word om die gedeelde familiële faktore na te vors. Die relatief etnies homogene groep Xhosa-sprekende inwoners in die Wes, Suid en OosKaap het die eerste groot kliniese fenotipering van skisofrenie in ‘ n Afrikane groep verskaf.

DOELWIT

Die doelwit van die studie was om gedeelde simptome of simptoomkomplekse in ‘ n groep Xhosa sprekende sibpare te identifiseer met die hulp van gestruktureerde evaluasieskale.

METODOLOGIE

DEELNEMERS

Xhosa deelnemers met skisofrenie is ingesamel vanaf binne- en buite-pasiënt hospitaal en kliniekdienste in die Wes, Suid en OosKaap van Suid Afrika. Die deelnemers was individue (n=299) en sibpare (n=104, 100 pare, 2 trios en 2

sibgroepe van 4 elk) van Xhosa oorsprong met ‘ n diagnose van skisofrenie. Vir die doel van die studie is die sibpare uitgesonder vir analise.

EVALUASIE

Die pasiënte is geevalueer met behulp van die “ Diagnostic Interview for Genetic Studies” (DIGS), weergawe 2.0 (Nurnberger et al., 1994). Die skaal bevat die “ Schedule for the Assessment of Negative Symptoms” (SANS) en die “ Schedule for the Assessment of Positive Symptoms” (SAPS).

DATA ANALISE

‘ n Voorlopige ontledende faktor ontleding (eigenwaardes > 1 en ‘ n geforseerde 5-faktor ontleding) is gedoen op die globale en individuele items van die SANS en SAPS resultate van beide die sibpaar en non-sibpaar groep. Die faktor ontleding is geroteer met gebruik van die varimax prosedure. Hierna is ‘ n konkordansie analise van die SANS en SAPS items gedoen (gegrond op voorheen gepubliseerde metodologie) op die sibpaar groep. Hierdeur kon ondersoek ingestel word na moontlike gedeelde familiële faktore deur te kyk na die vlak van ooreenkomste binne sibpare.

RESULTATE

Die faktor ontleding het ‘ n twee faktor uitkoms opgelewer (‘ n positiewe en negatiewe faktor). Die geforseerde 5 faktor ontleding was soortgelyk aan die van vorige publikasies in nie-sibpare en het verdeel in positiewe, negatiewe en gedisorganiseerde faktore. Verskeie individuele en globale items van die SANS en SAPS het hoër as verwagte konkordansie getoon. Verdeling van die sibpaar groep op grond van geslagte (manlik-manlik versus gemengde groep) het die konkordante faktore verminder nadat prevalensie as ‘ n verwarrende (“ confounding”) faktor geïnkorporeer is. Vervolgens het die modellering van die ander verwarrende faktore getoon dat oogkontak, gehoorshallusinasies, die globale hallusinasie telling en wane van beheer die mees waarskynlike items is wat gekoppel kan word aan moontlike gedeelde familiële faktore.

AFLEIDINGS EN SAMEVATTING

Die faktor analise het geen verskille getoon tussen die meer familiële sibpare en die non-sibpare. Ten einde die Xhosa populasie dus beter te subtipeer is geslag en verwarrende faktore in berekening gebring. Die proses het die simptome van belangstelling verminder tot oogkontak, gehoors- hallusinasies, globale hallusinasie telling en wane van beheer. Wane van beheer blyk die mees toepaslike kandidaat vir verdere genetiese studie te wees.

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CHAPTER 1

INTRODUCTION: RATIONALE FOR THE STUDY

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1. THE NEED FOR RESEARCH IN SCHIZOPHRENIA

Schizophrenia is a relatively common chronic disorder with a prevalence rate of approximately 1%. It is associated with substantial morbidity and high health care expenditure. Indeed, the morbidity associated with schizophrenia is comparable to that of diabetes mellitus and cardiovascular disease [2;3]. Furthermore, although myocardial infarction affects 12 times as many people, the per case cost is 6 times higher for schizophrenia [4]. The cost of schizophrenia, which is made up of both direct costs (hospital/institution costs, provider fees, prescription drugs) and indirect costs (including loss of productivity of family members) is the largest mental health expenditure item [5]. In the United States, the treatment of patients with schizophrenia consumes an estimated 2.5% of the annual total health care budget and an estimated 368 522 years of lost productivity among males [2;6;7].

Given the devastating impact of schizophrenia on the sufferers, care-givers and the health care system, it is imperative that the prevention and effective management of schizophrenia remain a priority for researchers and other health care practitioners.

2. THE SCHIZOPHRENIA PHENOTYPE AND ITS RELATIONSHIP WITH ETIOLOGICAL HETEROGENEITY

The main clinical features of schizophrenia include positive symptoms such as delusions, hallucinations, disorganized thinking, disorganized or catatonic behaviour, and negative symptoms, such as affective flattening, alogia and avolition (DSM-IV - Criteria A)[8]. However, even the earliest writings recognized its considerable clinical heterogeneity; Kraepelin considered " dementia praecox" a " number of disease entities" [9].

The clinical heterogeneity reflects the heterogeneous nature of susceptibility factors for schizophrenia. To date, several risk factors have been identified: (1) a family history of schizophrenia, (2) lower social class, (3) gender (earlier onset in men), (4) infective processes (low incidence of rheumatoid arthritis in schizophrenia), (5) winter birth, (6) obstetric, birth and early developmental insults, (7) substance abuse, (8) stress, and (9) geographic location i.e. urban environment [10].

Of these, family history of schizophrenia is considered a strong confirmed susceptibility factor, with estimated heritability approaching 80% and a life-time morbid risk of 4.8 for relatives of affecteds, based on a large dataset of family studies that, despite methodological differences, support the hypothesis of inherited factors in schizophrenia susceptibility [11-13]. In addition, the

susceptibility risk for schizophrenia and its spectrum disorders seems to be higher if a narrow spectrum definition is used [12]. A broad-spectrum diagnosis, which does not exclude patients with alcoholism, anxiety disorders and mood disorders (unipolar and bipolar), shows less convincing results. This is also reflected in twin studies where broadening of the phenotype leads to a reduction in the risk of family members developing schizophrenia [14].

Taken together, these factors suggest a constitutional model and, by implication, a genetic component influenced by environmental factors, for the development of schizophrenia [15;16]. Furthermore, it seems that schizophrenia display a degree of genetic heterogeneity and/or epistatic gene interaction [17]. Therefore, it is necessary to use techniques (family based association studies such a transmission disequilibrium testing and haplotype relative risk design) that are able to detect genes with a less robust overall effect. The power of these methods depends heavily on careful phenotyping of clinical samples [18]. The need for careful phenotyping is underlined by the preliminary finding that a single gene (WKL 1) may confer a risk for the development of a subtype of schizophrenia, namely catatonic subtype [4;19-22]. Stober et al. (2001) suggested that this gene acts in concert with predisposing factors, a fact that again calls attention to the heterogeneity of schizophrenia, and also offers hope of researchers finding other subtypes

linked to specific genes which may have comparatively substantial effects in phenotypic subgroups [23].

The possibility therefore exists that putative drug targets or mutable susceptibility factors may be unlocked through genetic studies. The implications for prevention and treatment programs are far-reaching. Tailored treatment strategies based on the genetic make-up of the individual promise to be a powerful tool for the treating physician. However, finding other genes linked to specific phenotypes will depend heavily on careful phenotyping of schizophrenic patients.

Researchers who carry out genetic studies involving schizophrenic subjects should, therefore, aim to describe each subject' s phenotype accurately, and attempt to assemble clinically homogeneous samples.

3. METHODS OF LIMITING HETEROGENEITY

Considerable attempts have been made to elucidate the heterogeneity of the schizophrenia phenotype by exploring the relationships between the various symptom dimensions and possible subtypes. Several divisions or subtypes have been proposed based on proposed susceptibility factors and theories on

the pathophysiology of schizophrenia [24-27]. These range from positive versus negative dimensions to deficit versus non-deficit subgroups.

Most studies attempting to identify subtypes rely on factor analysis as a means of delineating the subgroups. Factor analysis of symptom rating scales such as the SANS and SAPS have thus far converged towards a three-dimensional model if global scores are considered (a negative and two positive symptom factors) [28;29]. The global ratings for avolition/apathy, anhedonia/asociality and affective flattening constituted the negative dimension, hallucinations and delusions constituted a "psychosis" dimension, and bizarre behaviour and formal thought disorder constituted a "disorganisation dimension" [1;30-34;35]. Analysis of individual items led to a separation of the negative factor into two components (negative signs and social dysfunction), while the " psychosis" factor separated into delusions and hallucinations [36]. Toomey et al. (1997) also reported two negative symptom factors (diminished expression and disordered relating) and two positive symptom factors (bizarre delusions and auditory hallucinations) in addition to the disorganisation symptom dimension [37].

Emsley et al. (2001) reported on a heterogeneous Xhosa sample of 422 subjects [38]. Principal component and analytic methods revealed a five-factor solution for the global items of the SAPS and SANS and accounted for

55% of the variance. The five factors were negative symptoms, psychotic symptoms, disorganization, impaired attention and alogia. When individual symptom items were analysed, a five-factor model, similar to those in Caucasian studies, was found. The five factors included diminished expression, disordered relating, psychosis, thought disorder and bizarre behaviour and accounted for 55% of the total variance. Thus despite methodological differences, studies seem to reveal similar symptom dimensions.

4. THE USE OF SIB PAIR STUDIES IN LIMITING HETEROGENEITY

From a genetic perspective, it would be important to establish whether these symptom subtypes or dimensions reflect shared familial factors or whether they merely indicate random events. The use of concordant siblings assumes that shared clinical features and - by implication - subtypes, are likely to be related to shared familial factors that could include both environmental and genetic factors. Subtypes generated in studies of concordant sib pairs are more likely to represent " true" familial subtypes.

Affected sib pair studies, despite methodological differences (retrospective versus prospective, different diagnostic criteria) and small sample size (8/14

studies reported on less than 90 sib pairs), revealed significant concordance for a range of symptoms and symptom factors. Loftus et al. (2000) found two symptom factors that accounted for 67% of the total variance in a principal component analysis involving 103 sib pairs with either schizophrenia or schizo-affective disorder (DSM-III-R) [39]. Factor 1 (49.8% of variance) included thought broadcasting, thought insertion, thought withdrawal and delusions of control. Factor two (16.9% of variance) was characterized by third-person auditory hallucinations, running commentary and thought echo. Kendler et al. (1997) also performed factor analysis and latent class analysis on the 11 items of the Major Symptoms of Schizophrenia Scale and found a three symptom factor model and a five class solution to be the best fit [40]. The three symptom factors included a negative symptom factor (affective deterioration, poor outcome, chronic course and negative thought disorder), a positive symptom factor (hallucinations, any delusions and Schneiderian delusions) and an affective symptom factor (manic symptoms) and positive thought disorder. The five class solution suggested that class 1 more closely resembled schizo-affective disorder, class 2 core or negative symptoms, class 3 poorer outcome against a background of positive and negative symptoms, class 4 paranoid schizophrenia and class 5 remitting or relapsing catatonic schizophrenia. This separation of catatonic schizophrenia into a separate class is of interest, considering reports suggesting a possible genetic susceptibility gene in catatonic schizophrenia [41]. Burke et al. (1996)

reported a similar three-factor solution of which the negative and reality distortion factors closely resembled those of Kendler et al. (1997) [42]. The third factor, a disorganised symptom factor, included positive thought disorder and inappropriate affect.

It is difficult to compare the results obtained from mixed samples (familial and sporadic cases) with those found in sib pair samples, since no exact methodological replication studies exist. Nevertheless, Cardno et al. (1998) found no statistically significant within-pair correlations for seven SAPS/SANS symptoms, namely inappropriate affect, affective flattening, alogia, hallucinations, delusions, bizarre behaviour and positive formal thought disorder [43]. To address this paucity of data the factor structure of the SAPS and SANS rating scales in sib pairs should be investigated and compared with findings of non-sib pair studies' results.

5. WHY USE AN AFRICAN POPULATION?

Since the majority of factor analysis and sib pair studies have focused on Caucasian samples, it is essential that indigenous African populations also be investigated. The suggestion of ethno-specific loci in an African-American and African sample and an apparent ethno-specific pharmacological response to atypical antipsychotic treatment offer further promise for unique etiological

findings in this group [44-47]. Nevertheless, the seemingly uniform core symptom profile reported in both Caucasian and African groups (including the Xhosas) makes a symptom-based approach possible [48].

It is therefore important to investigate an indigenous African population in order to identify unique clinical subtypes that may account for ethno-specific loci. The Xhosa people are an appropriate group to study, as they are culturally distinct and genetically related to the above-mentioned African grouping. This population diverged within the last 2000 years providing a similar genetic background [49-54]. The marked paucity of clinical and susceptibility data amongst Xhosa-speaking schizophrenic subjects is another compelling reason for genetic research in this group.

6. SUMMARY

In summary, schizophrenia seems to be a heterogeneous disorder

(1.) In which both environmental and genetic risk factors and causes are present (discussed in Chapter 2).

(2.) In which family history (genetic loading) of psychosis seems to be one of the strongest risk factors for the development of schizophrenia (discussed in Chapter 2).

(3.) In which affected sib pairs can highlight the shared familial factors (discussed in which Chapter 3).

(4.) In which exploratory factor analysis can highlight symptom factor differences between the sib pair and non-sib pair[1] group (discussed in Chapter 3).

(5.) These symptom factor differences should then more likely represent " true" shared familial factors (higher genetic loading) and could be of value if one wants to subtype this population for genetic analysis (discussed in Chapter 3).

(6.) There is a large Xhosa-speaking population in the Western, Eastern and Southern Cape, a fact which can present researchers with a unique opportunity to investigate an African population of relatively homogenous ethnicity. The advantages of examining this population in terms of heritable and non-heritable factors are two-fold: first, there is the

[1] Non-sib pair group refers to participants (single individuals with schizophrenia) with no affected sibling

opportunity of assembling the first large clinical phenotype of schizophrenia in a Xhosa population, and second, the lessons learned from this study in terms of methodological and ethical challenges should enable us to design appropriate follow-up studies (Discussed in Chapter 4 and 5).

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CHAPTER 2

SCHIZOPHRENIA AS A HETEROGENEOUS ILLNESS: THE ROLE OF GENETIC AND ENVIRONMENTAL RISK FACTORS.

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1. BACKGROUND

The search for risk factors for schizophrenia has been an ongoing effort, resting on the possibility that risk factors may be avoidable and/or mutable, thus offering some hope of amelioration or even prevention of psychotic illness. Three groups of variables postulated to contribute to schizophrenia have been arbitrarily classified as (a) demographic variables, (b) innate predisposing or protective factors and (c) environmental stressors [1].

Demographic risk factors include social class, age, gender and marital status, whereas innate predisposing or protective factors extend to season of birth, developmental complications, infective or autoimmune factors, substance abuse and familial background. Environmental stress includes maternal stress in utero, familial and social stress and geographic stressors [2].

According to Bromet et al. (1999) these risk factors can be classified into two levels of scientific certainty (viz. confirmed and possible risk factors) [3]. Confirmed factors can be subdivided into confirmed strong and potentially strong risk factors.

In line with current knowledge, confirmed strong risk factors constitute family

history (innate factor) and social class (demographic factor), while the confirmed, potentially strong factors include age and gender (demographic factor), rheumatoid arthritis, season of birth and developmental complications (innate/protective factors). Substance abuse (innate factor), stress and geographic location (environmental factors) are classified as possible risk factors for the development of schizophrenia [4]. Since the more influential studies supporting these risk factors investigated mainly Caucasian populations, of which Finnish, Dutch, British and North American samples predominated [5], very little is known about the role of these factors in indigenous African populations. Since this study will investigate the role of sib pairs in the heterogeneity of schizophrenia, the discussion will focus mainly on family history as a risk factor. However, other risk factors will be briefly discussed here in order to provide a background for the reader.

2. POSSIBLE RISK FACTORS: SUBSTANCE ABUSE, STRESS AND GEOGRAPHIC LOCATION

2.1. SUBSTANCE ABUSE

It is difficult to establish whether substance abuse is a risk factor for schizophrenia or whether it merely hastens its onset. A risk factor does not necessarily have to cause an illness, but merely elevate its risk [6]. The inability to differentiate between cause and risk is illustrated by the results of a

15-year follow-up study of 45 750 Swedish army recruits [7]. It showed that recruits who had smoked cannabis on more than 15 occasions were 6 times more likely to develop schizophrenia than those who had used less frequently, or not at all. The majority of findings seem to suggest that cannabis either causes schizophrenia or triggers its onset in vulnerable individuals [8;9]. However, the results could also be interpreted as reflecting the predilection of pre-patients with schizophrenia for cannabis use [10]. The latter explanation was offered in view of the fact that the increase in cannabis use over the past few decades has not been accompanied by a concomitant rise in the incidence of schizophrenia. The precise role that cannabis plays in the pathophysiology of schizophrenia is still unclear [11].

2.2. STRESS AS A RISK FACTOR

Studies on the roles of stress have focused on maternal stress during pregnancy and on early life events, including familial stress. Maternal stress as a risk factor is supported by a recent finding that children of mothers who had experienced bomb raids in the first trimester of pregnancy during World War II were at increased risk of developing schizophrenia [12]. However, a similar study on women who had been pregnant during the Israeli War did not reveal an increased risk for schizophrenia in their offspring and thus the evidence remains insufficient to draw firm conclusions in this regard [13].

Numerous other possible stressful life-events have also been the focus of investigations and migration serves as excellent example of the complexities involved in assigning causality. Studies in the United Kingdom have shown migratory populations to have a higher risk for schizophrenia than those in their native country. However, the second generation were at an even higher risk for the development of schizophrenia, indicating that factors other than migration elevate this risk even further [14].

The interpretation of these results is complicated by the influence of other environmental and genetic factors and our inability to quantify the effects of stress.

High expressed emotion within family environments has now been linked to an increase in the number of relapses and is no longer considered a risk factor for the development of schizophrenia. It has also been shown to play a similar role in other psychiatric disorders [15;16].

2.3. GEOGRAPHIC LOCATION

The incidence of narrowly defined schizophrenia seems to be similar across diverse populations, according to a World Health Organization study [17].

The risk of schizophrenia may be elevated in persons residing in certain geographic localities, especially urban environments.

A study by Lewis et al. (1992) of 50 000 Swedish conscripts, found that being raised in an urban environment increased the risk 1.65 times [18]. Demographic pockets with higher than expected rates of schizophrenia have been found, but the generation of specific hypotheses is difficult since factors such as morbidity, service availability, comorbidity, selective migration and social and physical environmental factors may have had an influence on these patterns [19;20].

The Xhosa population has undergone rapid geographic relocation. Since the abolition of the " pass laws" in 1986, rapid urbanization has taken place [21], resulting in the establishment of shanty towns on the periphery of Cape Town. They are characterised by poverty and overcrowded living conditions. One such settlement is Khayelitsha, which has a population of about 350 000 people, is predominantly informally organized and is made up of both serviced and unserviced shacks. Only one in five dwellings are classified as houses. The population is in constant flux because of continual migration from rural areas into Khayelitsha and movement within the settlement itself. Most inhabitants are migrants who were born in the Eastern Cape. Two-thirds are estimated to be unemployed, and of the working inhabitants more than half

earn less than the Household Subsistence Level. Nearly a quarter of the population is functionally illiterate [21]. The resultant socio-economic status/class could at best be considered a proxy marker for factors linked directly to the risk of schizophrenia in the Xhosa population. Exposure to infections or toxic agents and other non-biological factors such as social and psychological stress may even be causative [22].

3. CONFIRMED, POTENTIALLY STRONG RISK FACTORS: OBSTETRIC, BIRTH AND EARLY CHILDHOOD COMPLICATIONS; AGE AND AUTO-IMMUNE/INFECTIVE MARKERS.

3.1. OBSTETRIC, BIRTH, AND EARLY CHILDHOOD COMPLICATIONS

The neurodevelopmental model of schizophrenia is based on the assumption that early abnormal brain development due to genetic and/or environmental factors can give rise to schizophrenia [23;24]. The most robust findings seem to implicate prenatal nutritional deprivation [25], prenatal brain injury, and prenatal influenza [26].

3.1.1. PERINATAL FACTORS

3.1.1.1. OBSTETRIC COMPLICATIONS

Obstetric complications have been the most frequently studied environmental factors and there is evidence that they are associated with an increase in the risk for developing schizophrenia [24]. It is, however, important to note that most neonates who have experienced obstetric complications do not develop schizophrenia. In identifying patients in whom schizophrenia has been associated with obstetric complications, we may be looking either: (a) at a subgroup of schizophrenia sufferers in whom this factor (viz., obstetric complications) has increased their risk substantially [27] or (b) at factors that may merely have brought forward the age of onset of symptoms [28].

A meta-analysis of 18 studies looking at different pregnancy complications (including pre-eclampsia, low maternal weight, rhesus incompatibility, small head circumference and fetal distress) found an odds ratio of 2.0 (95% CI: 1.6-2.4) for schizophrenia following any obstetric complication [29]. While this seems to support the prenatal stress theory, publication bias and selection bias may have influenced the findings of the meta-analysis.

3.1.1.2. NUTRITIONAL DEPRIVATION

Perinatal nutritional deprivation may increase the risk of schizophrenia. The Dutch Hunger Winter study of 1944-1945 [30;31] showed that children (both male and female) born to nutritionally deprived mothers during the Dutch Hunger Winter were twice as likely to develop schizophrenia than those who were not. The Swedish National Birth Register study which analysed data pertaining to over 500 000 children born between 1973 and 1977 [32] showed that children exposed to malnutrition in utero were at increased risk, especially for early onset schizophrenia. These findings suggest that pre- and perinatal complications confer a risk for earlier onset schizophrenia [33].

3.1.1.3. VIRAL INFECTIONS

Exposure to viral infections in utero has been associated with an increased risk of schizophrenia [34]. There are several viral hypotheses of schizophrenia. One hypothesis states that a viral infection coincides with the onset of the illness. This hypothesis stems from the observation that the 1918 influenza epidemic seems to have triggered the activation of latent psychosis in a number of individuals [35].

A second possibility is that a latent viral infection becomes active only later in life. The classic example is herpes simplex virus infection. Activation of latent

infection can cause encephalitis, which in the early stages may resemble schizophrenia [36].

A third theory is that a virus may produce subtle alterations in cellular function, such as changes in the production and stability of neurohormones, cytokines and other neurospecific substances [37]. A viral hypothesis is clearly compatible with the prenatal stress theory since pregnant women who are subjected to various stressors might by virtue of a compromised immune system be vulnerable to viral infections. This hypothesis stems from the association between type A2/Singapore influenza infection during the second trimester of pregnancy and the later development of schizophrenia [38]. However, despite more than 20 studies, the results remain ambiguous to date as the existence of DNA or RNA viral components in the cells of schizophrenia sufferers has not been consistently demonstrated [39-41]. The evidence for infective markers remains circumstantial and until prospective studies report on confirmed viral infections diagnosed during pregnancy this theory should be viewed with caution.

3.1.1.4. PERINATAL AND EARLY CHILDHOOD BRAIN INJURY

Prenatal brain damage or mental impairment in childhood evidenced by delayed motor development, speech problems, lower educational test scores

and a preference for solitary play [42] may be associated with an increase in the risk for schizophrenia [43]. The predictive power of such evidence is modest and the specific etiological underpinning is uncertain, but it at least lends some support to the idea of a neurodevelopmental model [44;45].

In Stockholm County, 524 schizophrenia patients and 1 043 age, gender, hospital and parish of birth matched controls were compared in terms of birth complications, specifically asphyxia (Apgar score < 7 at birth) on the basis of a retrospective assessment of birth records. After adjustment for other obstetric complications, maternal history of psychotic illness and social class, asphyxia at birth was associated with the development of schizophrenia (OR 4.4; 95% CI 1.9-10.3) independent of gender or early onset [46]. This finding is in accordance with other studies that have shown foetal distress [47], high scores on the Risk for Asphyxia Scale [48] and the need for postnatal resuscitation [49] to be associated with an increased risk for schizophrenia. Hultman, et al. (1999) [50] reported an association between schizophrenia and intra-uterine growth retardation, but only in male patients ($p<0.05$).

Despite evidence for an association between schizophrenia and perinatal asphyxia, this finding is by no means consistent. Other community based studies [51;52] failed to demonstrate a significant effect of asphyxia on the

risk for schizophrenia but direct comparisons between these studies is complicated by several methodological differences [53;54].

The associations that have been demonstrated between birth complications and schizophrenia can be explained by three possible mechanisms: first, the patient was at risk for developing schizophrenia before the birth complications arose [55]; second, birth complications themselves cause schizophrenia [56]; and third, genetic determinants of schizophrenia increase the risk of birth complications [57].

It is difficult to arrive at a mechanism whereby perinatal factors might heighten the risk for schizophrenia. Nutrient deficiency during pre-eclampsia is a possible mechanism. Hypoxia may cause damage through acidosis or the generation of waste products, such as amino acids and free radicals [58;59]. N-methyl-D-aspartate receptors may play a central role in producing damage that is mostly located in the brainstem nuclei, hippocampus and cortex [60]. It is of note that reduced hippocampal volume has been described in patients with schizophrenia with a history of obstetric complications [61]. It has long been thought that this reduced hippocampal volume may account for the over-representation of non-right-handedness in schizophrenia and a recent meta-analysis of 19 studies on handedness in schizophrenia confirmed the overrepresentation of non-right-handedness in schizophrenia [62].

However, subtle brain damage is unlikely to be the sole explanation for the development of schizophrenia, since comparison of schizophrenic patients with those suffering from neurological and other psychiatric disorders indicated that non-right-handedness was still significantly greater in the schizophrenia group [63]. This finding introduces the opportunity to propose a more fundamental explanation for the decreased cerebral lateralization in schizophrenia, namely genetic mechanisms. The possibility of genetic mechanisms is suggested by the fact that healthy relatives of schizophrenia patients seem to have a higher prevalence of non-righthandedness than would be expected [64;65]. Genetic mechanisms will be discussed more fully later on in this chapter.

3.2. AGE AND GENDER

The 1-year prevalence rates of schizophrenia were 0.5% for males and 0.6% for females in the National Comorbidity study [66] although minor variations have been reported [67]. Although these studies could not prove conclusively that the development of schizophrenia is independent of gender, several studies focusing on treated cases have suggested a male excess in first-episode schizophrenia studies, especially if onset was before the age of 35 years [68-70]. It has been suggested that males have a younger age of onset

and are younger at first hospitalisation [71-73]. The earlier age of onset in males may not be limited to schizophrenia: the Suffolk County Study revealed earlier age of onset in three diagnostic categories namely schizophrenia/schizo-affective disorder (25 years for males and 28 years for females), psychotic bipolar disorder (23 years versus 29 years) and psychotic depression (27 years versus 33 years) [74].

Males and females have been shown to demonstrate differences in disease presentation. In men, the onset tends to be more insidious, with a larger number of negative symptoms [75-77]. Other studies, however, have failed to demonstrate these differences and some have even reported a greater frequency of typical hallucinations and delusions in men than in women [78]. Studies on the duration of untreated psychosis also showed contradictory results where gender is concerned [74;79].

Could these inconsistent patterns be explained by the inclusion of individuals experiencing familial transmission of schizophrenia? DeLisi et al. (1994) were unable to demonstrate differences between males and females in terms of age of onset in a sample of subjects suffering from familial schizophrenia [80]. This corroborates the findings of Hafner et al. (2003) who found that a strong family history of schizophrenia ameliorated the gender effect [81]. He argued

that the protective nature of estrogen may account for the early differences between men and premenopausal women [81].

Hultman, et al. (1999) reported an association between schizophrenia and intra-uterine growth retardation in male patients ($p<0.05$) [82]. Byrne et al. (2000) also demonstrated a gender effect; they observed a strong association between a definite history of birth complications and male schizophrenia manifesting before the age of 30 years [83]. In a study of subjects recruited from the Swedish Stockholm County inpatient register (January 1971 to June 1994), the effect of male gender failed to reach statistical significance; however this may have been due to insufficient power as a result of an inadequate sample size [74;84]. Many questions regarding the interrelationships between gender and intra-uterine brain damage in schizophrenia therefore remain unanswered.

3.3. AUTOIMMUNE DISEASE

The viral hypothesis of schizophrenia has been mentioned earlier. Autoimmune factors may also have some bearing on the risk of developing schizophrenia. Several studies, despite methodological difficulties, have alluded to a finding that could prove to be important in defining the pathogenesis of schizophrenia, namely that rheumatoid arthritis (RA) is

uncommon in schizophrenia (prevalence of RA 0.047% in schizophrenia, versus 0.16% in the general population) [85]. This suggests that an inverse relationship exists between protective factors for RA and those for schizophrenia.

The association between RA and schizophrenia has been the subject of several reviews and a meta-analysis of the more than 15 available studies reported an odds ratio (OR) of 0.29 ($p < 0.0001$; 95% CI 0.22-0.38) for RA in schizophrenia versus other psychiatric disorders [86; 87;88]. The nine studies that focused on schizophrenia revealed a median frequency of comorbid RA and schizophrenia of only 0.05%. It is argued that this figure could be artificially low, given the possibility that patients with schizophrenia might not be able to clearly communicate or appreciate RA symptoms. However, non-schizophrenic RA patients had lower scores on paranoid ideation (SCL-90 questionnaire) than did controls without RA, suggesting a negative association between paranoid ideation and RA on the dimensional level [89].

Since a negative association between RA and schizophrenia has been reported in large, controlled studies in several countries, it may suggest that a protective immune or genetic mechanism may be at play. Possible mechanisms include genetic mechanisms via HLA polymorphisms (DR4 antigen as possible candidate), tryptophan metabolism, serum interleuken receptor concentration, IGF II or microglia abnormalities [90].

3.4. SEASON OF BIRTH

Winter birth has been found to lead to a disproportionately larger number of patients with schizophrenia in later life (5-15% higher than other seasons), a finding that has not been replicated in other major psychiatric disorders (with the possible exception of autism) [91]. This differential was larger for females and where a positive family history was present [92-94]. More than 250 studies have examined season of birth as a risk factor for the development of schizophrenia [91]. These studies have almost consistently shown a winter-spring excess of 5-8%. Several possible reason for this have been proposed, including infective processes, genetic factors, obstetric complications, variations in light, environmental toxins, nutrition, climatic changes and even procreational habits of at-risk parents [92].

It has been argued that the excess could be explained by an age-incidence effect (individuals born earlier in the year should be at higher risk because they are older at the time of the investigation). However, a winter excess is still present even when the age-incidence has been controlled for [95].

Season of birth has also been associated with different subtypes of schizophrenia, differences in prognosis, demographic factors and clinical

presentation. Bralet et al. (2002) reported an excess of July births in French Kraepelin subtype patients with schizophrenia [96]. Summer births have also been reported in patients with deficit syndrome of schizophrenia [97;98]. Several other studies have suggested a more benign course for winter born patients with schizophrenia. Higher levels of anhedonia have also been reported (although not consistently) in schizophrenic patients born one month after a winter season with a high rate of infections. Troisi et al. (2001) reported that female patients born in winter and early spring had higher negative and anergia PANSS scores than those born in the other seasons, while males born in the other seasons had higher scores on the anergia factor [99].

Several other studies have found no relationship between season of birth and various variables such as age of onset, marital status, total duration of hospitalisation and number of hospitalisations [100;101].

To date, twelve southern hemisphere studies have been done and a meta-analysis of ten of these studies - involving over twenty thousand patients with schizophrenia - showed no specific winter birth excess [102]. There were many methodological problems, however, of which matching of controls and small sample sizes were the most important. According to Torrey and Miller (1997) [100], only one study was methodologically sound and this did show a

significant winter-spring excess of births [103]. The season of birth may however be only a proxy for several other underlying factors, such as viral infections and diet. At any rate, the overall contribution of this factor to the risk of schizophrenia appears to be relatively small [100;101].

4. STRONG CONFIRMED RISK FACTORS (SOCIAL CLASS AND FAMILY HISTORY)

4.1. SOCIAL CLASS

Several studies have pointed out that people with schizophrenia are more likely to occupy lower socio-economic positions and live in areas of higher social deprivation at the time of their first diagnosis than people without schizophrenia [104-106]. Social class is considered one of the strong predictors of illness [107] and an increased ratio has been calculated for the rate of schizophrenia in persons born into the lowest social classes compared to the rate in people born into the highest social classes [108]. It is still unclear to which extent social segregation caused by the prodromal symptoms may contribute to this.

Two possible explanations have been offered for this difference in rates. The first hypothesis states that adverse environmental factors may precipitate the

onset of schizophrenia (social causation). The second hypothesis (social drift theory) focuses on the fact that patients with schizophrenia may not reach their potential due to the clinical features associated with the premorbid, prodromal and early illness phases.

Harrison et al. (2001) [109] found an increased risk in those individuals in whom paternal social class had been lower than maternal social class or where the births had taken place in a deprived area (OR=2.1; 95% CI 0.8-5.5) [110]. If both of these factors were present, the odds ratio increased to 8.1 (95% CI; 2.7-23.9). While other studies support their findings [111], Done et al. (1994) (UK sample) [112] and Jones et al. (1994) (UK sample) [113] demonstrated an association between schizophrenia and higher, not lower, paternal social class. However, since the latter two studies were small and differed from each other in sample selection, the precise role of paternal social class on the development of schizophrenia needs further research, using larger, well-defined samples.

Of the theories pertaining to social class and schizophrenia, the social drift theory remains the most widely supported. However, all of these hypotheses may be valid depending on the subgroup of schizophrenia under consideration [114]. Further research may shed more light on the roles of

each of these hypotheses. The present study is unlikely to add materially to the understanding of the role of social class in the pathogenesis of schizophrenia: in South Africa, geographic location cannot be used as a measure of social class, because of the rapid urbanization that has taken place amongst Xhosa-speaking people [115].

Dohrenwend et al. (1992) [116], in their research into the social determinants of mental illness in Israel, investigated a birth cohort of 4914 Israeli-born adults in terms of social selection. They concluded that social selection might be of greater importance than social causation in producing the social class effects found in schizophrenia.

4.2. FAMILY HISTORY AS A RISK FACTOR

Numerous reviews on the genetics of schizophrenia support the notion of familial transmission of schizophrenia [117-119]. However, establishing the role of familial inheritance in schizophrenia is by no means straightforward. The first layer of complexity to be dealt with is to determine whether the condition is truly inherited in the genetic sense, whether one is dealing with the effects of nurture, or whether random, non-genetic factors that create phenocopies are involved. The latter situation may occur when someone

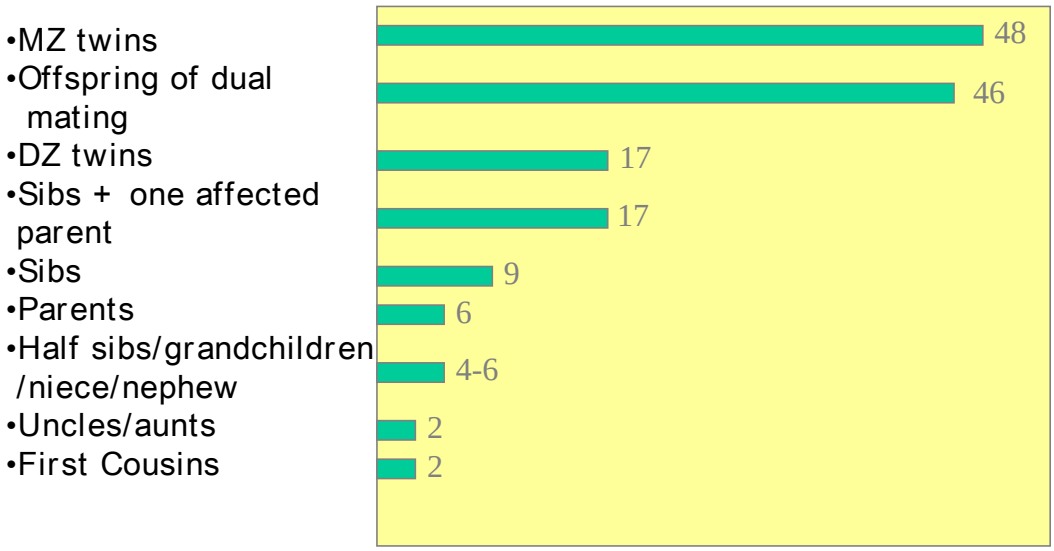
suffers a non-genetic event (e.g., a head injury), and subsequently develops a psychiatric disorder such as schizophrenia [120].

Several lines of evidence point toward the involvement of inherited factors in the disease process. Family studies, including twin studies, have offered some revealing insights into the role of the genetic determinants of schizophrenia. The consistently higher concordance rate for schizophrenia in monozygotic twins as opposed to dizygotic twins (approximately 50% vs. approximately 17%) [121], whether they were reared apart or not [122], suggests some shared susceptibility factors. However, the concordance rate in schizophrenia is not 100%, as one would expect if schizophrenia were solely a genetic disorder. It follows that a strong likelihood exists that gene-environment interactions contribute materially to the development of schizophrenia.

A large number of family studies conducted between 1921 and 1987, despite methodological differences, support the possibility of inherited factors in schizophrenia susceptibility [123]. They found the lifetime morbid risk (MR) for schizophrenia in the general population to be in the order of 1% while increased risks ranging from 2 to 48 times higher were demonstrated in

biological relatives of individuals with schizophrenia [124;125] (Figure 1).

FIGURE 1. LIFETIME MORBID RISK FOR SCHIZOPHRENIA (%) AS A FUNCTION OF FAMILY HISTORY



Criticisms levelled against these family studies include lack of proper controls, potential sampling errors, differing diagnostic criteria and the unblinded status of family members. These limitations should be borne in mind when interpreting the results. Kendler and Diehl (1993) [126] analyzed seven studies designed to address these problems. A lifetime MR of 0.5% for relatives of controls was reported compared to 4.8% for relatives of patients with schizophrenia. The estimated heritability was as high as 60- 80% [127;128].

The susceptibility risk for schizophrenia and its spectrum disorders seems to be higher if a narrow spectrum definition is used [126]. Less convincing results occur with a broad-spectrum diagnosis, i.e., one in which patients suffering from comorbid alcoholism, anxiety disorders and mood disorders (unipolar or bipolar) are included. This finding is also reflected in twin studies where broadening of the phenotype leads to a decreased estimate of risk for schizophrenia in family members [129].

A century of research therefore points towards a constitutional model for - and by implication a genetic component to - the development of schizophrenia. The translation of the observed familial patterns found in schizophrenia into molecular proof has not been easily forthcoming. It thus seems fair to state, that, while nearly a century of pre-clinical and clinical studies concerning the causes of schizophrenia have improved our knowledge about this disabling disease, we need new tools of discovery if we hope to uncover the secrets of schizophrenia.

The development and modernization of molecular biology automation technologies and statistical methodology now makes the identification of susceptibility loci for major psychiatric disorders such as schizophrenia a possibility [130]. The completion of the draft sequence of the human genome, and other associated projects, have provided researchers with a wealth of

information regarding the genetic make-up of the human species. Many of the suspected twenty-seven to forty thousand genes and their products may directly or indirectly influence the development, presentation and course of psychiatric disorders. It is hoped that by investigating the wealth of naturally occurring variants of the genes that have been uncovered by the genome project, those variants or combinations of variants that predispose an individual to developing psychiatric disorders will be delineated. However, it is already clear that psychiatric disorders such as schizophrenia result from a complex layer of influences, not all of which are genetic, and that dissecting out the genetic component is far from simple. Considering the multitude of possible combinations of factors operating in the pathogenesis of the disease, the flood of disparate findings cited in the literature (positive and negative, association and non-association, linkage and non-linkage, agreement and disagreement) is not wholly unexpected [131]. The prevailing sentiment regarding schizophrenia, namely that it is an excellent example of heterogeneity, was echoed in an editorial review on the current status of genetic studies in schizophrenia. Tsuang (2000) stated, "we can now conclusively reject the idea that there is one gene of major effect that causes schizophrenia" and the search is now on for the various genes that could be involved in the clinical expression of the disease of schizophrenia [131]. Schizophrenia in an individual could result from many genes of small effect. Certain subgroups of schizophrenia could also be brought about by single

genes of moderate effect [131]. An example of the latter is a susceptibility gene (Meyer et al. (2001) (WKL1 on chromosome 15) which confers a major risk for the development of a subtype of schizophrenia, namely catatonic subtype [132]. The fact that this gene most likely acts in concert with (currently unknown) predisposing factors provides further evidence for the heterogeneity of schizophrenia. It also bodes well for the quest for links between other subgroups of schizophrenia and specific genes of relatively major effect.

Although these findings together with results of family and twin studies support a role for genetic factors in the development of schizophrenia, they do not help to define the mode of inheritance. Neither have they been able to enumerate the inherited susceptibility factors that influence the molecular pathophysiology of schizophrenia. The mode of inheritance of a disorder determines the analysis needed to delineate the implicated gene(s); genes involved in simple Mendelian inheritance are more easily identified than those involved in complex polygenic or multifactorial disorders. It seems that in most psychiatric disorders a complex mode of inheritance is involved although psychiatric disorders inherited by classical Mendelian inheritance do exist. For instance, Brunner et al. (1993) studied a Dutch family in which five males exhibited low intellect and episodes of abnormal and overly aggressive behaviour, including arson, attempted murder and exhibitionism [133].

Genetic analysis of these five males led to the diagnosis of a form of X-linked borderline mental retardation characterized by behavioural abnormalities. MAO-A activity is absent in such individuals because of a single point mutation in exon 8 of the MAO-A gene. However, phenomena such as incomplete penetrance (in which someone carries the disease-causing or -predisposing gene variant in which symptoms of the disease are attenuated or delayed) and variable trinucleotide expansion (the mechanism underlying Huntington' s chorea and possibly schizophrenia and bipolar disorder), indicate that even classical Mendelian inheritance can be complicated by additional genetic or non-genetic factors [134].

Segregation analysis studies among European schizophrenic samples selected according to standard criteria indicated that neither the generalized single locus model (commonly used in linkage analysis) nor the multifactorial threshold model (MD) sufficiently explained the risk patterns observed in schizophrenia [135] . Of the two, the MD model showed the best fit. As has been found in OCD sufferers, a mixed model (multifactorial, with no single major gene) seems to best explain inheritance in schizophrenia at a genetic level [136].

Estimating the number of loci contributing to this model might be complicated by the occurrence of epistatic interactions. In epistatic interactions, the total

susceptibility/risk conferred by any number of genes is greater than the sum of the individual susceptibility genes. The fall in rate of concordance may be used to estimate the number of epistatic loci [137]. Using this technique, data from US studies suggested 3-4 epistatic loci in schizophrenia [137]. However, the utility of these results is complicated by the fact that the individual loci will show smaller effects than if the loci act in an additive manner. Furthermore, these loci must be biologically related (functionally, temporally or spatially) and therefore the genotype/phenotype of one gene must influence the genotype/phenotype of another gene. Further modelling will depend upon penetration at the different loci. Given the paucity of data on candidate gene loci, modelling is not currently possible.

The classical approach to disease gene mapping strategies, namely linkage analysis, is still extensively employed in schizophrenia (Appendix 1). In linkage analysis one computes the probability that multiple affected individuals in a family share a particular chromosomal segment (identified by specified genetic variations called markers) more often than would be predicated by chance alone.

Significant successes of the linkage method include the identification of amyloid beta precursor, presenilin-1 and 2 genes, as causal factors in early-onset Alzheimer' s disease (AD), and APO E as a susceptibility factor for

late-onset AD [138]. However, although linkage studies have singled out some chromosomal areas (including chromosome 12 and 18) as possibly harboring genes of importance in schizophrenia and bipolar mood disorder subsequent studies have not been able to replicate all these findings, even using the same family resources [139]. If strict criteria are followed (a lod score of 3.3 for parametric and 3.6 for non-parametric methods) no study has thus far yielded significant linkage results [140]. One reason for the inconsistent linkage analysis findings in schizophrenia could be that this method reliably detects only genetic factors that have a major influence on disease development. Possibly, multiple genes of smaller effect account for the development of schizophrenia. Alternatively, these diseases may not comprise single disorders at all, but could be manifestations of genetic heterogeneity; i.e., they may constitute similar clinical entities caused by different genes or gene-combinations. This is certainly plausible, given the demonstration of a single gene accounting for a major effect in catatonic schizophrenia [141;142]. As in OCD, different symptom factors in schizophrenia may result from differences in heritability [143].

Thus, it is becoming clear that most psychiatric disorders, like schizophrenia and OCD, display some genetic heterogeneity and/or epistatic gene interaction (where two or more genes act in concert to cause a psychiatric disorder). Therefore it is necessary to use techniques that can detect genes

with a minor effect. The power of these methods depends heavily on careful phenotyping of appropriate clinical samples.

Given the strength of familial risk factors for schizophrenia and the rapid development of genetic laboratory and statistical methods, the study of familial risk factors in a relatively heterogeneous clinical sample, such as one that can be drawn from the Xhosa population, may offer unique insights into the etiology of schizophrenia.

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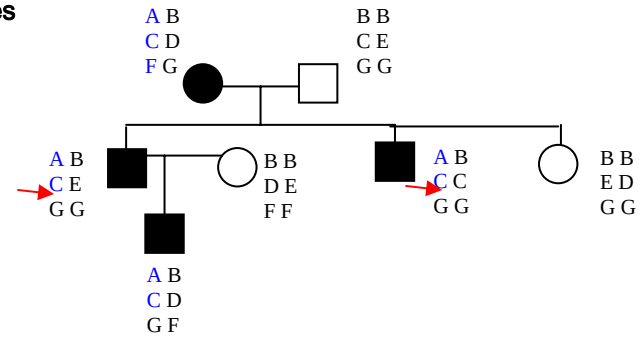
APPENDIX 1. GENE MAPPING STRATEGIES

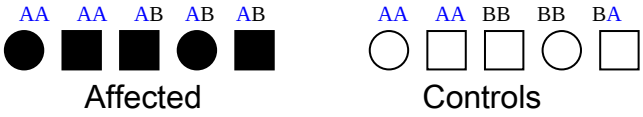
A. Linkage studies



Linkage analysis (which can also include affected sibpair and affected pedigree member analysis) considers whether multiple affected individuals in a family share a particular chromosomal segment more often that would be expected by pure chance. The figure shows that the chromosome containing the maternal segment ABF (in blue) is linked to the disease (filled symbols) and that ~~those~~ recombination events (red arrows) limit the disease gene-containing area to the AC segment (in blue).

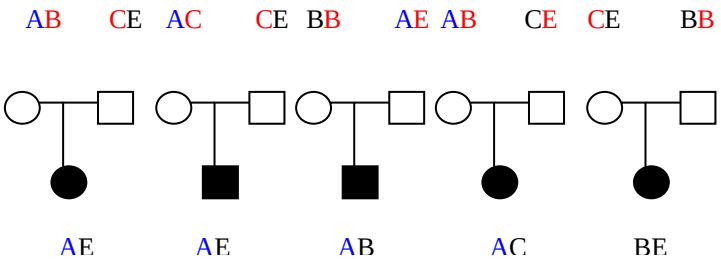
B. Association studies

1. Population based case-control association studies



Case-control association compares genotype distribution and allele frequencies of patient and appropriately matched control groups. The figure shows that allele A occurs more frequently in the patient group than in the control group.

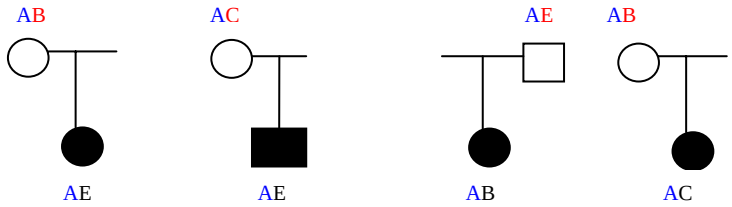
2. Family-based association studies



Family-based association studies use non-transmitted alleles (shown in red) as control samples.

2.1. Haplotype Relative Risk (HRR)

Alleles in affected	Alleles in unaffected
AE, AE, AB, AC, BE	BC, CC, BE, BE, BC



HRR uses non-transmitted alleles (shown in red) from parents as controls.

TDT compares the frequency of transmitted (in blue) and non-transmitted (in red) parental alleles from heterozygous parents (Adapted from Burmeister 1999).

Chapter 3

THE ROLE OF AFFECTED SIB PAIR STUDIES IN LIMITING THE HETEROGENEITY OF SCHIZOPHRENIA

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1. INTRODUCTION

In this chapter, the principles underlying studies of sib pairs will be discussed, reference will be made to the statistical methods commonly employed in their analysis, and a review of several seminal sib pair studies on schizophrenia will be performed. In considering the published sib pair studies, sample size, patient population, diagnostic criteria and statistical methods are important determinants of the validity of any one study.

Schizophrenia, according to current classification schemes, is not a single entity, but can be considered a spectrum of disorders displaying considerable heterogeneity in terms of clinical manifestations, age of onset, course and prognosis. Numerous attempts have been made to characterize the heterogeneity of the schizophrenia phenotype by exploring relationships between the various symptom dimensions and possible subtypes. It is highly probable that the observed clinical heterogeneity is a reflection of an underlying genetic heterogeneity.

Although the mode of inheritance remains elusive, studies suggest that it is most likely to be heterogeneous, with incomplete penetrance. Whether this susceptibility results in disease and what form it takes, is clearly influenced by environmental risk factors [1;2].

Studies involving concordant siblings are useful since investigators are able to examine genetic and environmental factors simultaneously. These studies are based on the assumption that shared *clinical* features are likely to be related to shared *familial* (environmental or genetic) factors [3].

Concordant sib pairs are particularly useful to detect genes of moderate effect in complex disorders by means of an allele sharing linkage method. In these studies, linkage is suggested by pairs of sibs inheriting the same alleles (at a specific locus) more often than expected by chance. This method has been used with success and a study by Owen (2000) has identified three areas of suggestive linkage namely on chromosome Xcen, 4p and 18q. Given the suggested polygenic (many genes of small effect) or oligogenic (few genes of moderate effect) models for the genetic basis of schizophrenia, it is expected that 600-800 sib pairs will be needed to identify alleles that confer an increased risk of 1.5-3 in an oligogenic model. If a polygenic model is followed, the number of sib pairs reaches into the thousands and association studies become a more viable option given the difficulties recruiting large sib pair samples. Sib pair studies afford a practicable means of identifying candidate genes based on hypotheses generated from well-characterized clinical phenotypes.

This review addresses twelve sib pair studies conducted over a period of 102 years on schizophrenic patients [4-17]. The earliest reported sib pair data set is that of Zender 1940 (Switzerland). This was followed by eleven further studies [18].

2. SUBJECTS AND METHODS

2.1 SUBJECTS

These studies reported on subjects from various countries: the United Kingdom (7 reports), the USA (3), France (2), the Island of Réunion (2), Switzerland (1) and Taiwan (1). It is important to note, however, that several of these reports probably include the same participants. Although it is difficult to compute the exact degree of overlap between study samples, it is probably safe to assume that Ross et al. (2000) [19], Kendler et al. (1997) [20] and Burke et al. (1996) [21] shared the subjects recruited in Ireland and Northern Ireland. Cardno et al. (1998) [22] recruited a sample from the UK and Wales. Two French studies (Fouldrin et al. (2001) [23] and Leboyer et al. (1992) [14]) both include a sample from Réunion and Normandy. Loftus et al. (1998, 2000) [24;25] reported two sets of findings on a sample from the USA,

London, Oxford and Dublin. DeLisi et al. (1987) [26] reported on a pure United States sample recruited from 22 states. An apparently independent sample was reported in Taiwan (Hwu et al. (1997)) [27]. In summary, it can be assumed that sib pair studies include eight independent samples, namely a sample from Ireland/Northern Ireland, a sample from the UK and Wales, a UK only sample, a French sample, a pure US sample, one Taiwanese sample, one mixed sample from the USA, UK and Ireland, and finally, a Swiss sample.

In several studies, psychiatric hospitals were used as recruitment sites ([28] Ross et al. (2000); [29] Kendler et al. (1997); [15] Tsuang (1967); [30] Fouldrin et al. (2001); [14] Leboyer et al. (1992); [31] Kendler and Adler (1984)). Burke et al. (1996) [32] (part of a large genetic study) and Hwu et al. (1997) [33] did not specify their recruitment sites. Loftus et al. (1998; 2000) [34;35] and Cardno et al. (1998) [36] recruited subjects from local psychiatric services and consumer groups. DeLisi et al. (1987) [37] used advertisements and targeted psychiatric services and consumer groups.

2.2 METHODS: ASSESSMENT OF SUBJECTS

The assessment tools were mostly DSM-III-R based ([14;38-44] (Appendix 1). Some researchers, however, used other instruments: ICD [15], RDC [45],

DSM-III [46] and DSM-IV [47]. Leboyer et al. (1992) [14] and Kendler and Adler (1994) [48] also used ICD-10 and ICD-9 criteria, respectively, as well as DSM-III and Tsuang-Winokur criteria. The researchers used a variety of methods and diagnostic instruments to identify subjects with schizophrenia and to rate various symptoms (Appendix 1).

Apart from a re-analysis of Zender' s sample (initially personal interviews) [49], a case report based study by Tsuang (1967) [15], a study using a combination of case reports and personal interviews [50;51]and telephonic interviews [52], most of the patients were interviewed personally by psychiatrists or trained social scientists. Most studies included blinded or independent raters and consensus diagnosis of the sib pairs by two or more raters.

The diagnostic spectrum included schizophrenia (including simple schizophrenia) [53] and schizo-affective disorder (Appendix 1).

2.3 METHODS: CHARACTERISTICS OF STUDY SAMPLES

The gender distribution of these samples shows a clear male preponderance (65.4%, assuming no study overlap), with only Tsuang (1967) [15] reporting on a sample consisting mostly of female patients (Appendix 2). Whether this

male preponderance reflects recruitment bias is not certain, but it is not representative of the roughly equal gender distribution expected in schizophrenia and, to a lesser extent, schizo-affective disorder. Very few studies gave clear indications of the gender groupings within the sib pairs, but as expected from the above-mentioned gender disparity, male-male pairs were most commonly reported (Appendix 2).

Because participants in such studies differ regarding the stage of illness at interview, it is important that confounding variables such as age at interview [discussed first], age of onset, and duration of illness should be reported. Ten studies reported interviewees' ages. Except for the Hwu et al. study (1997) [54], participants were in their middle thirties to late forties. The age of onset (eight studies reported this data) varied from 19.2 to 27.8 years and the duration of illness (data available for 5 studies) from 9 to 19.9 years (Appendix 2).

2.4 METHODS: STATISTICAL APPROACHES

A wide variety of approaches were followed to analyze psychiatric symptoms shared by affected sib pairs (Appendix 4). Researchers tried to identify specific symptom factors that could be used to subtype schizophrenia. This

approach rests on the assumption that symptoms in affected sib pairs may cluster together if they share a familial loading (either genetic or environmental). The second approach rests on the assumption that symptoms with a shared familial background will be more likely to be present in both siblings.

These approaches can thus be broadly classified into:

A. Methods that identify symptoms which cluster together

1. Factor analysis with varimax rotation [55-58]
2. Latent Class analysis [59]

B. Methods that identify symptoms which are shared by sib pairs

1. Kappa statistic [60]
2. Spearman correlation [61;62]
3. Likelihood ratio statistics [63]
4. Chi-square based techniques include the following:
    a. Sib pair method [64-66]
    b. Sibship method [14;67]
    c. Within pair association study [68;69]
    d. Observed versus Expected ratios [15]

2.4.1. METHODS THAT IDENTIFY SYMPTOMS WHICH CLUSTER TOGETHER

2.4.1.1 FACTOR AND LATENT CLASS ANALYSIS

Factor analysis is concerned with describing and interpreting interdependencies within a set of variables (such as interviewer ratings of psychiatric signs and symptoms) and reducing the number of variables into a smaller group, called factors. These factors cannot be understood intuitively until the reference axes are rotated, and derived factors are extracted. They can be viewed as biologically meaningful variables derived from the original data and can be used in further analyses, such as analysis of concordance between sib pairs. The eigenvalues of the extracted factors give an indication of the proportion of the total variance accounted for by the factors. Only factors with Eigenvalues > 1 are retained.

2.4.2. METHODS THAT IDENTIFY SYMPTOMS WHICH ARE SHARED BY SIB PAIRS

Which statistical methods should be used to examine concordance between sib pairs remains a dilemma. The most commonly used statistical methods entail the use of Chi-square based techniques since the complex nature of the clinical data (linear and non-linear) makes other forms of analysis, such as the

Kappa statistic, less likely to yield valid results. The sibship method, a Chi-square based technique, relies heavily on diagnostic concordance between all siblings in a sibship. If, for example, only three out of four siblings are concordant for symptom Y, this sibship will not be viewed as concordant. This invariably leads to underreporting of possible concordance in a given sibship. It is important to determine criteria for sibship selection carefully, since sibship size (i.e., the number of affected siblings in each pedigree) directly influences statistical significance and may bias the results in favour of studies with large sibship sizes (Appendix 3).

In contrast to this method, the sib pair method, which is based on concordance of symptoms between two siblings, tends to overestimate concordance (relative to the sibship method) if the pair is part of a larger sibship (Appendix 3). When interpreting studies using the sib pair method, it is important to determine which criterion was used for extraction of sib pairs. The criterion for selection of a sib pair from a sibship should preferably be based only on random extraction, since selection based on, for example, "first two to become ill" (DeLisi et al. 1987) [70] could reflect only the difference in ages of onset, and not necessarily concordance of symptom Y. Even though Hodge's weighting technique could be applied to adjust for this discrepancy, this is still only an approximation of the "true" results. Ideally, a study sample should have the smallest possible number of sibships with

more than two affected individuals in order not to rely on approximations such as Hodge' s weighting technique.

3. INTERPRETATION OF RESULTS: INDIVIDUAL SYMPTOM AND SUBTYPE RESULTS

Interpretation of the results is influenced first by the sample sizes of the studies which vary from 62 [71] to 466 subjects [72] with all but the Irish samples [73;74] constituting less than 200 participants. In addition to this, the statistical methods used in most studies relied on extracting two affected siblings for comparison, a sibship of 3 affecteds would have led to over-representation of larger sibships in the final statistical analysis. It is of note that sets consisting of only two affected siblings range from 16 [75] to 148 [76].

Despite these methodological difficulties, results from these studies have yielded valuable information on shared familial factors. Increased intra-pair correlation or concordance has been found for several of the symptoms and signs of schizophrenia (Appendix 5).

3.1. POSITIVE SYMPTOMS

Burke et al. (1996) [77] demonstrated significant intra-pair correlation for positive symptoms, both as a single factor, and as a group of symptoms. Although Loftus et al. (1998) [78] did not find support for such a correlation, Hwu et al. (1997) [79] reported a Kappa score of 0.55 for the same set of positive symptoms in a Taiwanese sample.

3.1.1. HALLUCINATIONS

Hallucinations as a group of symptoms were found to show significant correlation in the Kendler et al. (1997) study [80]. Third person auditory hallucinations showed significant concordance in the 2000 study by Loftus et al. [81] but not in an earlier report by the same group [82]. DeLisi (1987) [83] and Cardno et al. (1998) [84] also failed to find a significant concordance for auditory hallucinations. Visual hallucinations were concordant according to DeLisi (1987) [85].

3.1.2. DELUSIONS

Delusions as a group of symptoms were found to be significantly concordant by Kendler et al. (1997) [86], but not by Cardno et al. (1998) [87]. Nevertheless, the latter study did find the presence of delusions of influence as a single symptom to be significantly concordant in the sib pair sample,

which is in keeping with the positive finding of Loftus et al. (2000) [88] for delusions of control. Except for thought broadcasting in the latter study and grandiosity in the study of Cardno et al. (1998) [89], no support was found for individual delusions in any of the other studies.

3.1.3 POSITIVE THOUGHT DISORDER AND INAPPROPRIATE AFFECT

Loftus et al. (1998) [90] and Kendler et al. (1997) [91] found positive thought disorder and inappropriate affect to be concordant between siblings , while Burke et al. (1996) [92] found only partial support for this notion. Hwu (1997) [93] reported a Kappa score of 0.21 for thought disorder. DeLisi (1987) [94] and Cardno et al. (1998) [95] did not find significant concordance for this factor.

3.2. NEGATIVE SYMPTOMS

Kendler et al. (1997) [96] found negative thought disorder and affective deterioration to be significantly correlated between siblings. Similarly, Burke et al. (1996) [97] found the group of negative symptoms, namely negative thought disorder, flat affect, anhedonia and avolition, to show significant intra-pair correlations.

In contrast to these findings, DeLisi (1987) [98], Cardno et al. (1998) [99] and Loftus et al. (1998) [100] did not find significant concordance for negative symptoms. Hwu (1997) [101] found a Kappa of 0.29 for the group of symptoms: flat affect, alogia and asociality.

3.3. CATATONIA

The concordance of catatonic symptoms was supported by both Kendler et al. (1997) [102] and Tsuang (1967) [15]. Cardno et al. (1998) [103], however, did not support this observation.

3.4. MOOD SYMPTOMS

Support for significant concordance for depressive symptoms came from three studies [15;104;105]. However, a few other studies reported negative findings for depressive [106;107;108] and manic symptoms [109;110].

3.5. OTHER SUBTYPES

DSM-R, DSM-II-R, ICD-10 and Tsuang Winokur based subtypes were found not to be concordant in the sib pair samples [14]. Deficit versus non-deficit [111;112] subtypes found mixed support, with Ross et al. (2000) reporting significance and Fouldrin et al. (2001) reporting significant concordance only in a small non-Caucasian subsample. Some support was found for paranoid opposed to non-paranoid subtypes (ICD-9 and DSM-III) [113]. Neither classifying subjects into type 1, 2 and mixed subtypes nor into paranoid, hebephrenic and undifferentiated schizophrenic subtypes were successful in showing significant concordance [114].

4. FINDINGS FROM LATENT CLASS ANALYSIS OF SIB PAIRS

Kendler et al. (1997) [115] reported a five class solution (Appendix 6). Scrutiny of these individual classes reveals these observations: class one seems to resemble a more schizoaffective status, while class four seems to resemble the paranoid subtype described in DSM-IV. Class five suggests a catatonic subtype while classes two and three seem to represent the more typical positive and negative symptom complexes.

5. RESULTS FROM FACTOR ANALYSIS OF SIB PAIRS

Three of the sib pair studies employed factor analysis. They all reported two [116] or three factors [117;118] (Appendix 7). Burke et al. (1996) found negative, reality distortion and disorganized symptom factors with mixed support from the analysis of variance. Kendler et al. (1997) [119] reported a similar solution, i.e., a negative symptom factor, a positive symptom factor and an affective/manic symptom factor. In accordance with Burke' s results, the manic/affective factor also contained positive thought disorder [120]. Each of these factors showed significant concordance within sib pairs. Loftus et al. (2000) [121] reported a two factor solution which roughly translated into a hallucinations symptom factor and a delusions symptom factor. The low number of factors in these solutions is of concern, since the smaller the number of factors, the less reliable factor analysis becomes, and it would be important to interpret these results on this background of uncertain validity.

6. SUMMARY

The main value of sib pair studies lies in the possibility of identifying shared familial factors. These shared factors can be used to investigate underlying pathophyisiological processes by means of genetic or environmental studies. Given the large genetic contribution - estimated to be in excess of 70% - identification of shared factors promises to be of considerable value in genetic studies of schizophrenia.

Sib pair studies on the symptomatology of schizophrenia basically address two related though different issues. The first group of studies look for symptoms that cluster together in sib pairs (factor and latent class analysis). Of these, the large sample size (n=256 sib pairs), single geographic origin and the use of established factor analysis methods by Kendler et al. (1997) makes this study's results of particular interest. However, of concern are the inclusion of items of which the criteria may be difficult to replicate precisely (e.g., poor outcome and chronic course), and the use of less stringent eigenvalue criteria in the statistical analysis. In designing our study we therefore focused on a homogenous population (less genetic variation), used strict diagnostic criteria measured with a widely accepted assessment tool and employed a more rigorous eigenvalue criterion.

The second group of studies evaluate the concordance of symptoms within sib pairs. Here, not only is sample size an important determining factor, but the choice of statistical method can materially affect a researcher's results. Chi-square techniques that incorporate the sib pair method seem to be the most widely used and the studies that employed them were of specific interest to us in developing the protocol for this study [122;123]. Ideally our study should therefore include one diagnostic category (most studies used

schizophrenia and schizo-affective patients), use the sib pair method (only include one sib pair per sibship) and rely on chi-square statistical methods.

After a critical appraisal of the methodology employed in published studies on shared familial characteristics in schizophrenia, we selected the sib pair method (including only one sib pair per sibship) and utilized chi-square based statistical tests. Unlike most other studies, which used both schizophrenic and schizo-affective patients, we decided on only one diagnostic category, in order to assemble as homogeneous a patient sample as possible.

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APPENDIX 1. STRUCTURED ASSESSMENT TOOLS USED IN SIB PAIR STUDIES

Study*	Ross et al. 2000	Kendler et al. 1997	Burke et al. 1996	Fouldrin et al. 2001	Leboyer et al. 1992	Loftus et al. 2000	Loftus et al. 1998	Hwu et al. 1997	DeLisi et al. 1987	Cardno et al. 1998
SCID-III-R (modified)	X	X	X							
SADS-L				X	X	X	X		X	
DIGS						X	X			
PSE-9										X
Major symptoms of schizophrenia scale		X								
OPCRIT										X
SAPS						X	X			X
SANS			X			X	X			X
Chinese PANSS								X		
Schedule for the deficit syndrome of schizophrenia	X			X						
Krawiecka scale							X		X	
Premorbid social adjustment									X	
Levels of functioning scale			X							
SIS	X	X								

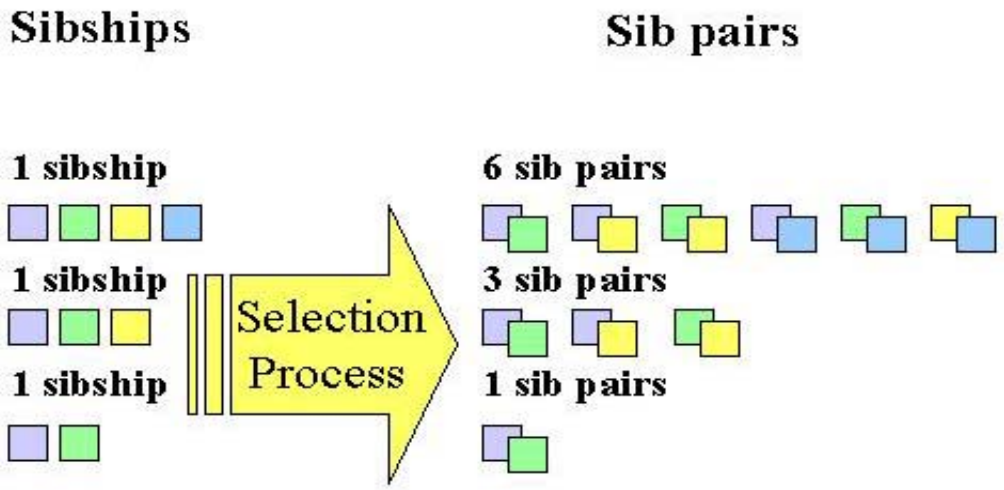
Relative psychiatric history questionnaire						X	X			
Family structured interview									X	
GAS						X	X			X

** Tsuang (1967) and Kendler and Adler (1984) used clinical diagnosis only.*

SCID-IIIR = Structured Clinical Interview for DSM-III-R; SADS-L= Schedule for affective disorders and schizophrenia-lifetime version; DIGS= Diagnostic Interview for Genetic Studies; PSE-9=Present State Examination; OPCRIT= Operational Criteria; SAPS=Schedule for the assessment of positive symptoms; SANS=Schedule for the assessment of negative symptoms; SIS = Structured interview for schizotypy for schizophrenia spectrum personality disorder.

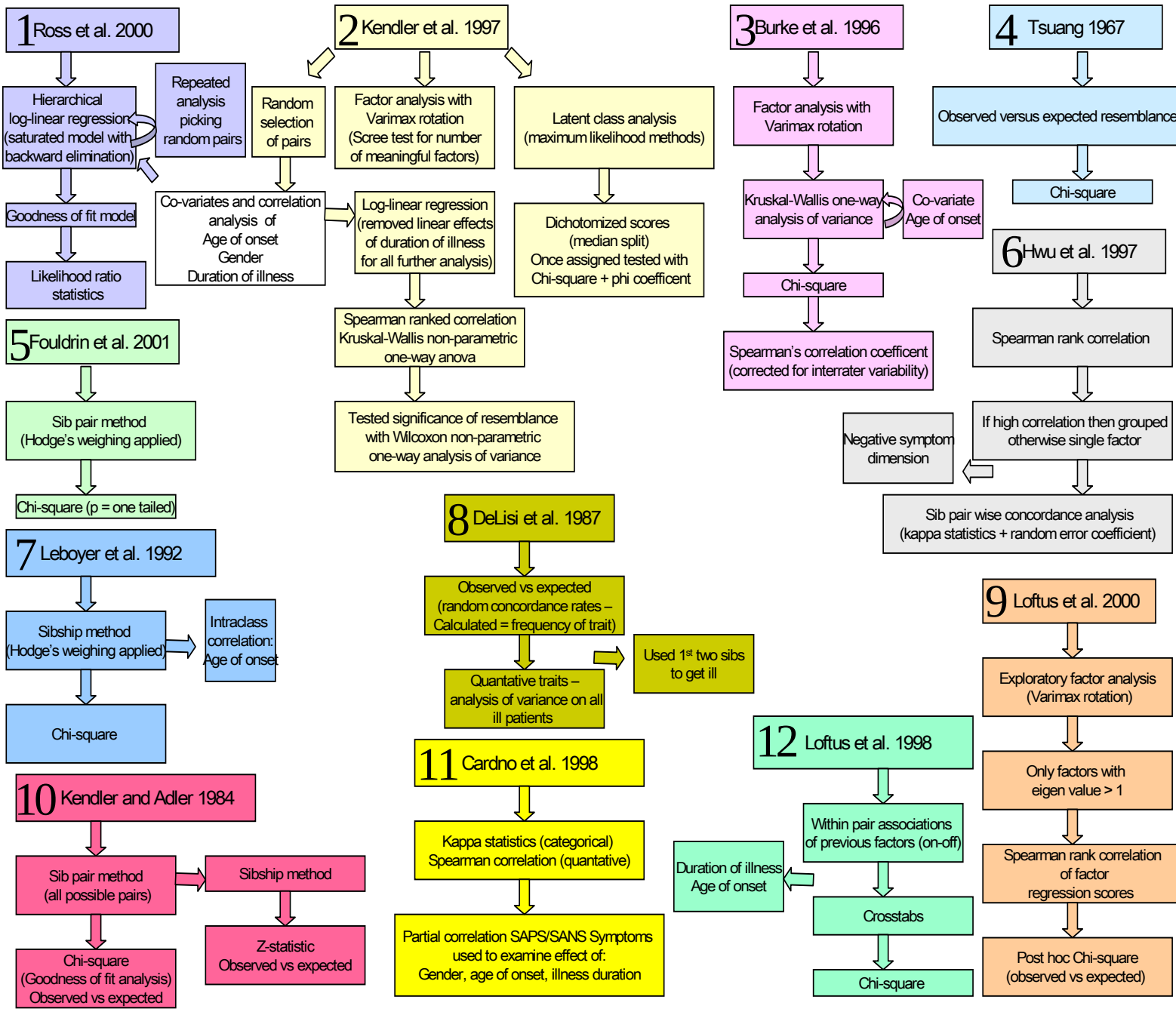
APPENDIX 2.SUMMARY OF CHARACTERISTICS OF SUBJECTS IN SIB PAIR STUDIES

APPENDIX 3. THE INFLUENCE OF SIBSHIP SIZE ON STATISTICAL ANALYSIS



1 sibship of 2 sibs can only yield 1 sib pair, while 1 sibship of 4 sibs can potentially yield 6 sib pairs. This will bias the findings in favour of factors that may be unique to these families with multiple affecteds

APPENDIX 4. SUMMARY OF STATISTICAL METHODS USED IN SIB PAIR STUDIES

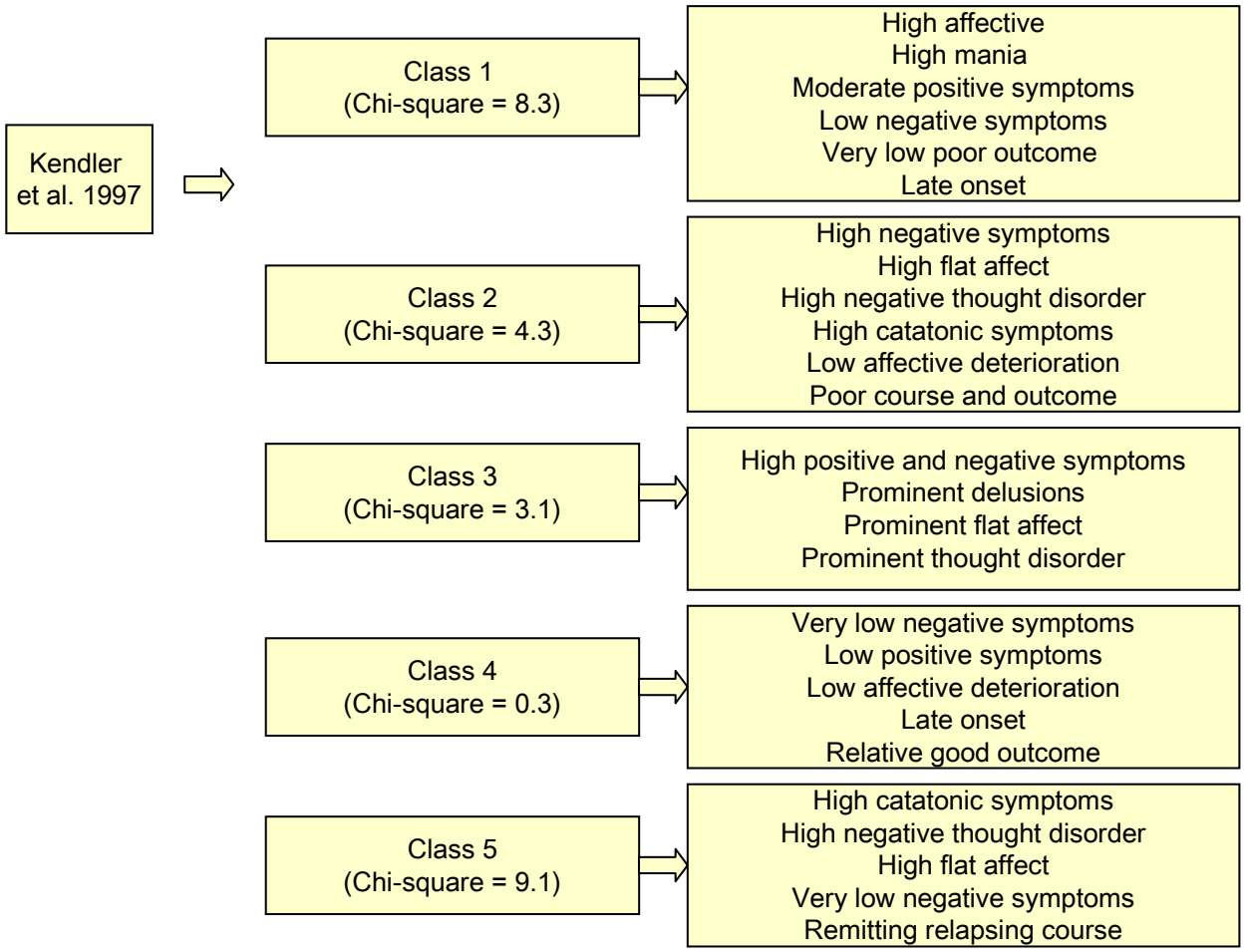


Appendix 5. Concordance findings: individual symptoms

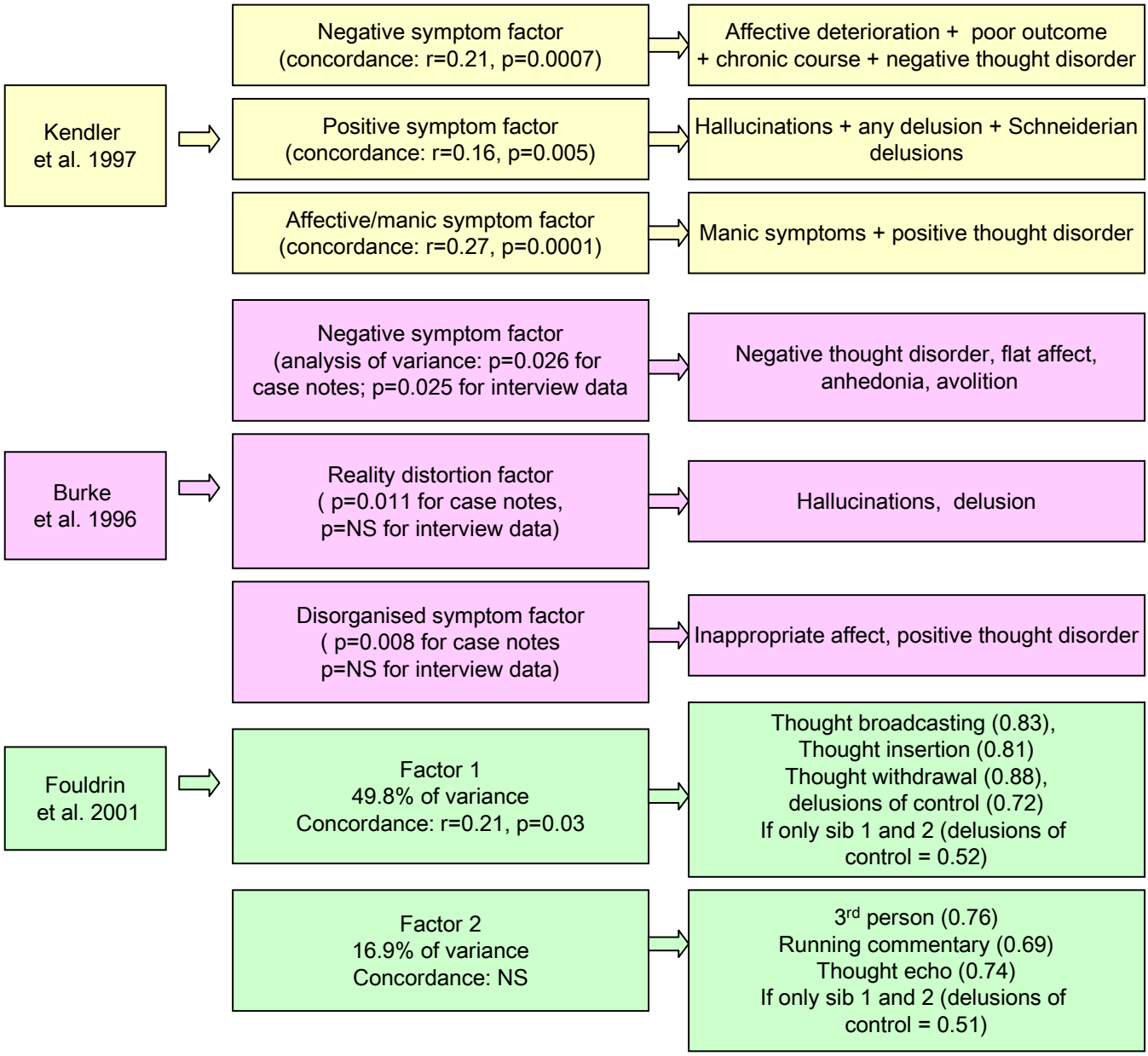
Ross et al. 2000	**Deficit vs Non deficit:** Chi-square (Wald) = 5.34, df=1, p=0.02; OR=3.35, 95%CI=1.2-9.34
Kendler et al. 1997	**Individual symptoms: Hallucinations** (r=0.05, p=0.16); **delusions** (r=0.16, p=0.02); **Schneiderian delusions** (r=0.16, p=0.02); **positive thought disorder** (r=0.23, p=0.002); **catatonic symptoms** (r=0.11, p=0.04); **affective deterioration** (r=0.13, p=0.02); **negative thought disorder** (r=0.15, p=0.02); **depressive symptoms** (r=0.28, p=0.002); **manic symptoms** (r=0.43, p=0.0001); **illness course** (r=0.15, p=0.02); **outcome** (r=0.25, p=0.003)
Burke et al. 1996	**Intra-pair correlation results: Negative symptom factor** (negative thought disorder, flat affect, anhedonia, avolition): Case notes: p<0.05, r=0.226 (0.228 with Corrections for unreliability) Interview data: p<0.01, r=0.258 (0.261); **Disorganised Symptom factor** (inappropriate affect, positive thought disorder): Case notes: p<0.01, r=0.299 (0.280) Interview data: p=NS, r=0.127 (0.154); **Reality distortion factor** (hallucinations, delusions): Case notes: p<0.001, r=0.335 (0.447) Interview data: p=NS, r=0.071(0.079); **Age of onset**: Case notes: p<0.01, r=0.259 Interview data: p<0.01, r=0.242; **Depressive symptoms**: Case notes: p=NS, r=0.127 Interview data: p=NS, r=0.095; **Manic symptoms**: Case notes: p<0.05, r=0.229 Interview data: p=NS, r=-0.014; **Outcome:** Interview data: p<0.05, r=0.177 **Interview data reflects data gathered during direct interview of subject* *** Case notes refer to data extracted from case notes*
Tsuang 1967	Results not applicable since wide diagnostic categories, but **catatonia** (p=0.025-0.0125) and **affective symptoms** (p=0.0125-0.005)(depression alone p=0.005-0.0025)
Fouldrin et al. 2001	**Deficit vs non-deficit**: Chi-square=6.4, p<0.02, one-tailed (non-Caucasian group = Chi-square=2.1, p=NS)
Leboyer et al. 1992	**DSM-R, DSM-II-R, ICD-10, Tsuang-Winokur subtypes**=NS (slight excess of classic paranoid/hebephrenic); **Age of onset** intrafamilial correlation: F=2.54, p=0.0007
Loftus et al. 2000	Post-hoc Chi-square results: **3rd person auditory hallucinations** p=0.05; **control** p=0.02; **broadcasting** p=0.04

Loftus et al. 1998	Krawiecka scale results: **Positive symptoms** (delusions + hallucinations) NS; **disorganised symptoms** (inappropriate affect + positive thought disorder) Chi-square =9.15, p<0.01, phi=0.28 and when weighted Chi-square=8.69, p=0.01, phi=0.31; **negative symptoms** (poverty of speech + flat affect) NS; **affective symptoms** (mood elation + depression) NS; 1st Rank symptom results: **audible thoughts** NS, **running commentary** NS, **passivity experiences** NS, **3rd person auditory hallucinations** NS, **thought withdrawal** NS, **thought insertion** NS, **thought broadcasting** NS, **delusional pre-occupation and made feelings** NS
Hwu et al. 1997	**Positive symptom group** (DHS)(hallucinations and delusions): Kappa=0.3, Random error=0.3 and Kappa=0.55, RE=0.56 when controlled for negative symptoms; **Negative symptom group** (NGS) (flat affect + alogia + asociality – used global score): Kappa=0.29, RE=0.35; If **severe negative symptoms only** (SNGS): Kappa=0.35, RE=0.43; **Thought disorder** (TDS): Kappa=0.21, RE=0.3 and Kappa=1.00, RE=1.00 (controlled for negative symptoms) DHS+NGS+TDS is not independent
DeLisi et al. 1987	Concordance analysis results: diagnosis (schiz/schiz vs schi-affect/schiz-affect) Chi-square=5.44 p=0.025; **Visual hallucinations** Chi-square=5.3, p<0.025 (p=0.15 after multiple test correction), **major depression** Chi-square=8.16, p<0.005; **auditory hallucinations** NS, **paranoid delusions** NS, **thought disorder** NS, **negative symptoms** NS; Type 1 and 2 NS, Predominantly positive vs negative symptoms NS; age of onset r=0.39, p<0.004
Cardno et al. 1998	Schizophrenia subtypes (paranoid/hebephrenic/undifferentiated and paranoid/ hebephrenic and paranoid-like/hebephrenic-like and type I/type II/mixed and **1st rank symptoms** present or absent) NS; SAPS/SANS scores (NS) for **Inappropriate affect, affective flattening, alogia, hallucinations, delusions, bizarre behaviour, positive formal thought disorder** NS; OPCRIT symptoms **catatonia, speech difficult to understand** (K=0.26, SE=0.1for schizophrenia group only), **positive and negative thought disorder, restricted/inappropriate affect, persecutory delusions, grandiosity** (K=0.21, SE=0.11 for schizophrenia group only), **delusions of influence** (K=0.23, SE=0.1 for schizophrenia group only), **passivity and nihilism**, **bizarre delusions, thought insertion and broadcast, 3rd person voices, commentary and abusive voices, other auditory hallucinations, any other hallucinations; affective symptoms** NS; **age of onset** (n=80, r=0.26, p=0.02); same-sex pairs NS; premorbid adjustment (K=0.23, SE 0.11); GAS (worst ever rating) (r=0.34, p=0.001)
Kendler & Adler 1984	**Paranoid versus non-paranoid** (n=12) according to ICD-9 (Z=1.73, p=0.04), DSM-III (Z=1.59, p=0.056), Tsuang-Winokur (Z=0.11, NS) significant for sib pairs but not sibships

APPENDIX 6. RESULTS FROM LATENT CLASS ANALYSIS



APPENDIX 7. FACTOR ANALYSIS RESULTS



CHAPTER 4

CAN STUDIES IN THE XHOSA POPULATION HELP TO LIMIT THE HETEROGENEITY OF SCHIZOPHRENIA? SUITABILITY AS A STUDY POPULATION

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1. THE XHOSA: A CONTEXTUAL HISTORY

The Xhosa is the southernmost indigenous African population belonging to the Nguni linguistic group and is the second largest African grouping within South Africa. It is estimated that the Nguni linguistic grouping (to which the Zulu also belongs) split linguistically 2000 years ago. The large Xhosa-speaking population of South Africa offers researchers a unique opportunity to study schizophrenia in a homogeneous population with an apparently common ancestry [1]. Since the first reported genealogical records (King Tshawe ruled the Xhosa in the sixteen hundreds), internal revolts have led to the political fragmentation of the Xhosa kingdom, although the cultural norms remained largely intact. In addition to internal revolts the Xhosa was also closely linked to the protracted frontier wars and has played a key role in shaping the political landscape of South Africa through decades of protest action and the successful transformation to political and social freedom in 1994 [1]. The socio-political situation in South Africa contributed to the relative geographic isolation in homelands within the Eastern Cape and townships in the major South African cities, thus ensuring a relatively homogenous cultural and genetic constitution.

2. THE XHOSA CULTURE AND SCHIZOPHRENIA

2.1. BACKGROUND

Early descriptions of the traditional Xhosa people revealed unique cultural norms with an emphasis on communal interests (“ Ubuntu”) rather than individual autonomy, and strong beliefs in supernatural powers [1-3]. Although the intricacies of culture fall outside the focus of this study, it would seem prudent that the reader have at least some insight into the influence of culture on the experience, interpretation of symptoms and subsequent health seeking pathways since these may have an influence on the conduct and outcome of studies within a culturally defined grouping such as the Xhosa. For a detailed analysis of the cultural influences on mental health, it is proposed that the reader study “ Culture and mental health: a Southern African view” by Leslie Swartz (1998) [3] and “ Frontiers” by Noël Mostert (1992) [1]. This discussion will focus on the influence of culture and belief systems on the perception regarding and treatment of schizophrenia within the Xhosa population.

2.2. BELIEFS AND ATTITUDES TO SCHIZOPHRENIA

The Xhosa population, as is the case with Caucasian populations, seems to have misconceptions regarding the causes and treatment of schizophrenia, as

is evident from studies conducted in lay communities and in Xhosa patients and their families [4-9].

In a parallel study in the Xhosa population, the author and his colleagues found that the misconceptions seem to differ among various cultural groupings. Studies in German lay people [10-12] found that they regard schizophrenia as being caused mainly by psychosocial stressors and biological and intra-psychic factors. This contrasts with the parallel study conducted by the author and his colleagues on 100 caregivers or close family members of Xhosa patients with schizophrenia [13].

The participants were interviewed by a trained psychiatric nurse who visited the family at home and administered a structured questionnaire (English version) that was based on the work of Angermeyer and Matshinger et al. (1993, 1996) [5;14;15]. It focused on the respondents' views on the causes, treatment options and course of schizophrenia. The responses to the 29 questions were recorded as yes, no or unsure. Two additional items in the treatment section (a. the use of traditional healers' services and b. traditional rituals) assessed the role of traditional healing methods.

The respondents (76% female; mean age 61.1 (±13.0); 6.0 (±3.5) years of schooling; 59.2% mothers and 21.4% fathers) ascribed the development of schizophrenia to various causes (Table 1).

TABLE 1. PERCEIVED CAUSES OF SCHIZOPHRENIA IN 100 CAREGIVERS OR CLOSE FAMILY MEMBERS OF XHOSA PATIENTS WITH SCHIZOPHRENIA

	Yes	No	Unsure
Family relationship problems	12*	46	42
Work difficulties	13	68	19
Stressful events	38	40	22
Brain disease	46	41	13
Heredity	34	50	16
Lack of will power	10	72	18
Expecting too much of oneself	14	82	4
Unconscious conflicts	3	84	3
Being brought up in broken home	25	59	16
Lack of parental affection	31	54	15
Over protective parents	19	75	6
Loss of traditional values	29	56	15
Loss of a natural way of life	3	84	13
Will of God	31	49	20

Witchcraft, evil spirits	67	18	15
Being poisoned	37	48	15
Signs of the Zodiac	2	52	46

*All values are percentages

Witchcraft or possession by evil spirits (67%), brain disease (46%) and a stressful life event (38%) were the most commonly reported causes. Unconscious conflict (3%), loss of natural ways of life (3%) and signs of the Zodiac (2%) were uncommon responses. Nevertheless, it is of interest that supposedly more " biomedical" or " Western" causes, such as stressful life-events (38%), broken homes (25%) and lack of parental affection (31%) were also endorsed. This suggests a complex explanatory model for schizophrenia in the Xhosa population (3-8).

The Xhosa layperson' s explanatory models of disease are intimately related to cultural beliefs such as an acceptance of the phenomena of witchcraft and possession by evil spirits, and the notion that ancestors play an important role in protecting the community [16-21]. It is therefore not surprising that the respondents emphasized the role of witchcraft and evil spirits as a cause for schizophrenia.

It is accepted within the cultural belief system that the ancestors require appeasement with rituals. According to Xhosa beliefs, neglecting such rituals may lead to withdrawal of ancestral protection and may even precipitate mental illness. –

It follows that the development of mental illness in this context is likely to be closely linked to "culture bound syndromes". This term refers to any one of a number of recurrent, locality-specific patterns of aberrant behaviour and experiences that appear to fall outside conventional Western psychiatric diagnostic categories [22]. Most of these patterns are indigenously considered to be "illnesses" , and most have local names [23;24]. However, the illnesses coined "amafufunyana" and "thwasa" are not (yet) included in the Diagnostic and statistical manual of mental disorders (4th edition) [25] as "culture bound syndromes"; but they are nonetheless considered to be cultural phenomena and found in the indigenous African Xhosa population [3;26;27].

"Thwasa", a condition characterized by social withdrawal, irritability and auditory hallucinations, is an important cultural phenomenon according to the Xhosa belief system [3;28]. Within the context of this specific culture, "thwasa" is seen as a calling to serve the ancestors as a traditional healer, suggesting that this is a special, but normal, event. However, according to

traditional healers, resisting this calling by the ancestors may lead to illness, whereas complying with this "divine calling" confers special powers.

The term "Amafufunyana", on the other hand, was originally described as "a hysterical condition characterized by people speaking in a strange muffled voice in a language that cannot be understood, and strange and unpredictable behaviour" [3;29]. Despite apparent overlap with schizophrenia [25], it was viewed as a condition without any equivalent in Western culture, and one that could not be fitted into Western classification systems [30;31].

Given that different explanatory models may have contrasting implications for health seeking behaviour, it might be helpful to understand when and why these models (i.e. "amafufunyana" and "thwasa") are applied. Cultural concepts, values and beliefs influence health-seeking pathways, and traditional healers play an important role in the management of disease in many cultures (e.g. the Xhosa) where " Western" medicine is either unavailable, viewed with scepticism or used in parallel with traditional treatment methods [32;33]. In many societies, it is common practice for patients and/or families to seek help from the traditional healer first, and then to turn to, or be referred to " Western" medicine if the traditional methods fail [32;34].

The frequency with which culture-specific models ("amafufunyana" and "thwasa") are used by traditional healers to explain schizophrenia in the Xhosa population had not been studied systematically prior to a parallel study by the author [35]. Two hundred and forty-seven subjects (62 female and 185 male) were allocated to one of 3 groups, viz. an "amafufunyana"-group, a "thwasa"-group, and a group with diagnoses other than "amafufunyana"/"thwasa" based on structured questions on the use of traditional treatment. The structured questions were based on the researchers' clinical experience and made use of available collateral information. The questions on the use of traditional diagnostic and treatment methods consisted of four open-ended questions (interviewer rated) focusing on the life-time use of services, the explanatory model or diagnosis given by the traditional healer, the suggested treatment (medication/other and dosage) and the period of compliance to this treatment.

Two hundred subjects (80.97%) had used traditional diagnostic and treatment services and were included in this analysis (i.e. the 47 patients who had not seen a traditional healer were excluded). Of these 200 participants, one hundred and six (53%) were diagnosed with "amafufunyana" (82 male and 24 female), and nine (4.5%) as having "thwasa" (4 male and 5 female). Two patients were diagnosed with both "amafufunyana" and "thwasa", and were therefore excluded from the study. Eighty-three subjects (63 male and 20

female) received other diagnoses (e.g., the patient had been poisoned, had made the ancestors angry, etc.).

The mean age at interview was 34.1 years (±8.0) for the "amafufunyana" group and 43.9 years (±6.8) for the "thwasa" group (p=0.001; t=-3.6). The age of onset was similar in both groups (21.9 years [±4.6] versus 22.9 years [±5.8]). Forty-nine percent of the "amafufunyana" and thirty-three percent of the "thwasa" group were living in urban areas. The majority of subjects in both groups were single at the time of interview (101/106 [95.3%] and 8/9 [88.9%] in the "amafufunyana" and "thwasa" groups, respectively). Forty-four percent of the "thwasa" group and fifty-eight percent of the "amafufunyana" group were unemployed.

Comparisons between the two groups based on the OPCRIT measurements indicated that a family history of schizophrenia (χ^2=8.059, p=0.004) or other psychiatric disorders (χ^2=9.899, p=0.008) was significantly more common in the "thwasa" group. Fifty-four (50.9%) subjects in the "amafufunyana" group had a positive family history of schizophrenia compared to nine (100%) in the "thwasa" group. Fifteen (14.2%) of the subjects in the "amafufunyana" group and five (55.6%) of those in the "thwasa" group had a family history of other psychiatric disorders (Table 2). No significant differences were detected for the core symptoms of schizophrenia.

TABLE 2. PHENOMENOLOGICAL CHARACTERISTICS OF THE "AMAFUFUNYANA" AND "THWASA" GROUPS

PHENOMENOLOGICAL CHARACTERISTICS	"AMAFUFUNYANA" GROUP (N=106)	"THWASA" GROUP (N=9)	GROUP DIFFERENCES (STATISTICAL SIGNIFICANCE)
Family history of schizophrenia	50.9*	100	χ^2=8.059 p=0.004
Family history of other psychiatric disorders	14.2	55.6	χ^2=9.899 p=0.008
Bizarre or aggressive behavior	82	88.9	NS
Positive formal thought disorder	37.7	55.6	NS
Negative formal thought disorder	77.4	88.8	NS
Affective changes:			
Restricted	47.2	77.8	NS
Blunting	65.1	55.6	NS
Inappropriate	16.9	44.4	NS
Delusions:			
Persecutory delusions	94.3	77.8	NS
Grandiose delusions	46.2	55.6	NS
Delusions of influence	63.2	44.4	NS
Bizarre delusions	37.7	33.3	NS
Hallucinations:			
Auditory (3rd person)	68.9	77.8	NS
Running commentary	59.4	55.6	NS
Hallucinations (any)	80.2	88.9	NS

NS NO SIGNIFICANT DIFFERENCE DETECTED

* **Values given as percentages**

The " amafufunyana" and " thwasa" groups were combined and then compared with those subjects who had received other diagnoses from the traditional healers (n=83). Significantly more individuals from the non-" amafufunyana/thwasa" group were married (p=0.007), from a rural environment (p=0.005), had a definite stressor prior to onset of illness (p=0.022) and had a history of cannabis abuse/ dependence with psychopathology (p=0.022) (Table 3).

TABLE 3. STRATIFICATION BASED ON THE PRESENCE OR ABSENCE OF AN "AMAFUFUNYANA/THWASA" DIAGNOSIS.

PHENOMENOLOGICAL CHARACTERISTICS*	"AMAFUFUNYANA / THWASA" PRESENT (N=115)	"AMAFUFUNYANA / THWASA" ABSENT (N= 83)	GROUP DIFFERENCES (SIGNIFICANCE)
Married	5.2*	18.1	p=0.004; χ^2=8.37
Urban environment	47.8	28.9	p=0.007; χ^2=7.31
History of a definite stressor	5.2	14.5	p=0.026; χ^2=4.93
History of Cannabis abuse/dependency	0.9	7.4	p=0.015; χ^2=5.92

* *values given as percentages*

*** Only significant differences shown*

Our findings indicated that, in this group of Xhosa patients with schizophrenia no symptoms significantly differentiated between the diagnoses “ amafufunyana” and “ thwasa” . On the other hand, in contrast to patients with "amafufunyana" or "thwasa", patients with neither of these diagnoses were more likely to live in an urban environment, to be married, and to have had identifiable stressors or substance abuse apparently predating psychotic symptoms.

In the Xhosa culture, persons with a history of schizophrenia may be diagnosed as "thwasa" or “ amafunyana” by the traditional healer. Our findings suggest that psychotic symptoms may in some instances be perceived as "good" and in other instances as an illness condition necessitating treatment. We found that subjects with a family history of schizophrenia or other psychiatric disorders were more likely to receive the diagnosis of "thwasa" than “ amafunyana” . This suggests that psychotic symptoms are more likely to be seen as "abilities" or "giftedness" passed on from one generation to the next in the case of "thwasa", but as illness in the sporadic ("amafufunyana") cases.

It is important to realize that "thwasa", although seen as a potentially positive event, may herald the onset of schizophrenia and that the family members of such an individual may be at greater risk for the development of psychiatric disorders. Furthermore, although "thwasa" is not considered an illness in the Xhosa culture, our data suggests that, in at least a subgroup of subjects, "thwasa" is indistinguishable from "amafufunyana" in terms of the core symptoms of schizophrenia.

Rural married subjects with identifiable stressors were less likely to be diagnosed as having “ amafufunyana” or “ thwasa” . One explanation for this finding is that the traditional explanatory models were more likely to have been applied in the less Westernized, rural patients than in urban subjects. Another possible explanation is that these terms were less likely to have been used in patients with higher levels of premorbid functioning (e.g. married subjects) and in those in whom other, more apparent explanations for their symptoms could be offered. Our study was not designed to address the question whether subjects with “ thwasa” and “ amafufunyana” do in fact have a less severe form of schizophrenia with a milder course and although corrections for multiple testing were not employed, the significant differences found are certainly consistent with our clinical experience.

The discipline of cross-cultural psychiatry emphasizes the importance of determining patients' explanatory models of their symptoms [36;37]. Although the application of standardized "Western" diagnostic criteria (DSM-IV or ICD-10) to illness/disease presentation in other cultures has brought about a degree of consistency in patient management, the danger exists that the application of these theoretical frameworks may hinder detection of unfamiliar categories and downplay socio-cultural influences on nosology [38]. Certainly, in Xhosa-speaking patients with schizophrenia, our data underline the value of ascertaining which cultural diagnosis has been given in terms of a higher risk for multiple affecteds within a " thwasa" family. However, in terms of the clinical phenotyping the core symptoms remain indistinguishable.

The use of cultural/traditional treatment methods requires our consideration for possible influences on the clinical phenotyping. From information gathered as part of the above-mentioned study Mbanga et al. (2000) [39] concluded that although psychotropic medication was the most commonly recommended form of treatment in the Xhosa population, the vast majority of respondents (care-givers and family members) supported the simultaneous use of traditional treatment methods. Respondents most commonly recommended treatment with psychotropic medications (88%), traditional healer's methods (32%) and rituals (30%). Psychotherapy (4%) and

meditation (1%) were the treatment methods least often recommended (Table 4).

TABLE 4. TREATMENT METHODS PREFERRED BY 100 CAREGIVERS AND FAMILY MEMBERS OF XHOSA PATIENTS WITH SCHIZOPHRENIA

	Yes	No	Unsure
Relaxation	25*	64	11
Pull oneself together	6	82	12
Talk it over	7	87	6
Nature will cure it	2	91	7
Meditation	1	55	44
Psychotherapy	4	56	40
Psychotropic medications	88	5	7
Traditional healer	32	58	10
Traditional rituals	30	61	9

** Values given as percentages*

Many felt that traditional healers' methods protected individuals from invasion by "bad spirits", but that Western treatments prevented the symptoms from worsening. In fact 92% of participants who favoured traditional health care, also endorsed the simultaneous use of " Western" medicine. Most family members (63%) became concerned when probands discontinued medication for a month, with some (32%) becoming worried after even a week of non-compliance. Non-compliance was only seen as a problem one month after

medication discontinuation. This may be explained partly by the fact that many probands in this study received depot preparations).

Results obtained during the above-mentioned study [40] revealed that 198 (84%) of 236 Xhosa schizophrenia sufferers (recruited throughout the Western, Southern and Eastern Cape; mean age 36,25 (SD±9,41; 75% males) admitted visiting a traditional healer during some stage of their illness and following the treatment prescribed by the healer. Treatments varied considerably and included: oral solutions (n=109), emetics (oral solutions or tablets) (n=89), washing (n=61), enemas (n=33), inhalation therapy (“ steam”) (n=24), snuff (n=23), cutting (n=14), wearing beads (n=7) and the slaughter of cattle (n=2). Contrary to expectation, ancestral appeasement methods e.g., slaughter of cattle and brewing traditional beer were not commonly prescribed treatment methods. The mean number of treatments per patient was 1.87 (SD±1,43). It is worth mentioning that 60% of the subjects who had used traditional treatment methods were urban residents. Gender and urbanicity did not have a statistically significant influence on the treatment method of choice.

Traditional healers clearly play an important role in the treatment of schizophrenia in this population. The traditional healer’ s involvement in the diagnoses and treatment of schizophrenia may imply a holistic view of the

causation of mental illness [41]. Alternatively, it may be seen as an indictment of " the reality of mental health care in a country with eleven official languages (in which the health care workers are) unable to communicate in a patient' s home language" . The use of traditional treatment methods is, however, not limited to this population. A recent study in KwaZulu/Natal of 300 physiotherapy patients showed that 70% preferred to consult a traditional healer as their first choice [42]. Further north on the African continent, a Nigerian study [32] found that the general population favoured the involvement of traditional healers in the treatment process, while the majority (69%) of Malaysian patients presenting for the first time at a psychiatric clinic admitted to having visited a traditional healer (" bomoh") prior to the clinic consultation [43].

The use of multiple models and interventions can arguably be seen as representing a flexible and pragmatic response to the occurrence of a serious medical disorder. Xhosa family members most commonly supported psychotropic medications and traditional healing methods (for example, rituals such as beer brewing and the slaughter of cattle), in contrast to the poor support for psychotropic medication in, for example, Germany [44-47].

Despite the encouraging support for psychotropic medication, our previous studies revealed several stigmas and misconceptions related to the course of

the illness [48;49]. Family members were of the opinion that probands were more dirty (52%), weak (48%), unpredictable (45%), dangerous (44%), delicate (41%) or foolish (39%) than the "average person". Furthermore, forty-one percent of respondents believed the natural course of schizophrenia to be one of remission with the possibility of relapse, while 24.2% believed that the disorder could be cured without medication. Twenty eight percent of respondents stated that if optimal treatment were to be given, cure could be possible, with 30.3% holding that optimal treatment led to remission with the possibility of relapse. Two possible interpretations could be postulated for these results, namely that a lack of knowledge of the course of schizophrenia exists or that the Xhosa may have a unique course of illness.

The results of these studies should be interpreted keeping a number of important limitations in mind. Family members were generally relatively old and poorly educated; generalization of results to younger, more educated respondents should therefore be made with caution. This is partly reflected in the number of "unsure" responses to concepts such a meditation, signs of the zodiac and even psychotherapy. Furthermore, the fact that interviewers were nurses may have biased respondents away from endorsing traditional beliefs and towards endorsing the importance of psychotropic medication. Nevertheless, our impression was that respondents were open and frank about their agreements and disagreements with the standard biomedical

model. These studies furthermore relied on recall of past events and as such are vulnerable to recall biases.

Nevertheless, taken together these data only partially support a biomedical explanatory model of schizophrenia as a disease of the brain in Xhosa patients and their caregivers, and that although some underlying familial pattern could be observed in the diagnostic preference of cultural diagnosis, the stigma associated with mental illness was still evident. Furthermore, the culture-bound syndrome "amafufunyana" and the culture-specific phenomenon of “ thwasa” were both used to explain symptoms in patients with schizophrenia (DSM IV). "Thwasa" and "Amafufunyana" as explanations for schizophrenia may distinguish between familial and sporadic cases. Whether the positive connotations associated with “ thwasa” , as opposed to the more negative connotations associated with “ amafufunyana” hold any implications for treatment or prognosis, as well as the possibility of a population specific course of illness, remains to be clarified.

3. RESEARCH ETHICS AND THE XHOSA POPULATION

Like ourselves, other researchers in the field of genetics have shown a growing interest in samples from homogeneous populations [50-52]. Such biogenetic research is fraught with sensitive ethical issues. The ethics of

genetic and other biomedical research is usually guided by the Nüremberg paradigm [53;54]. The status and integrity of ethical research guidelines based on the Nüremberg (1947) and Helsinki (1964) Codes, and later revisions thereof, are well established. However, strict adherence to the Nüremberg paradigm may at times be inappropriate [55]. For example, where the research population is non-Western and does not have a strong Judeo-Christian orientation, the effect of the guidelines may be in direct conflict with the values of the relevant culture. A case in point is the current emphasis on the right of autonomy of the individual in modern Western culture. This Western individualism may not find favour in those cultures and subcultures that value communal interests rather than individual interests and as such conflict with the needs of the Xhosa population.

Other problems associated with adhering to the Nüremberg paradigm whilst doing psychiatric research in general [56;57], and psychiatric genetic linkage studies in particular [58], have been highlighted. For example, the difficulty involved in obtaining informed consent from people who have a diagnosis of schizophrenia is well-known to researchers in psychiatry [59;60]. For consent to be legally and ethically acceptable, individuals must understand the true meaning of what is communicated to them. This implies that the method of communication, and the content of the message, must be appropriate to the participants' culture, language, cognitive abilities, academic qualification and

so forth. In a study involving a large number of persons with schizophrenia as well as their family members, it is perhaps inevitable that when contacted, some probands are likely to be experiencing an episode of active illness. Some patients may not be competent to provide informed consent by virtue of the fact that they are psychotic at the time of evaluation. In others, their clinical condition may have deteriorated to such an extent that they are no longer capable of understanding the information, or deciding rationally.

In genetic research, further ethical problems are frequently encountered. For instance, intrusion into research subjects' personal lives is often unavoidable, and interviewers may reveal information of which the subjects may prefer to have remained ignorant. There is at least a theoretical risk that significant distress may precipitate relapse.

Preparing research protocols for use in different cultures is likewise problematic. First, the concept of culture is fundamental to the understanding of mental illness. While there is reason to believe that universal biophysical conditions exist, culture shapes the final presentation of these disorders [61]. The meanings people give to their symptoms are a product of their interactions with other members of their culture, their beliefs, their customs and the symbols of their culture [62]. Second, in genetic research projects, information about biological family members of probands is essential.

Knoppers (1993) [63] points out that genetic research requires reconstruction of biological pedigrees, during which process " family secrets" may be revealed.

Finally, in some cultural settings individual autonomy is subsumed by collective or substituted decision making. Therefore, while the prevailing current thinking in Western cultures emphasises the right of the individual to make decisions, some non-Western cultures believe that the clan, or head of the clan, should give such consent. The principle of cultural relativism suggests that researchers should consider the cultural beliefs of subjects and adjust procedures accordingly. However, the use of cultural relativism to obviate the need to obtain informed consent from subjects has been criticized [64;65]. These critics point out that cultures are in a dynamic process of change and that many assumptions about specific cultures are based on dated anthropological data. Another problem in respect of cultural relativism is the fact that people within a specific culture may be at different levels of acculturation. Today it is therefore not possible to generalise within a culture. In fact, as Bodibe (1993) [66] demonstrates, specific individuals within a culture may have reached different stages of acculturation in respect of various aspects of their of functioning. Bodibe (1993) [66] describes how he, an urbanised person with postgraduate qualifications in psychology who had adopted Christian practices, paradoxically felt the need to engage in

traditional practices when his paternal grandfather died: paradoxically, because the premises of these traditional practices go against Christian and rational Western thinking. Therefore, while there is a need to be cautious about blind adherence to the principle of cultural relativism, researchers dare not ignore cultural diversity.

4. THE XHOSA SCHIZOPHRENIC: APPROPRIATENESS FOR RESEARCH ON CLINICAL PHENOTYPING

Taken together, the available data suggest that (1.) the Xhosa population seems to be a culturally homogenous group, given the historical and geographic influences that formed this group, (2.) the traditional belief systems are still active but do not seem to critically influence the presentation of the core symptoms of schizophrenia, (3.) the traditional belief systems do however raise questions to the possibility of a population specific course of schizophrenia both in terms of the " culturally sanctioned" " thwasa" and the perception of family members on the course of schizophrenia, (4.) finally, if the possible ethical issues are carefully considered the Xhosa population should provide an appropriate basis for a phenotypical subtyping study of schizophrenia.

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CHAPTER 5

CAN STUDIES IN XHOSA SIB PAIRS HELP TO LIMIT THE HETEROGENEITY OF SCHIZOPHRENIA? LESSONS LEARNT FROM COMORBIDITY WITH OBSESSIVE-COMPULSIVE DISORDER AND SUICIDE ATTEMPTS.

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1. BACKGROUND

Schizophrenia is a heterogeneous disorder, which is diverse in its phenotypic manifestations. Since the development of the first operational criteria (first rank symptoms) for the diagnosis of schizophrenia, several revised criteria have been proposed, the DSM-IV (APA) and ICD-10 being two of the most extensively employed [1]. The use of operational diagnostic criteria has not adequately addressed the heterogeneity of schizophrenia, judging from the nine-fold increase in diagnosis when the most liberal of these criteria are used as opposed to the most conservative [2].

In a classic example of the influence of phenotyping on genetics, Cardno et al. (2002) [3] studied 224 twin pairs from the Maudsley Twin Register for lifetime ever first rank symptoms, using the OPCRIT system. They found a concordance rate of 26.5% for monozygotic twins and 0-4.3% for same-sex dizygotic twins, giving a heritability estimate of 71% (95% CI, 57-82%). This was lower than estimates arrived at when the following diagnostic criteria were used: RDC (82% CI, 71-90%), DSM-III-R (84% CI, 19-92%) and ICD-10 (83% CI, 7-91%). Even though heritability estimates vary depending on the diagnostic criteria used, calculating concordance rates in mono- and dizygotic twins offers some degree of consistency in research protocols and has thus been used in the search for genetic liability factors.

2. COMORBID OCD AND SUICIDAL BEHAVIOUR IN SCHIZOPHRENIA

Two specific comorbid clinical entities, namely OCD and suicide attempts, allow us to investigate clinical heterogeneity in terms of criteria that rely on memory recall, observed behaviour and collateral information. Furthermore, OCD is of interest as a prototype for genetic subtypes since OCD and schizophrenia share a possible common etiological factor in chromosome 22q11-13. This interesting chromosomal area is known for micro-deletions that are associated with an increased risk for schizophrenia and OCD [4]. In a sib pair study this would be a valuable departure point for future chromosomal analysis in this population. Suicidal behaviour has a genetic component, but, in contrast to conceptions regarding OCD, several researchers believe that the environmental loading is significantly higher than that for OCD [5;6].

The neurobiology of diagnostic overlap may offer new insights into the pathophysiological process underlying these disorders, and have implications for the treatment and functional outcomes of these patients [7;8].

3. COMORBID OCD IN SCHIZOPHRENIA

The reported prevalence of OCD in patients with schizophrenia varies between 7.8% and 31.7% [8;9]. Eisen et al. (1997) [10] reported that when obsessions were defined as "persistent unwanted ideas not related to delusions", 7.8% of personally interviewed patients with schizophrenia or schizoaffective disorder (n=77) (SCID DSM-III-R) met the criteria for OCD. Using DSM-IV criteria, Bermanzohn et al. (2000) [11] found that 29.7% of consecutively admitted chronic schizophrenia patients met criteria for OCD. Community surveys such as the ECA study (n = 20 861) have yielded an OCD co-occurrence rate of 23.7%, but the measurement instrument used (DIS) did not contain diagnostic hierarchy rules [12]. In a study that did include diagnostic hierarchy rules (SCID - DSM-IV), 14% of 50 first episode schizophrenia, schizophreniform or schizoaffective patients met criteria for OCD [13]. Comparisons between studies and estimates of prevalence rates have been complicated by differences in study design (chart review versus direct interview, patient versus community samples, schizophrenia versus schizophrenia spectrum subjects, lay versus clinician assessments, cross-sectional versus longitudinal design) and differences in the ways in which OCD was diagnosed (symptoms as opposed to disorder). Nevertheless, calculated co-morbidity rates support the conclusion of many studies that comorbidity of OCD with schizophrenia is more than an incidental finding [14-16] and raises the question of whether shared susceptibility factors, such as

dopamine dysregulation, characterize patients with comorbid OCD and schizophrenia.

Studies to date have focused primarily on Caucasian patients. Both schizophrenia and OCD are disorders with significant commonality across different cultures and ethnicities [17;18]. Nevertheless, there is some evidence of variation in the phenomenology of schizophrenia across ethnic groups [19], and it has also been suggested that OCD may be less common in certain communities [20;21]. To date, however, there has been little rigorous study of comorbid OCD in non-Caucasian patients with schizophrenia.

4. SCHIZOPHRENIA AND COMORBID SUICIDAL BEHAVIOUR

Suicidal behaviour is a large contributor to the mortality and morbidity of schizophrenia. Although this phenomenon has an impact throughout the lifespan, it is especially significant in the first 10 years of illness [22]. Previous studies suggest that 18-55% of patients with schizophrenia attempt suicide, with 10%-13% succeeding, often after multiple attempts [23;24]. Indeed, the risk seems to be particularly high where a history of a previous suicide attempt exists, as well as in the period immediately after an acute psychotic episode and in the first 6 months after hospitalization [22;25].

Other reported risk factors for suicide include male gender, substance use/abuse, longer duration of untreated psychosis, the presence of mood, negative or psychotic symptoms and loss of social support systems [23;26;27]. The general population trend towards an excess of male suicide completers is less pronounced in schizophrenia, but is still present [28]. However, no gender bias is present in the rates of attempts [23].

Various studies have examined the influences of substance abuse, mood, positive symptoms and negative symptoms on suicide risk. The findings regarding substance abuse and negative symptoms are inconclusive [29-31], but depressed mood and major depressive episode probably increase suicide risk in an already vulnerable individual [32].

Positive symptoms on the other hand do exert a causative effect on suicidal behaviour [33;34], the majority (78%) of suicide completers experiencing psychotic symptoms at the time of suicide [35;36]. Reports indicate that 4% of patients with schizophrenia who engage in suicidal behaviour do so in response to command hallucinations, while 10% do so because of the distress caused by positive symptoms [37;38]. Research thus suggests a stress-diathesis model, whereby, when faced with environmental stressors, already vulnerable individuals engage in suicidal behaviour [39].

Several authors suggest that heritability of suicidal behaviour in schizophrenia is low; non-shared environmental factors may contribute to suicidal behaviour to a greater degree than shared familial (including genetic) factors [6]. The investigation of schizophrenia sib pairs may prove useful in efforts to distinguish between shared and non-shared risk factors for suicidal behaviour. It is notable that previous studies dealing with concordance of clinical symptoms or demographic variables in schizophrenia sib pairs did not specifically report on suicidal behaviour (see chapter 3).

Therefore, the data collected and published parallel to this study not only afforded us an opportunity to further investigate the universality of demographic risk factors for suicidal behaviour as well as the role of affected sibship status, but also a chance to broaden our knowledge base with regards to this indigenous African population.

5. OCD AND SUICIDE ATTEMPTS IN A XHOSA POPULATION

The author previously investigated suicidal behaviour and OCD in an earlier cohort of 454 participants included in the current study (Niehaus et al. in press). This study is briefly described here, in order to highlight the possible

role that these factors might play in the search for shared familial factors. Two hundred and eight individuals (165 males and 43 females) constituting 100 sib ships (95 pairs, 2 trios, 3 fours) were evaluated. The pairs consisted of 65 same-sex (61 male-male and 4 female-female) and 30 opposite sex pairs. The two trios comprised male participants only, while the fours had a mixed gender make-up (4 males; 3 males and one female; 3 males and one female).

In order to examine predictors of suicidal behaviour, logistic regression was performed. The following explanatory variables were employed in the model: socio-economic status, gender, religion, education, occupation, marital status, living arrangements, number of children, age of onset and duration of illness, number of suicide attempts and lethality of the most serious attempt. Taking into account that some of these subjects were from the same sibship, Generalized Estimating Equations were used to deal with the correlated nature of the data. The sibship responses were assumed to be equally correlated, implying an exchangeable correlation structure.

First, a univariate model was fitted and the parameter estimates presented for each explanatory variable. All explanatory variables with a $p<0.25$ were considered for the multiple model. A sequence of models was fitted resulting in a multiple model with the estimates indicating the independent contribution

of the specific explanatory variable to the model. All estimates, which were significant at the 5% level, were retained in the model.

The sibship group did not differ significantly from the total group in terms of the demographic variables listed in Appendix 1A. Ninety (19.8%; 21 female and 69 male) participants from the total group reported one or more suicide attempt (mean = 1.3; SD=0.8). Thirty (14.6%; 21 male and 9 female) individuals from the one hundred sibships reported one or more suicide attempt. This was significantly fewer individuals than from the non-sib pair group (z=-2.41; p=0.016). Four of the sib pairs (none of the trios or fours) were concordant for suicide attempts (mean number of attempts 1.25 [SD 0.5; Range 1-3]). No concordance for suicide method was noted.

Of the demographic variables tested, only marital status and age of onset of illness predicted suicide attempts in a univariate model (Appendix 1 A&B). Separation, divorce or no previous marriage increased the risk for suicide attempts significantly (z=-2.11; p=0.0345), with earlier age of onset (before 26 years of age) showing a similar association (z=-2.65; p=0.008). Religious affiliation, schooling, occupational status, living arrangements and parenthood did not predict suicide attempts (Appendix 1A&B).

The univariate model (Table 1) indicated that marital status, age of onset and sib pair status may contribute to an increased risk for suicide attempts.

TABLE 1 A AND B. NUMBER OF SUICIDE ATTEMPTS AND LETHALITY OF MOST SERIOUS ATTEMPT

A. NUMBER OF SUICIDE ATTEMPTS					
			Number of Attempts		
Variable		N	0	1	More than 1
Part of Sib pair	No	248	188 (76%)	50 (68%)	10 (4.0%)
	Yes	206	176 (85%)	24 (12%)	6 (2.9%)

B. LETHALITY OF MOST SERIOUS SUICIDE ATTEMPT								
			Lethality					
		N	No attempt	No danger	Minimal danger	Average Danger	Average to serious	Very serious
Part of sib pair	No	240	188 (78%)	9 (4%)	12 (5%)	6 (3%)	13 (5%)	12 (5%)
	Yes	201	176 (88%)	6 (3%)	3 (1%)	4 (2%)	6 (3%)	6 (3%)

The multiple model (Table 2) excluded marital status as an independent risk factor. However, age of onset (< 26 years) (Odds ratio 2.5) and not being part of a sib ship (Odds ratio 1.7) significantly increased the risk for suicide attempts in this group of schizophrenic subjects. Furthermore, the non-sibship group reported about one and three quarters as many suicide attempts as the sibship group (z=2.3, p=0.02, 95%CI: 1.1 to 2.8). The data

indicated that " the most serious suicide attempt" reported in the non-sibship group was more lethal than that ~~of~~ found in the sibship group (z=2.5, p=0.01, OR=1.9; 95% CI: 1.2 to 3.2) (Table 1 A and B). In addition to the environmentally based statistical model, the presence of comorbid mood, anxiety and substance abuse or dependency symptoms were considered but showed no significant association with suicide attempts.

TABLE 2. PREDICTORS OF SUICIDE ATTEMPTS IN XHOSA PATIENTS WITH SCHIZOPHRENIA: A MULTIPLE MODEL

Variable	Parameter estimate	SE	Z	P	Odds ratio	95% CI
Age of onset < 26 years	0.915	0.364	2.51	0.012	2.5	1.2 to 5.1
Not part of sib ship	0.538	0.260	2.07	0.038	1.7	1.0 to 2.9

In this study, the prevalence of comorbid OCD in schizophrenia was very low in the Xhosa ethnic group (0.002%), with no concordance noted. However, prevalence rates have tended to vary widely depending on patient and disease characteristics. A recent study in hospitalized patients with chronic

schizophrenia found a 23.5% prevalence of OCD, while a 3.8% prevalence of OCD was documented in patients with first-admission psychosis [40]. Tibbo et al, (2000) [41] reported a 25% rate of OCD in a community sample of patients with schizophrenia. However, despite the low rate, the four patients meeting criteria for OCD in our study displayed similar symptom patterns (as described in the case studies) to those reported in previous studies [42]. The low rate of comorbid OCD (1.2%) was partly supported by a study in two groups of South African male patients of mixed ethnic origin [43]. The first group of participants (n=24) had first-episode psychosis (schizophrenia, schizo-affective disorder or schizophreniform disorder) and the second group (n=63) schizophrenia with at least one previous admission for a psychotic episode. Only one patient (diagnosis of schizophrenia; male; treatment-naive) in the first-episode (5%) and none in the multiple episode group fulfilled criteria for OCD.

Only one participant was diagnosed with obsessive compulsive disorder. This patient, who was in the non-sibship group, fulfilled the criteria for OCD in the relevant section of the DIGS. He was a thirty-two year old, unmarried Xhosa male, with seven years of schooling, and was receiving a disability grant. The patient had previously been treated for pulmonary tuberculosis (no temporal relationship to onset of symptoms). Positive symptoms of psychosis had been present since the age of 19, but there was uncertainty regarding

prodromal symptoms. The patient had experienced two prior episodes of psychosis (in 1985 and 1996/1997), with inter-episodic residual symptoms. Psychotic symptoms included auditory (more than two voices), tactile and gustatory hallucinations. Delusions were paranoid and somatic in theme and included delusions of control (mind reading, thought broadcasting, thought insertion and thought withdrawal). At interview, disorganized behaviour, echolalia, avolition, alogia and blunted affect were present. He reported two previous suicide attempts occurring at the age of 16 years (non-psychosis linked) and 22 years (related to command hallucinations). He had received treatment with trifluoperazine (15mg/day) and orphenadrine (100mg/day) for 6 years.

Apart from the psychotic symptoms, the patient also reported overwhelming intrusive thoughts about the cleanliness of his face. These intrusive thoughts had been present since his psychotic symptoms first appeared. During psychotic episodes he experienced tactile facial sensations described as "itchiness", which he tried to relieve by repeated cleansing with various traditional medications, soaps and even abrasive material. The latter had caused substantial scarring of his face. Other compulsive behaviours included washing of clothes, bathing rituals, ordering, checking of doors and windows, compulsions related to symmetry, and pathological doubt. These

concerns consumed more than one hour per day. No other anxiety disorder was present.

6. CONCLUSION

The novel findings of a very low prevalence of obsessive-compulsive disorder and the protective nature of affected sibships on suicide attempts makes it possible that this population may yield unique susceptibility factors and clinical phenotypes,

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APPENDIX 1 A. PREDICTORS OF SUICIDE ATTEMPTS IN XHOSA SCHIZOPHRENICS

Suicide Attempt	No	Yes	Parameter estimate	SE	Z	P
Total sample (N=460*)	364 (80.2%)	90 (19.8%)				
Gender			0.014	0.28	0.05	0.962
Male	349	69 (19.8%)				
Female	105	21 (20.0%)				
Religion			-0.558	0.540	-1.03	0.304
None	17	5 (29.4%)				
Any	433	85 (19.6%)				
Schooling (in years) 0-8	276	59 (21.4%)	-0.223	0.256	-0.87	0.385
More than 8	162	29 (17.9%)				
Occupation			-0.229	0.309	-0.74	0.459
Disability support	350	71 (20.3%)				
Any other	91	15 (16.5%)				
Marital status			0.974	0.461	2.11	**0.0345****
Widow/married	55	5 (9.1%)				

Sep/div/never married	391	84 (21.5%)				
Part of sibpair			-0.613	0.254	-2.41	**0.016****
No	248	60 (24.2%)				
Yes	206	30 (14.6%)				
Living arrangement			-0.272	0.292	-0.93	0.352
With parents						
Other	344	73 (21.2%)				
	100	17 (17.0%)				
Age of onset***			-0.936	0.354	-2.65	**0.008****
11-25	321	77 (24.0%)				
26-53	105	12 (11.4%)				
Children			-0.107	0.319	-0.33	0.738
None	92	20 (21.7%)				
Any number	151	31 (20.5%)				
Duration of illness			0.070	0.239	0.09	0.769
< 13 years						
>= 13 years	216	44 (20.4%)				
	209	45 (21.5%)				

** Insufficient data in six patients (excluded for this analysis)*

***parameter values are significant at the 5% level*

Appendix 1 B. *** Subjects with previous suicide attempts and the age of onset of schizophrenia

Age of onset ****	Total number of subjects in age group	Subjects with previous suicide attempt
11-15	20	6 (30.0%)
16-20	145	31 (21.4%)
21-25	156	40 (25.6%)
26-30	64	7 (10.9%)
31-53	41	5 (12.2%)

***** Subjects excluded if age of onset unsure*

CHAPTER 6

METHODOLOGY

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6.1 METHODOLOGY OVERVIEW

The following diagrammatic overview of the study is given here to serve as an outline of the research methods used.

Recruitment

513 Xhosa patients with schizophrenia were recruited as part of a large multi-site genetic study. This sample was then divided into 104 affected sibling pairs (n=214 participants) and 299 patients with schizophrenia without an affected sib

Phenotyping

Statistical analysis (A)

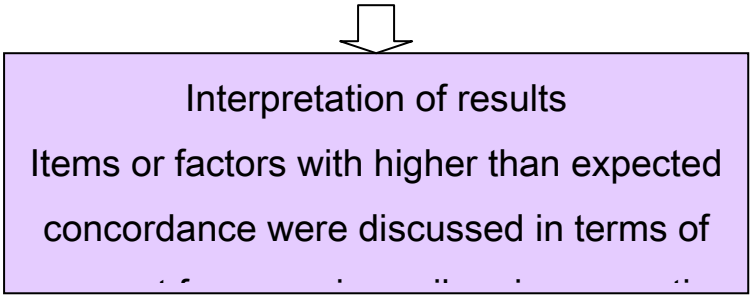
Descriptive statistics: demographic and clinical data of sibling pairs

Statistical analysis (B)

Factor analysis of SANS/SAPS items in the non-sib pair group and then in the sib pair group so that any factor unique to the sib pair group could then be analyzed for concordance within the sib pair group

Statistical analysis (C)

Failing the identification of any unique factor, concordance analysis of the individual items from the SANS/SAPS was done. Items with higher than expected concordance were further analyzed in terms of the influence of confounding variables, including gender.


Interpretation of results
Items or factors with higher than expected
concordance were discussed in terms of

6.2 STUDY SUBJECTS

Subjects were recruited from in- and outpatient hospital services and community clinics throughout the Western, Southern and Eastern Cape Provinces of South Africa as part of a large multi-site genetic study.

Potential participants had to be of Xhosa ethnicity (all of the grandparents of Xhosa origin), have one living parent and suffer from schizophrenia (Table 1: Inclusion/Exclusion Criteria).

TABLE 1. INCLUSION/EXCLUSION CRITERIA

Inclusion criteria

A. *Diagnosis of schizophrenia (DSM-IV Criteria)*

B. *In the case of affected sib pairs, participation of both siblings was required.*

C. *Xhosa ethnic origin (4/4 grandparents reported as of Xhosa origin)*

D. *Inclusion depended on written approval for participation from the patients or their legal caregivers.*

E. *Various stages of illness allowed*

Exclusion criteria

A. *Patients with known organic aetiology were excluded.*

B. *Patients were excluded if they had prominent mood symptoms that could obscure the distinction between schizophrenia, schizo-affective disorder and bipolar mood disorder.-*

Mental health workers were asked to identify all possible participants, who were then screened for suitability and diagnosed according to DSM IV criteria [1]. Patients and their parents were included in the study after providing written, informed consent. The father and/or mother and/or unaffected sib of the proband were contracted to the study in order to provide phenotypical and genealogical information.

6.3 ASSESSMENT

6.3.1 PRIMARY ASSESSMENT MEASURE

The Diagnostic Interview for Genetic Studies (DIGS), version 2.0 [2] was the primary diagnostic tool and provided the basis for statistical analysis of clinical

measurements. The DIGS is a clinical assessment tool designed for diagnosing major mood and psychotic spectrum disorders and includes the Schedule for the Assessment of Negative Symptoms (SANS) and the Schedule for the Assessment of Positive Symptoms (SAPS), validated assessment scales for positive and negative symptom complexes [3;4] (Appendix 1). The interviewers also used hospital chart records (where available) and information gathered from family members, to supplement these interviews. Relevant demographic data, medical history, treatment history and pedigree information were collected from the proband and family.

A trained psychiatrist and/or Xhosa psychiatric nurse with extensive clinical experience interviewed each participant, using an English (oral translation to Xhosa) version of the standardized instrument (DIGS). Where necessary, the help of an interpreter was utilized. In order to maintain optimal rating consistency over the two-year period of recruitment, all subjects were assessed by both raters simultaneously during the first year of the study, followed by regular calibration meetings during year two.

6.4 DATA ANALYSIS

The goal of this study was to improve our understanding of the shared familial factors (genetic and non-genetic) implicated in schizophrenia. As early as

1984, Risch and Baron suggested a polygenic (possibly even oligogenic) or mixed model for the development of schizophrenia [5]. The estimated components of variance for both of these models suggested that genes contributed more than 80%, while common sib environment (6.9% and 6.6% respectively) and random environment (11.2% and 11% respectively) accounted for only a small percentage of the variance [5-7].

Given that sibling pairs share approximately half their genes, the use of affected sibling pairs enriches the genetic risk factors within the sample and findings will thus be less likely to reflect random environmental contributions. This study therefore allowed for the possibility of identifying " more strongly familial" subtypes based on exploratory factor structure and concordance analysis. This study focuses only on the role of studies of sib pairs in the establishment of clinical subtypes of schizophrenia. However, a non-sib pair group of patients with schizophrenia (n=299) was used to establish a baseline against which to measure the findings from the factor analysis of the SANS and SAPS. Differences between the sib pair and non-sib pair groups in terms of certain factors would be of interest since these factors may suggest a shared familial underpinning (shared genes or shared sib environment). Any factors that occur only in the sib pair group would then have to be evaluated in terms of their concordance within the sib pair group and, if concordance between siblings is established, the possible genetic or shared sib

environmental factors that may account for this. Since this study forms part of a larger effort to identify the genetic causes of schizophrenia, such distinctive factors would serve as a benchmark against which candidate genes could be tested.

6.4.1 VARIABLES

6.4.1.1 DEPENDENT VARIABLES

The initial primary dependent variables of interest were the clinical ratings of schizophrenic symptoms, assessed by the individual and global items of the SAPS and SANS, in both the sib pair (n=214) and non-sib pair group (n=299).

6.4.1.2 INDEPENDENT VARIABLES

The independent variables of interest were the various demographic (see 6.4.2.1) and clinical (see 6.4.2.2) variables assessed by the DIGS. The non-sib pair group' s clinical data obtained from the DIGS forms part of another study.

6.4.1.3 POTENTIAL CONFOUNDING FACTORS

Potential confounding factors (age of onset, duration of illness, age at interview and gender) were identified prior to the analyses and were taken

into account during the factor analysis and concordance analysis of the gender groups.

6.4.2 DESCRIPTIVE ANALYSIS

6.4.2.1 DEMOGRAPHIC DATA

Descriptive statistics were computed for the following demographic variables in the sib pair group: gender, geographic distribution, mean age at interview, level of education, religious affiliation, marital status and current employment.

6.4.2.2 CLINICAL DATA

Clinical variables such as medical and developmental difficulties, age of onset, presence of prodromal symptoms, number of psychotic episodes, number of hospitalizations, presence of residual symptoms, and the full DSM-IV criteria for schizophrenia were assessed. Comorbid diagnoses were assessed in terms of lifetime prevalence. The presence of any significant mood or anxiety symptoms (i.e., fulfilling DSM-VI symptom descriptions) was noted and patients were classified as either category 1. absence of any symptom, or category 2. presence of any symptom. Unsure responses or lack of collateral information were weighed up clinically by the investigators for classification into either category 1 or 2.

6.4.3 EXPLORATORY FACTOR ANALYSIS FOR POSITIVE AND NEGATIVE SYMPTOMS

The study design allowed for an exploratory factor analysis of global and individual scores on the SANS and SAPS rating scales. Only two sibs per sibship were used (n=208). In sibships with more than one sib pair, only one pair was extracted (1st and 2nd to be evaluated). This method was chosen, because it was considered the best way to ensure geographic proximity of study subjects during assessment and increase our chances of identifying shared familial factors.

Principal component analysis was done (on the sib pair and non-sib pair group separately) on the nine global ratings and then on the individual items of the SANS and SAPS. Alogia and concentration were excluded from the analysis based on previous published methodology and results [8;9]. Age of onset and duration of illness were taken into account as potential confounding factors for the principal component analysis. The factor solution was then rotated using the varimax procedure.

6.4.4 CONCORDANCE ANALYSIS

The sib pairs were used for further concordance analysis of sib pair specific factors identified in the factor structure solution. The SANS and SAPS items (see Appendix 1) were dichotomised as follows:

A rating of 0 or 1 was rated as absence of symptom

Ratings of 2 or greater were rated as presence of symptom

For these categorical variables, the observed distributions were compared to those expected under the null hypothesis (random distribution into three categories) using the chi-square test (one degree of freedom) [10] in the sib pair group.

6.4.5 ANALYSIS OF CONFOUNDING VARIABLES

Items that remained concordant after adjustment for the prevalence of individual symptoms were then assessed for the confounding influence of age at interview, years of schooling, age of onset, duration of illness, number of episodes, presence of any substance abuse or dependency, presence of significant mood symptoms, significant anxiety symptoms and a stressor prior to onset of illness.

The sample was subdivided into male-male male-female subgroups in order to control for the possible confounding effect of gender.

The sib pair sample (male-male and male-female group separately) was then subdivided into groups concordant and disconcordant for presence and absence of the specific confounding variables. Expected and observed concordance for each of the SANS/SAPS items were determined and compared (Chi-square method). Concordant items that were not influenced by these variables were then considered candidates that could be used for subtyping schizophrenia, based on shared familial factors.

6.5 ETHICAL CONSIDERATIONS

The study formed part of a large multi-national effort to identify the genetic risk factors involved in schizophrenia and complied with the stringent ethical norms laid down by the Ethical Committee of the University of Stellenbosch (Project number: 97/005; Appendix 2).

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The study procedures and aims were explained in lay terms to patients and their caregivers or legal guardians. Informed consent was accepted to be in order only if patients could understand and communicate this understanding to the researchers. Legal guardians/caretakers were also asked to give consent if doubt existed as to any patient' s competence in this regard.

Participation was voluntary and a request for withdrawal was immediately effective upon receipt of such request. The conclusions of the study are available to all participating individuals, should they require them. Participating individuals did not incur any costs.

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APPENDIX 1. SANS AND SAPS SCALES

See SANS coding definitions (N. Anderson, 1984).

Interviewer: Ratings are to be based on the last 30 days

Affective Flattening or Blunting	NONE →					SEVERE	
1. Unchanging Facial Expression The patient's face appears wooden-changes less than expected as emotional content of discourse changes	0	1	2	3	4	5	U
2. Decreased Spontaneous Movements The patient shows few or no spontaneous movements, does not shift position, move extremities, etc	0	1	2	3	4	5	U
3. Paucity of Expressive Gestures The patient does not use hand gestures or body position as an aid in expressing his ideas.	0	1	2	3	4	5	U
4. Poor Eye Contact The patient avoids eye contact or stares through interviewer even when speaking.	0	1	2	3	4	5	U
5. Affective Nonresponsivity The patient fails to laugh or smile when prompted.	0	1	2	3	4	5	U
6. Inappropriate Affect The patient's affect is inappropriate or incongruous, not simply flat or blunted.	0	1	2	3	4	5	U
7. Lack of vocal Inflections The patient fails to show normal vocal emphasis patterns, is often monotonous	0	1	2	3	4	5	U
8. Global rating of Affective Flattening This rating should focus on overall severity of symptoms, especially unresponsiveness. Inappropriateness and an overall decrease in emotional intensity.	0	1	2	3	4	5	U

ALOGIA

9. Poverty of Speech The patient's replies to questions are restricted in amount, tend to be brief, concrete, unelaborated.	0	1	2	3	4	5	U
10. Poverty of Content of Speech The patient's replies are adequate in amount but tend to be vague, over concrete or over generalized, and convey little in information.	0	1	2	3	4	5	U

SANS CODES		
0 - None/Not at all	3 - Moderate	U - Unknown/
1 - Questionable	4 - Marked	Cannot Be Assessed/
2 - Mild	5 - Severe	Not Assessed

	NONE						SEVERE
11. Blocking The patient indicates, either spontaneously or with prompting, that his train of thought was interrupted.	0	1	2	3	4	5	U
12. Increased Latency of Response The patient takes a long time to reply to questions, prompting indicates the patient is aware of the question.	0	1	2	3	4	5	U
13. Global Rating of Alogia The core features of alogia are poverty of speech and poverty of content.	0	1	2	3	4	5	U

AVOLITION / APATHY

14. Grooming and Hygiene The patient's clothes may be sloppy or soiled, and he	0	1	2	3	4	5	U

may have greasy hair, body odor, etc.

15. Inpersistance at Work or School 0 1 2 3 4 5 U
    The patient has difficulty seeking or maintaining employment, completing school work, keeping house, etc. If an inpatient cannot persist at ward activities, such as OT, playing cards, etc.
16. Physical Anergia 0 1 2 3 4 5 U
    The patient tends to be physically inert. He may sit for hours and not initiates spontaneous activity.
17. Global Rating of Avolition/ Apathy 0 1 2 3 4 5 U
    Strong weight may be given to one or two prominent symptoms if particularly striking

ANNEDONIA / ASOCIALITY

18. Recreational Interests and Activities 0 1 2 3 4 5 U
    The patient may have few or no interest. Both the quality and quantity of interests should be taken into account.

SANS CODES		
0 - None/Not at all	3 - Moderate	U - Unknown/
1 - Questionable	4 - Marked	Cannot Be Assessed/
2 - Mild	5 - Severe	Not Assessed

NONE SEVERE

19. Sexual Activity 0 1 2 3 4 5 U
    The patient may show decrease in sexual interest and activity, or no enjoyment when active.
20. Ability to Feel Intimacy and Closeness 0 1 2 3 4 5 U

The patient may display and inability to form close or intimate relationships, especially with opposite sex and family.

21. Relationship with friends and Peers 0 1 2 3 4 5 U
    The patient may have few or no friends and may prefer to spend all his time isolated.
22. Global Rating of Anhedonia / Asociality 0 1 2 3 4 5 U
    The rating should reflect overall severity, taking into account the patient's age, family status, etc.

ATTENTION

23. Social Inattentiveness 0 1 2 3 4 5 U
    The patient appears uninvolved or unengaged. He may seem "spacey".
24. Inattentiveness During Mental Status Testing 0 1 2 3 4 5 U
    Refer to tests of "Serial 7" at least five subtractions and spelling "world" backwards
25. Global Rating of Attention 0 1 2 3 4 5 U
    This rating should assess the patient's overall concentration, both clinically and on tests.

SANS CODES		
0 - None/Not at all	3 - Moderate	U - Unknown/
1 - Questionable	4 - Marked	Cannot Be Assessed/
2 - Mild	5 - Severe	Not Assessed

See SAPS Manual for detailed coding definitions (N. Andresson, 1984).

NONE SEVERE

HALLUCINATIONS

1. Auditory Hallucinations 0 1 2 3 4 5

The patient reports voices, noises, or other sounds that no one else hears

2. Voices Commenting 0 1 2 3 4 5
   The patient reports voices which makes a running commentary on his behavior or thoughts
3. Voices Conversing 0 1 2 3 4 5
   The patient reports hearing two or more voices conversing.
4. Somatic or Tactile Hallucinations 0 1 2 3 4 5
   The patient reports experiencing peculiar physical sensations in the body.
5. Olfactory Hallucinations 0 1 2 3 4 5
   The patient reports experiencing unusual smells which no one else notices.
6. Visual Hallucinations 0 1 2 3 4 5
   The patient sees shapes or people that are not actually present.
7. Global Rating of Hallucinations 0 1 2 3 4 5
   This rating should be based on the duration and severity of the hallucinations and their effects on the patient's life.

DELUSIONS

8. Persecutory Delusions 0 1 2 3 4 5
   The patient believes he is being conspired against or persecuted in some way.
9. Delusions of Jealousy 0 1 2 3 4 5
   The patient believes his spouse is having and affair with someone.
10. Delusions of Guilt or Sin 0 1 2 3 4 5
    The patient believes that he has committed some terrible sin or done something unforgivable.

11. Grandiose Delusions 0 1 2 3 4 5

The patient believes he has special powers or abilities.

SAPS CODES	
0 - None/Not at all	3 - Moderate
1 - Questionable	4 - Marked
2 – Mild	5 - Severe

	NONE					SEVERE	
12. Religious Delusions This patient is preoccupied with false beliefs of a religious nature.	0	1	2	3	4	5	U
13. Somatic Delusions The patient believes that somehow his body is diseased, abnormal, or changed.	0	1	2	3	4	5	U
14. Delusions of References The patient believes that insignificant remarks or events refer to him or have special meaning.	0	1	2	3	4	5	U
15. Delusions of being controlled The patient feels that his feeling or actions are controlled by some outside force.	0	1	2	3	4	5	U
16. Delusions of Mind Reading The patient feels that people can read his mind or know his thoughts.	0	1	2	3	4	5	U
17. Thought Broadcasting The patient believes that his thoughts are broadcast so that he himself or other can hear them.	0	1	2	3	4	5	U
18. Thought Insertion The patient believes that thoughts that are not his own have been inserted into his mind.	0	1	2	3	4	5	U

19. Thought Withdrawal 0 1 2 3 4 5 U

The patient believes that thoughts have been taken away from his mind.

20. Global Rating of Delusions 0 1 2 3 4 5 U

This rating should be based on the duration and persistence of the delusions and their effect on the patient's life.

BIZARRE BEHAVIOR

21. Clothing and Appearance 0 1 2 3 4 5 U

The patient dresses in an unusual manner or does other strange things to alter his appearance.

22. Social and Sexual Behavior 0 1 2 3 4 5 U

The patient may do things considered inappropriate according to usual social norms (e.g., masturbating in public.

SAPS CODES		
0 - None/Not at all	3 - Moderate	U - Unknown/
1 - Questionable	4 - Marked	Cannot Be Assessed/
2 - Mild	5 – Severe	Not Assessed

NONE SEVERE

23. Aggressive and Agitated Behavior 0 1 2 3 4 5 U

The patient may behave in an aggressive, agitated manner, often unpredictable.

24. Repetitive or Stereotyped Behavior 0 1 2 3 4 5 U

The patient develops a set of repetitive actions or rituals that he must perform over and over.

25. Global Rating of Bizarre Behavior This rating should reflect the type of behavior and the extent to which it deviates from social norms.	0	1	2	3	4	5	U

POSITIVE FORMAL THOUGHT DISORDER

26. Derailment A pattern of speech in which ideas slip off track onto ideas obliquely related or unrelated.	0	1	2	3	4	5	U
27. Tangentiality The patient reply's to a question in an oblique or irrelevant manner.	0	1	2	3	4	5	U
28. Incoherence A pattern of speech that is essentially incomprehensible at times.	0	1	2	3	4	5	U
29. Illogically A pattern of speech in which conclusions are reached that do not follow logically.	0	1	2	3	4	5	U
30. Circumstantiality A pattern of speech that is very indirect and delayed in reaching its goals.	0	1	2	3	4	5	U
31. Pressure of Speech The patient's speech is rapid and difficult to interrupt, the amount of speech produced is greater than that considered normal.	0	1	2	3	4	5	U
32. Distractible Speech The patient is distracted by nearby stimuli, which interrupt his flow of speech.	0	1	2	3	4	5	U
33. Changing A pattern of speech in which sounds rather than meaningful relationships govern word choice.	0	1	2	3	4	5	U
34. Global Rating of Positive Formal Thought Disorder	0	1	2	3	4	5	U

The frequency of this rating should reflect the frequency of abnormality and degrees to which it affects the patient's ability to commicate.

SAPS CODES		
0 - None/Not at all	3 - Moderate	U - Unknown/ Cannot Be
1 - Questionable	4 - Marked	Assessed/ Not Assessed
2 – Mild	5 - Severe	

CHAPTER 7

RESULTS

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1. DEMOGRAPHIC CHARACTERISTICS OF THE SUBJECTS

Five hundred and thirteen Xhosa individuals with schizophrenia participated in the global study and were stratified into two samples: a sib pair group and a non-sib pair group (comparator group). Two hundred and fourteen participants (41 [19.2%] female and 173 [80.8%] male) formed part of the sibling pair sample, and were included in the further analysis of the role of sibling pairs in identifying shared familial factors. Twenty two percent of the siblings were recruited from the Greater Cape Town area and 14.4% from Port Elizabeth and East London, while the majority of patients were from rural Western, Southern and Eastern Cape areas.

The majority of the siblings were single (78%), only 13.6% being married at the time of the interview. Three percent were separated or divorced and another three percent widowed. Sixty-nine of the participants had children (range of 1-8 children; mean 1.46; SD 1.78). Most patients stayed with their parent(s) (74.8%) or other relatives (5.6%). Only 1% was in residential care and 3.3% were staying alone. More than 90% of the participants were affiliated to a religious movement or church. Seventy eight percent of the participants received disability grants and eleven percent were unemployed,

but not receiving disability allowances. The remainder were either gainfully employed (5.8%) or students (1.4%). Participants completed an average of 6.8 (SD 3.02) years of schooling. Approximately six percent of the participants had attained a level of education of grade twelve or higher (0.5% had some kind of tertiary education) and a similar percentage had never attended school.

The age at interview (n=205; see footnote[2]) ranged from 17 to 70 years of age (mean 37.8 years SD 9.32; not significantly different from the non-sib pair group). At the time of interview participants had been ill for a mean period of 14.5 years (SD 8.71; range 6 months to 45 years; age at onset 23.2 [SD5.4]).

2. CLINICAL FEATURES OF SIBLING PAIRS

All clinical features reported in this chapter relate to lifetime symptoms and not merely to symptoms elicited at the time of interview, except for those rated in the SANS and SAPS which is linked to the previous 30 days and symptoms elicited at the time of the interview.

2.1 PSYCHOSIS

[2] Number of patients that was able to provide information. Age of onset shown in Table 9.

In 17.7% of cases no history could be elicited regarding the prodromal period. Almost a quarter of the group had a sudden onset (less than 1 week before onset of overt psychosis), while 6% had a gradual onset lasting more than 6 months. Eight percent of cases reported a stressful life-event as the precipitating factor. These events included marital or relational conflict (n=4), significant losses (death, financial) (n=6), pregnancy (n=6), stress associated with studies (n=3), cannabis use (n=1) and court cases, riots and assault (n=2).

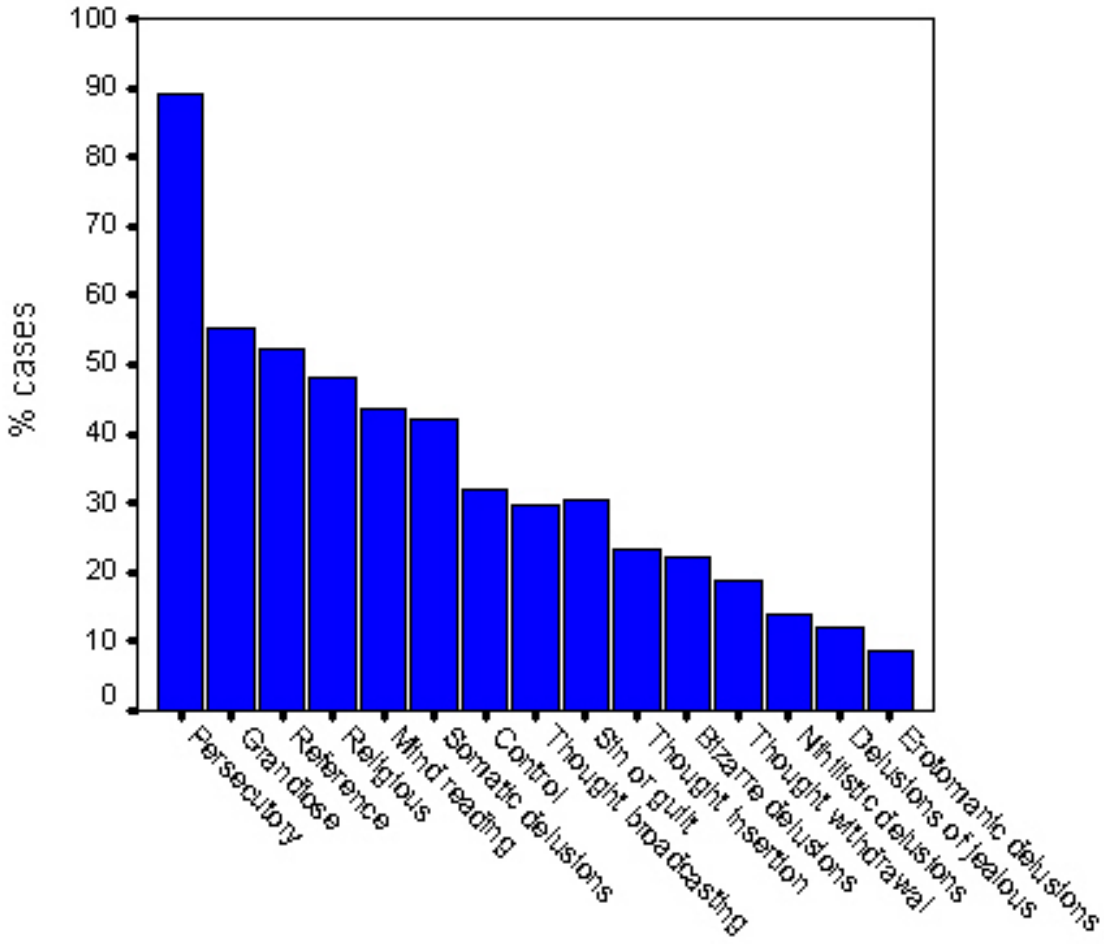
Most patients reported 1 or 2 episodes of psychosis (mean 2.5; SD 1.63; range 0 to 12) and the number of hospitalizations ranged from none (9.4% of the sample) to fourteen times (0.5% of the sample; mean 2.6; SD 2.34; n=177).

The lifetime duration of florid psychosis (sum of episodes of psychosis) varied considerably (range 2 weeks to more than 500 weeks; mean duration 28.5 (SD 66.8) weeks). Twenty five percent of the subjects were floridly psychotic at the time of the interview. Very few participants (3%) denied residual symptoms. Establishing the exact duration residual symptoms was difficult within this patient group and only 57 individuals were able to give reliable information (mean = 231.7 (SD 225.8) weeks; range 2 weeks to 700 weeks).

2.1.1 DELUSIONS

Eighty eight percent of subjects had experienced paranoid delusions during their lifetime, while grandiose (55%), religious (46.7%) and reference content (51.1%) was also found in a substantial proportion of the sibs. The least common delusions involved erotomanic (8.3%) and nihilistic delusions (13.3%) and jealousy (11.7%) delusions (Figure 1).

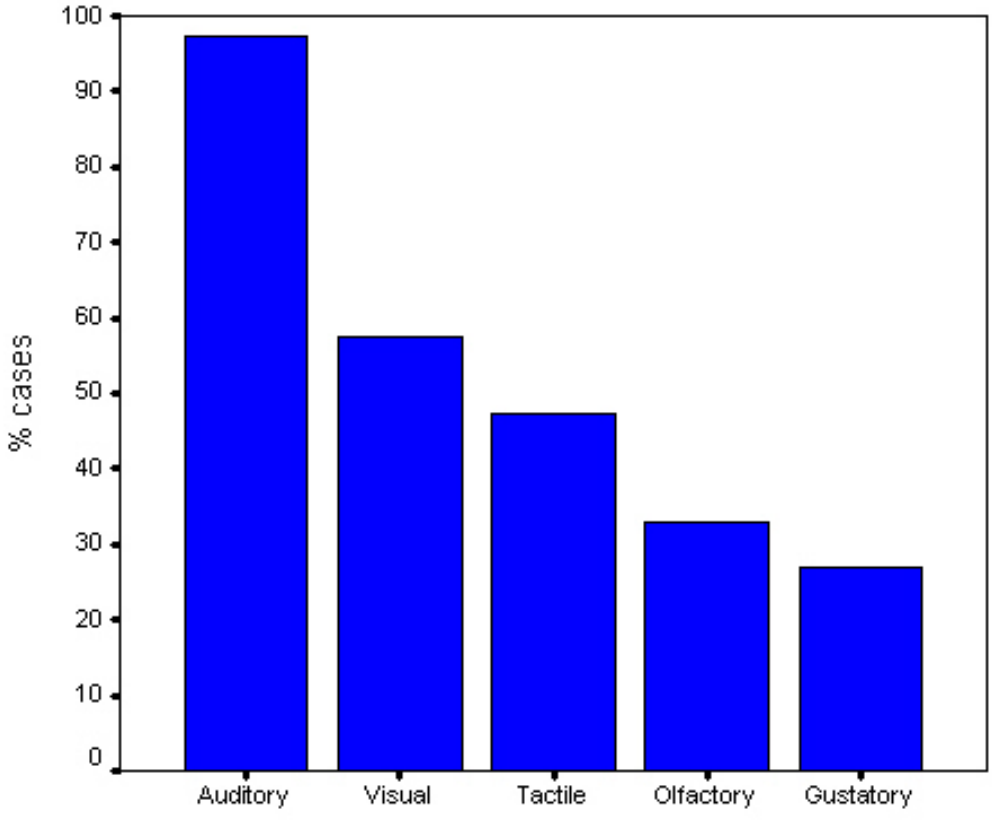
FIGURE 1. PERCENTAGE OF INDIVIDUAL CASES FROM THE SIB PAIR GROUP WITH A LIFE-TIME HISTORY OF SPECIFIC DELUSIONS



2.1.2 Hallucinations

Auditory hallucinations had been experienced by 97.2% of the sibs. The commonest types were those that were of a commentary nature (56.1%) and conversing voices (56.1%). Patients reported hearing noises in 21.1% of cases and command hallucinations in 19.4% of cases. A substantial proportion (46.7%) of the participants complained that the voices had a threatening nature. Visual hallucinations had occurred in the majority of patients (56.7%). Tactile hallucinations were also surprisingly common (45.6%) (Figure 2).

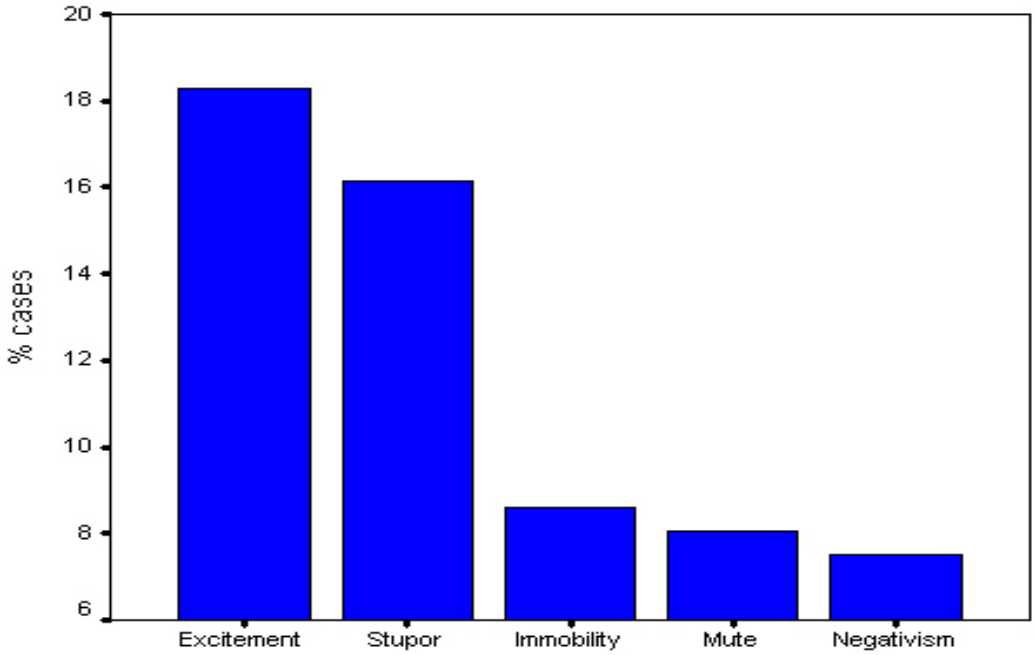
FIGURE 2. PERCENTAGE OF INDIVIDUAL CASES FROM THE SIB PAIR GROUP WITH A LIFE-TIME HISTORY OF SPECIFIC HALLUCINATIONS



2.2 Behavioral features

The vast majority of participants (96.7%) reported some behavioral abnormalities, of which aggression (verbal and physical) was the most common complaint (78.3%). Bizarre behaviour, including hoarding (n=21) and arson (n=27), had occurred in half of the patients, while catatonic symptoms were reported in a third of the sample. Stupor and excitement had occurred in 15.6% and 17.8% of patients, respectively (Figure 3).

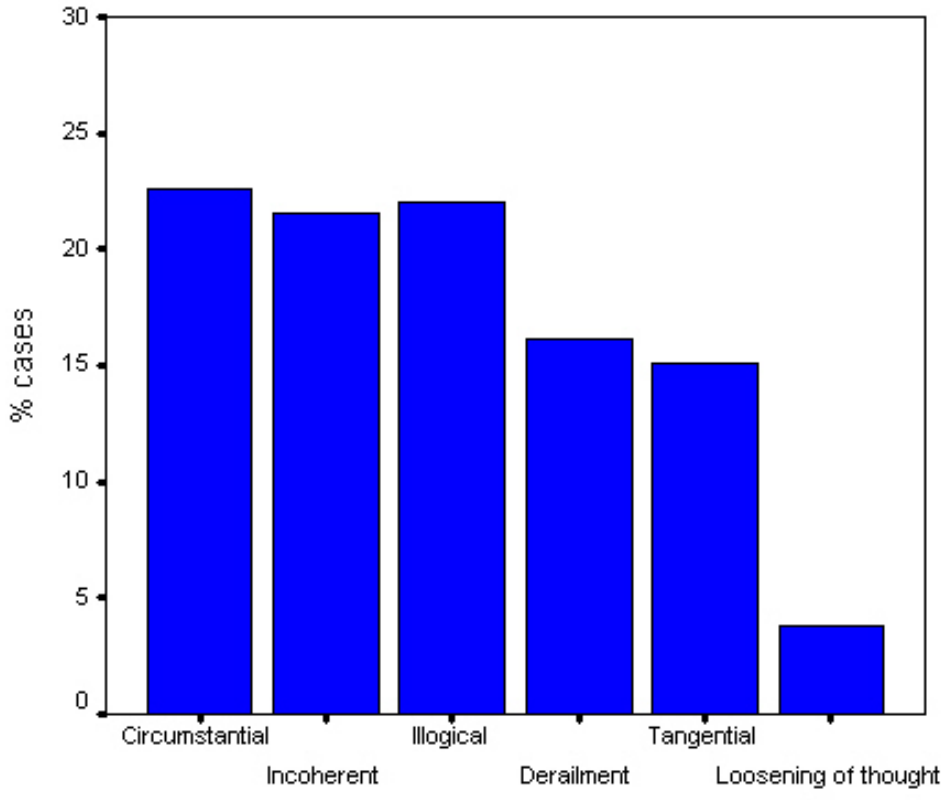
Figure 3. Percentage individual cases from the sib pair group with a life-time history of specific catatonic symptoms



2.3 THOUGHT DISORDER

Thought disorder occurred in 57.2% of the sample, while another 13.5% had a history suggestive of thought disorder (Figure 4).

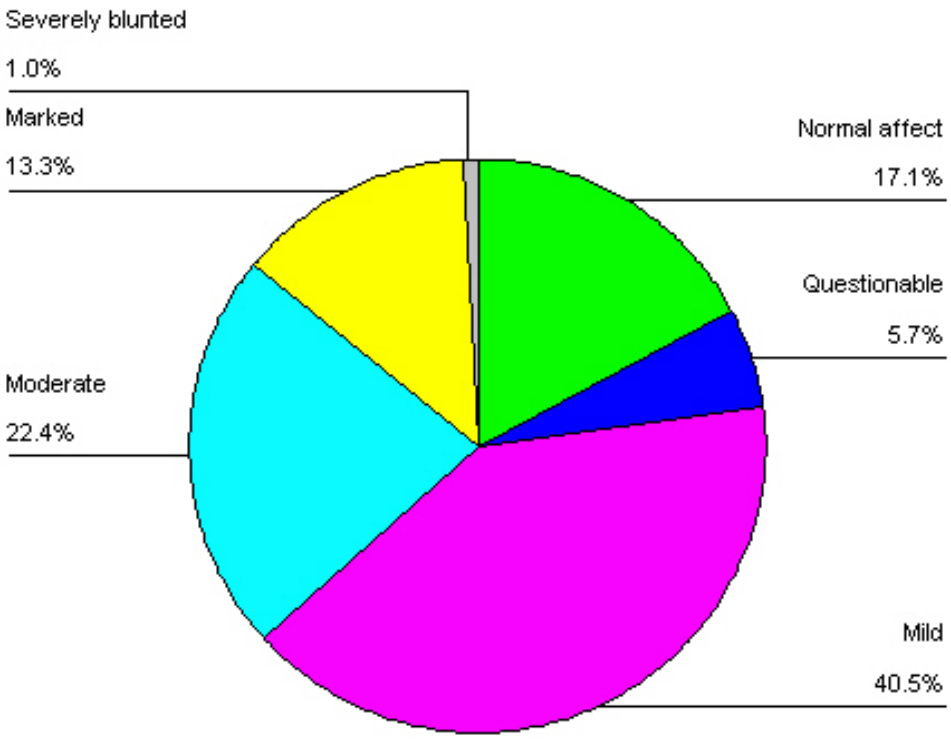
FIGURE 4. PERCENTAGE OF INDIVIDUAL CASES FROM THE SIB PAIR GROUP WITH A LIFE-TIME HISTORY OF SPECIFIC THOUGHT DISORDER SYMPTOMS



2.4 Affective changes

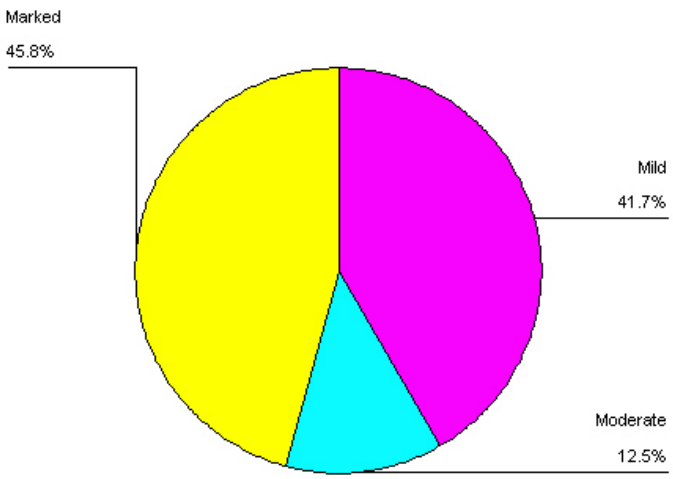
Varying degrees of affective flattening was reported in 78.4% of this group (Figure 5).

FIGURE 5. PERCENTAGE OF CASES FROM THE SIB PAIR GROUP WITH SPECIFIC AFFECTIVE FLATTENING SCORES ON THE SANS



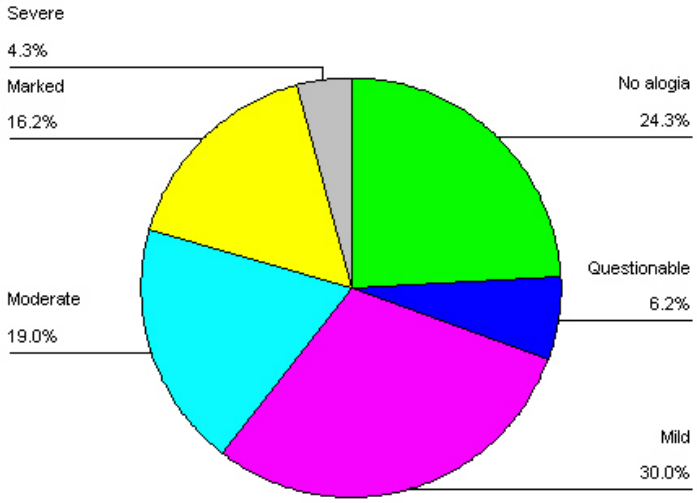
Inappropriate affect was confirmed from collateral information and seen by the interviewer in 21.6% of the sample. In an additional 4.4% of cases affect was possibly inappropriate. The majority were mildly to markedly affected (Figure 6).

FIGURE 6. PERCENTAGE OF CASES FROM THE SIB PAIR GROUP WITH SPECIFIC INAPPROPRIATE AFFECT SCORES ON THE SANS



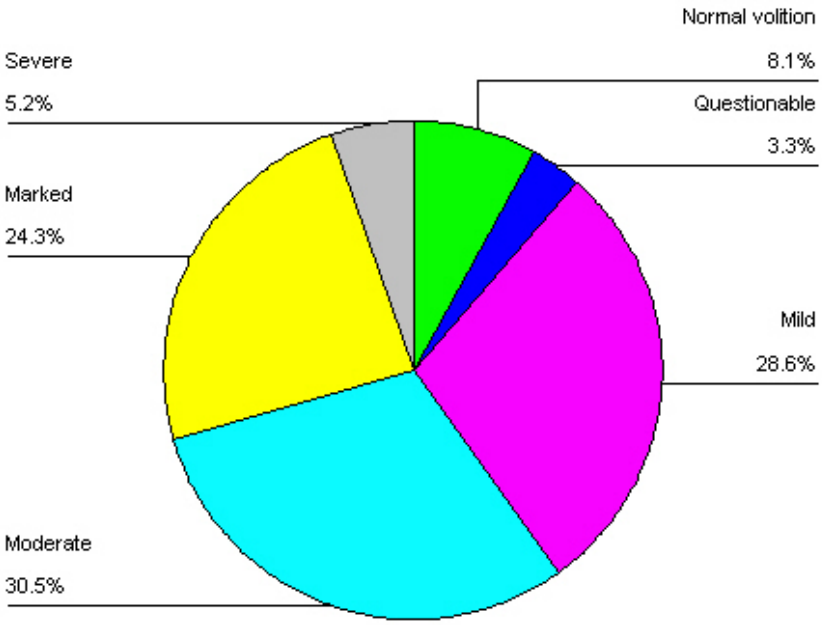
Alogia was noted in 72.6% and was almost evenly spread across the mild to markedly affected spectrum (Figure 7).

FIGURE 7. PERCENTAGE OF CASES FROM THE SIB PAIR GROUP WITH SPECIFIC GLOBAL ALOGIA SCORES ON THE SANS



Avolition and anhedonia were found in approximately 80% of the participants (Figure 8).

FIGURE 8. PERCENTAGE OF CASES FROM THE SIB PAIR GROUP WITH SPECIFIC GLOBAL AVOLITION/APATHY SCORES ON THE SANS



Concentration difficulties were reported in 25% of the sample.

2.5 SUBTYPES

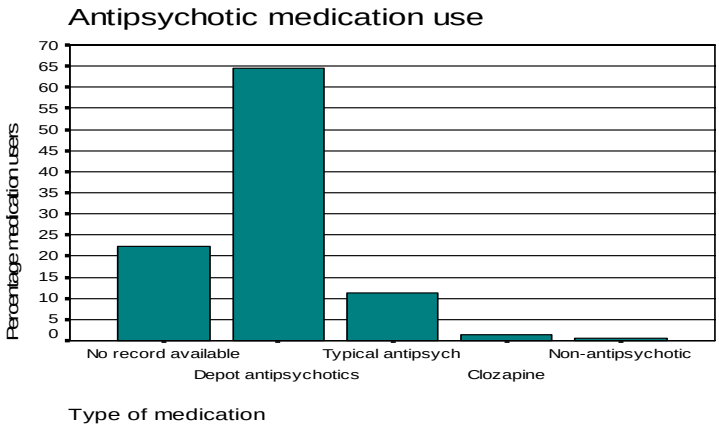
The clinical impression of the interviewers was that the undifferentiated subtype (DSM-IV) occurred most commonly (49%). Eight subjects fulfilled the criteria for the catatonic subtype and 22.5% for the disorganized subtype.

After compilation of all data sources two individuals had a history suggestive of schizo-affective disorder.

2.6 TREATMENT

The participants used a wide range of medications. Only a small minority (4.3%) denied taking their prescribed or suggested medication. In 10% of subjects, reliable information regarding medication use could not be obtained, because neither the patients nor the records could provide us with this information. Figure 9 shows the types of medication used at the time of interview. Depot antipsychotics were still by far the most common treatment chosen by medical practitioners. Surprisingly, fewer than 5% of patients used clozapine.

FIGURE 9. BAR CHART SHOWING THE PERCENTAGE OF CASES FROM THE SIB PAIR GROUP USING VARIOUS MEDICATIONS



** Note that 54 of these patients used a combination of depot and oral antipsychotics.*

The depot antipsychotics were commonly used in combination with oral antipsychotic medication. Four cases received clozapine in combination with depot antipsychotics.

Slightly more than 20% of the participants used anticholinergic medication. Mood stabilizers were given to eight patients and antidepressants to three.

2.7 COMORBID CONDITIONS

2.7.1 MEDICAL CONDITIONS AND EARLY DEVELOPMENTAL INCIDENTS

Twenty percent of the participants reported significant medical illnesses. A history of respiratory illness (14 pulmonary tuberculosis and 4 for other respiratory illnesses) was the most commonly reported medical illness. The others included convulsions (n=9), gastro-intestinal complaints (n=8),

hypertension (n=6), orthopaedic problems (n=3), head injuries (not related to the onset of schizophrenia) (n=2), ear nose and throat conditions (n=1) and arthritis (n=1).

Early developmental incidents occurred in five percent of the participants (n=8). Of these, five cases of antenatal and intra-partum complications (including pre-eclampsia, forceps delivery and prematurity) were reported. One patient was born with dysmorphic feet. One patient was described as mildly mentally retarded, three had slow milestones and one had experienced significant difficulties at school.

2.7.2 SUBSTANCE ABUSE AND DEPENDENCY

Twenty seven percent of participants had a history of possible substance abuse or dependency (cannabis and/or alcohol). Alcohol abuse was present in 3.4% of the participants and it was suspected – but not confirmed by collateral information - in anther 3.4%. Only 2% of the sample admitted to symptoms consistent with a diagnosis of alcohol dependence and another 0.5% were suspected of being dependent on alcohol during their lifetime.

Cannabis abuse was more prevalent, with confirmed abuse diagnosed in 2.9% of cases and almost 9% giving a history suggestive of current or past

cannabis abuse. Only 3.4% admitted to cannabis dependence while the history provided by another 0.5% suggested cannabis dependence.

Most (69.2%) participants had a history of tobacco smoking.

2.7.3 COMORBID MOOD AND ANXIETY DISORDERS

Almost five percent of the siblings were diagnosed with mood disorders (adjustment disorder with a depressed mood, dysthymia, major depression, hypomania or mania) while in another 11.1% mood disorders was suspected.

Almost four percent of the participants had symptoms of anxiety disorders (panic disorder, phobias), while another 7.2% of this group gave a history of suspected anxiety disorders. No OCD cases were identified in the sib pair group. The prevalence of OCD in the sample (combined sib and non-sib groups) was 0.2%.

3. COMPARATOR GROUP

3.1 SIMILARITIES BETWEEN THE SIB PAIR AND NON SIB PAIR GROUPS

In order to establish a baseline and to identify possible confounding factors in a later analysis, the sib pair and non-sib pair samples were compared in terms of demographic features (Appendix 1) and the global items of the SAPS and SANS (factor analysis). The non-sib pair group was similar to the sib pair group in that there was a predominance of male participants (non-sib pair group = 75.6% males) and subjects were mostly unmarried (82.9%), living with relatives (66.8%) and receiving disability allowances (72.9%).

Seasonality of birth: Neither the sib pair group nor the non-sib pair group demonstrated increased birth rates during the southern hemisphere winter months, as determined by the monthly birth interval. However, a control group from the general population is needed before any definite conclusions can be drawn. Peaks were observed in January (non-sib group most pronounced) and June (Figure 12).

FIGURE 12A. SIB PAIR GROUP: MONTH OF BIRTH

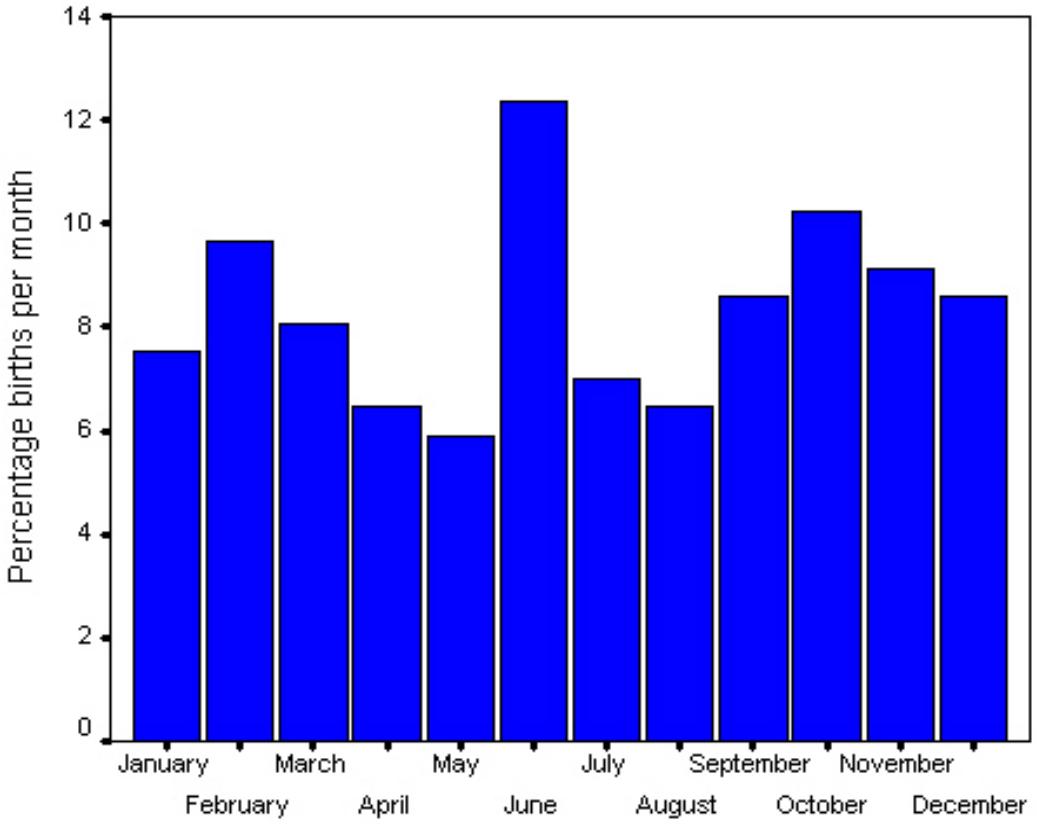
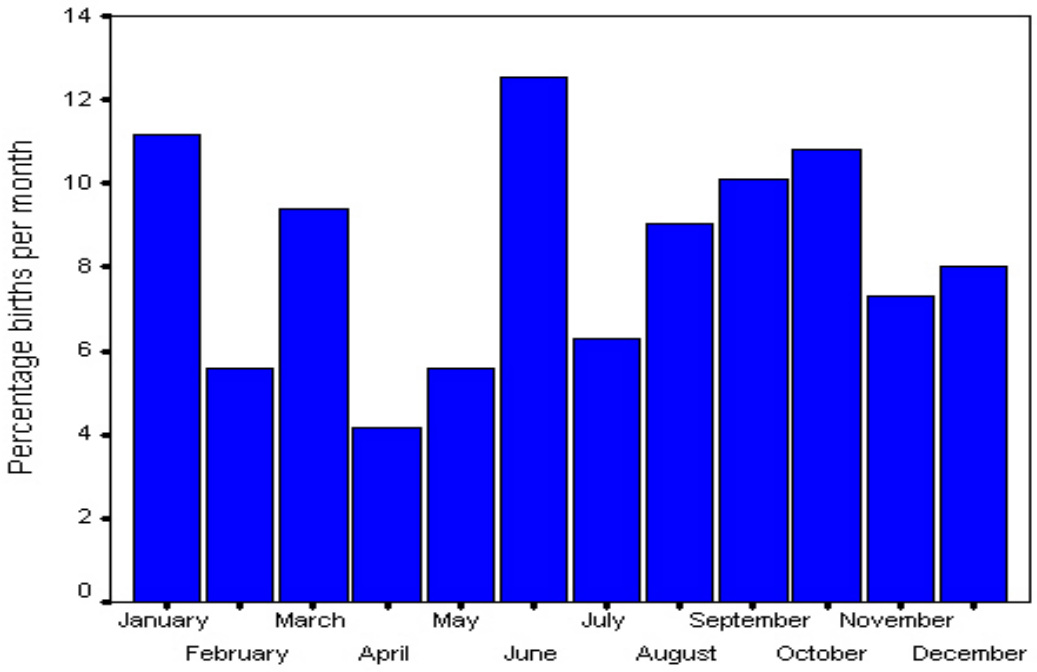


FIGURE 12B. NON-SIB PAIR GROUP: MONTH OF BIRTH



Careful examination of the birth dates revealed that an excess of births occurred on the 1st January (n=12) and the 6th June (n=7). This is in line with anecdotal information that the Department of Home Affairs allocates fictitious birth dates to individuals where these are unknown. The most common dates were 1 January (10 births in non-sib pairs and 2 births in the sib pair group) and 6 June (7 births in the non-sib pair group and 5 in the sib pair group). Other smaller peaks were observed for 8 August (n=3 in non-sib pair group), 12 December (n=4 in non-sib pair group), 25 December (n=4 in non-sib pair group) and 3 March (n=3 in the non-sib pair group). Two other dates were also more commonly reported, namely 1 March (n=5 in non-sib pair group) and 20 October (n=3 in sib pair group).

3.2 DIFFERENCES

There were only a few significant differences between the two groups. The mean age at interview was significantly greater in the sib pair group (37.8 years [SD = 9] versus 35 years [SD = 10] and the mean number of years of schooling also differed between the groups (7.7 years for non sib pair group vs 6.7 years for the sib pair group; p=0.001).

4. SAPS AND SANS: EXPLORATORY FACTOR ANALYSIS OF THE SIB PAIR GROUP AND NON-SIB PAIR (COMPARATOR) GROUP

4.1 DESCRIPTION OF SIB PAIR GROUP EXTRACTED FOR FACTOR ANALYSIS

Out of the 513 schizophrenic subjects, 104 affected sibships (100 pairs, 2 trios, 2 fours) could be assembled. The sibling pairs consisted of sixty-seven same-sex (64 male-male and 3 female-female) and thirty three opposite sex pairs. The trios consisted of males only and the fours of three males and one female each. One male-male sib pair (proband and second interviewed sib) was extracted from each of the trios and each of the fours. The age at

interview (n=204) ranged from 17 to 70 years (mean 37.8 years SD 9.32; not significantly different from non-sib pair group). At time of the interview participants had been ill for a mean period of 14.5 years (SD 8.71; range 6 months to 45 years).

The SAPS and SANS formed the basis of the factor analysis. The SANS and SAPS mean global rating scores (sum of global ratings) were 10.35 (SD 4.74; range 0-24) and 3.35 (SD 4.2; range 0-18), respectively, while table 1 shows the ratings of the individual items.

TABLE 1. PERCENTAGE OF INDIVIDUAL CASES FROM THE SIB PAIR GROUP (N=208) SHOWING THE RATINGS (0 TO 5) FOR EACH OF THE SAPS AND SANS ITEMS

Item		Rating					
		None (0)	Questionable (1)	Mild (2)	Moderate (3)	Marked (4)	Severe (5)
SANS	Affective changes	12.5	5.8	43.8	21.2	12.0	2.9
	Alogia	25.0	6.4	29.4	18.6	16.2	4.4
	Avolition	8.3	3.4	28.4	31.4	23.0	5.4
	Anhedonia	7.8	4.9	19.6	33.8	27.5	6.4

	Attention	81.3	7.4	4.4	2.5	2.0	0.5
SAPS	Hallucinations	68.5	1.0	7.4	14.3	8.4	0.5
	Delusions	68.6	0.0	9.8	9.8	10.8	1.0
	Bizarre behaviour	77.3	3.9	6.9	3.4	5.9	2.5
	Thought disorder	70.9	2.5	15.8	6.9	3.4	0.5

*Values given as percentages

4.2 EXPLORATORY FACTOR ANALYSIS DATA

Exploratory factor analysis was first applied to identify homogeneous symptom dimensions (or factors) represented by the items of the SAPS and SANS. Analysis of the global and individual items of the SAPS and SANS revealed that the global items could replace the respective individual items. Principle component analysis of the global items of the SAPS and SANS identified two factors with eigenvalues > 1 (a positive factor, accounting for 22.6% of the variance, and a negative factor, accounting for 48.8% of the variance) (Table 2).

TABLE 2. FACTOR LOADINGS FOR THE SANS AND SAPS GLOBAL ITEMS WITH THE TWO ROTATED FACTORS (SIB PAIR GROUP; N=208).

Items		Factor 1 (Negative factor)	Factor 2 (Positive factor)
SANS	Affective changes	0.821	0.169
	Alogia*		
	Avolition	0.879	0.203
	Anhedonia	0.883	0.137
	Attention*		
SAPS	Hallucinations	0.049	0.786
	Delusions	0.080	0.889
	Bizarre behaviour	0.250	0.635
	Thought disorder	0.330	0.573
	Eigenvalue**	3.218	1.418
	% Variance	48.80	22.6
	Cumulative proportion	45.97	66.23

Extraction Method: Principal Component Analysis. Rotation Method: Varimax with Kaiser Normalization.

Rotation converged in 3 iterations.

Highlighted factor loadings indicate that the relevant SAPS and SANS items can be considered a major constituent of the corresponding factor.

**The inclusion of alogia (factor 1) and attention (factor 2) yielded the same solution.*

*** Only components with eigenvalues > 1 were retained.*

In a forced five-factor solution (i.e., irrespective of eigenvalue) the first two factors accounted for 66.2% of the variance. The solution indicated that

thought disorder loaded highly on factor 3, bizarre behaviour on factor 4 and affective changes on factor 5, while factor one and two constituted a negative and positive symptom dimension (Table 3). The individual item factor analysis reinforced the five factor solution of the global scores, except for a shared loading of delusions items (data not shown).

TABLE 3. FIVE FACTOR STRUCTURE FOR SANS AND SAPS GLOBAL RATINGS FOR THE SIB PAIR GROUP (N=208)

Items		Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Communality
SANS	Affective changes	0.444	0.086	0.140	0.119	0.870	0.996
	Avolition	0.880	0.118	0.087	0.194	0.229	0.885
	Anhedonia	0.911	0.108	0.141	0.011	0.199	0.901
SAPS	Hallucinations	0.110	0.934	-0.003	0.060	0.094	0.897
	Delusions	0.108	0.803	0.326	0.254	0.084	0.827
	Bizarre behaviour	0.135	0.206	0.170	0.944	0.100	0.978
	Thought disorder	0.165	0.172	0.938	0.166	0.119	0.991
	% Variance	45.97	20.25	11.47	8.77	6.02	
	Cumulative proportion	45.97	66.23	77.70	86.47	92.49	

Extraction Method: Principal Component Analysis. Rotation Method: Varimax with Kaiser Normalization.
Rotation converged in 5 iterations.
Highlighted factor loadings indicate that the relevant SAPS and SANS items can be considered a major constituent of the corresponding factor.

The factor solution (eigenvalues more than 1) of the non-sib pair group revealed a two-factor solution similar to that of the sib pair group with the positive factor (hallucinations, delusions, bizarre behaviour and thought disorder) and negative factor (affective changes, avolition and anhedonia). The forced five factor solution also showed a similar factor structure to that of the sib pair group (Table 4).

TABLE 4. FIVE FACTOR STRUCTURE FOR SANS AND SAPS GLOBAL RATINGS FOR THE NON-SIB PAIR GROUP (N=299)

Items		Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Communality
SANS	Affective changes	0.362	0.143	0.108	0.108	0.907	0.997
	Avolition	0.874	0.055	0.200	0.150	0.163	0.856
	Anhedonia	0.898	0.036	-0.072	0.061	0.215	0.863
SAPS	Hallucinations	0.064	0.908	0.162	0.162	0.037	0.881

	Delusions	0.029	0.885	0.208	0.148	0.140	0.868
	Bizarre behaviour	0.085	0.329	0.911	0.170	0.103	0.986
	Thought disorder	0.168	0.256	0.1641	0.932	0.102	0.999
	% Variance	23.592	44.214	9.158	8.063	7.128	
	Cumulative proportion	23.592	67.806	76.964	85.027	92.156	

Extraction Method: Principal Component Analysis. Rotation Method: Varimax with Kaiser Normalization.

Rotation converged in 5 iterations.

Highlighted factor loadings indicate that the relevant SAPS and SANS items can be considered a major constituent of the corresponding factor.

5. CONCORDANCE OF SANS AND SAPS ITEMS

A wide range of concordant items was found in the analysis of the SANS and SAPS items in the sib pair group (Table 6; see appendix 2 for complete ordinal data).

TABLE 6. CONCORDANCE OF SANS AND SAPS INDIVIDUAL ITEMS BETWEEN THE 104 SIB PAIRS (N=208)

Symptom	Concordant for presence of symptom	Concordant for absence of symptom	Disconcordant	CHISQUARE	P-value (5% level)

Total group SANS Items	Observed	Expected	Observed	Expected	Observed	Expected		
Unchanging facial expression	61	60.4	6	5.4	35	36.17	0.107	NS
Decreased spontaneous movements	39	33	25	19	38	50.04	5.904	0.015
Paucity of expressive gestures	46	42.7	16	12.7	40	46.59	2.040	NS
Poor eye contact	38	31.9	26	19.9	38	50.29	6.095	0.014
Affective non responsivity	38	33	24	18.9	40	50.04	4.106	0.043
Inappropriate affect	3	1.3	82	80.3	17	20.41	2.843	NS
Grooming and hygiene	33	24.5	35	26.5	34	50.98	11.316	0.0008
Impersistence	83	81.2	3	1.2	16	19.63	3.484	NS
Physical anergia	53	50.8	11	8.8	38	42.35	1.077	NS
Recreational interests	78	73.4	7	2.4	17	26.29	12.735	0.0001
Relationships	70	68.4	5	3.4	27	30.29	1.203	NS
SAPS items								
Auditory hallucinations	16	9.7	55	48.7	31	43.54	8.465	0.004
Voices commenting	5	2.2	77	74.2	20	25.59	4.865	0.027
Voices conversing	8	4.3	68	64.3	26	33.35	4.957	0.026

Somatic/tactile hallucinations	3	0.9	86	83.9	13	17.23	6.149	0.013
Olfactory hallucinations	3	1.1	84	82.1	15	18.84	4.234	0.04
Visual hallucinations	1	0.6	88	87.6	13	13.90	0.425	NS
Persecutory delusions	8	6.9	57	55.9	37	39.23	0.330	NS
Delusions of jealousy	0	0.01	100	100.01	2	1.98	0.010	NS
Delusions of guilt or sin	0	0.2	93	93.2	9	8.60	0.217	NS
Grandiose delusions	1	0.7	86	85.7	15	15.58	0.143	NS
Religious delusions	2	1.1	83	82.1	17	18.84	0.971	NS
Somatic delusions	0	1.4	78	79.4	24	21.18	1.813	NS
Delusions of reference	3	1.8	78	76.8	21	23.43	1.094	NS
Delusions of being controlled	3	0.7	88	85.7	11	15.58	8.824	0.003
Delusions of mind reading	4	1.5	81	78.5	17	21.94	5.165	0.02
Thought broadcasting	2	0.9	85	83.9	15	17.23	1.709	NS
Thought insertion	2	0.6	89	87.6	11	13.90	4.433	0.035
Thought withdrawal	1	0.3	92	91.3	9	10.41	1.864	NS
Clothing and appearance	0	0.7	85	85.7	17	15.58	0.843	NS

Social and sexual behaviour	3	1.3	82	80.3	17	20.41	2.843	NS
Aggressive, agitated behaviour	3	1.5	80	78.5	19	21.94	1.828	NS
Repetitive behaviour	0	0.2	94	94.2	8	7.69	0.170	NS
Derailment	4	2.8	72	70.8	26	28.33	0.692	NS
Tangentiality	5	3.4	70	68.4	27	30.29	1.203	NS
Incoherence	5	2.7	74	71.7	23	27.66	2.897	NS
Illogicality	6	2.7	75	71.7	21	27.66	5.916	0.015
Circumstantiality	4	3.4	69	68.4	29	30.29	0.185	NS
Pressure of speech	0	0.01	100	100.01	2	1.98	0.010	NS
Distractible speech	0	0.01	100	100.01	2	1.98	0.010	NS

Alogia items, intimacy and clanging items not reflected in table. See methods for reasons.

NS non-significant

Only valid cases with full information included, see individual items

All observed and expected values expressed as counts

The global items of hallucinations (p=0.002), delusions (p=0.01) and anhedonia (p=0.037) had higher than expected concordance, while global affect (p=0.725), global alogia (p=0.367), global avolition (p=0.13), global bizarre behaviour (p=0.108) and global thought disorder (p=0.669) showed no significant concordance.

Neither the negative nor the positive symptom factors revealed higher than expected concordance (p=0.256 and p=0.524 respectively).

6. Limiting concordant symptoms

6.1 Gender based analysis

The sib pair group was divided into a male-male sib pair group and a male-female group. It could be argued that the concordant factors in the male-male sib pair group, by neutralizing the gender effect, would be more likely to represent shared familial factors, and more likely shared genetic variation within for example the pseudo-autosomal region [1-6].

In the concordance analysis (Table 6) seventeen items, mostly from the SAPS (14/17) had higher than expected concordance. Only 4 of the items (Table 7) were found in the male-male group namely eye contact (p=0.027), grooming (p=0.003), auditory hallucinations (p=0.010), global hallucinations (p=0.017) and delusions of control (p=0.001).

Table 7. SANS and SAPS items with higher than expected concordance in the Male-Male (n=67) sib pair group

Symptom	Concordant for presence of symptom		Concordant for absence of symptom		Disconcordant		CHISQUARE	P-value (5% level)
Male-Male group	Observed	Expected	Observed	Expected	Observed	Expected		
Eye contact	26	21.6	17	12.55	24	32.90	4.899	0.027
Grooming	28	22.1	18	12.12	21	32.75	8.628	0.003
Auditory hallucinations	9	4.8	40	35.84	18	26.33	6.704	0.010
Global hallucinations	9	5.1	39	35.11	19	26.78	5.658	0.017
Delusions of control	2	0.3	60	58.30	5	8.40	10.960	0.001

6.2 ITEM PREVALENCE AND CONCORDANCE FINDINGS

However, the stratification of the sample by gender pairs made it imperative for us to evaluate whether any significant differences existed in the prevalence of the individual symptoms between the male-male and male-female group, since this would directly impact on the interpretation of the concordance analysis. The prevalence of grooming difficulties and religious delusions differed significantly between the gender pairs (more common in male-male pairs) while mind reading approached significance (Table 8).

Based on the preset exclusion criteria (see Methods) grooming difficulties was excluded from further analysis.

TABLE 8. COMPARISON OF INDIVIDUAL SYMPTOM PREVALENCE BETWEEN THE MALE-MALE AND MALE-FEMALE SIB PAIR GROUPS

Differences between M-M and M-F groups (%)				
Symptom	M-F	M-M	z	p
Grooming	35.9	57.0	-2.51	0.012
Religious*	3.1	14.2	-2.92	0.004

** item did not show a higher than expected concordance in gender groups.*

6.3 CONFOUNDING VARIABLES AND CONCORDANCE FINDINGS

In order to exclude the possible effects of confounding variables on the findings of concordance analysis it was important to further compare the groups in terms of potential confounding variables. Certain DIGS variables (developmental history, drug use and demographic variables) were identified as possible confounding variables. The sample size of the sib pair group allowed comparisons between the male-male and male-female groups in terms of 9 of these variables (Table 9).

TABLE 9. COMPARISON OF CONFOUNDING VARIABLES BETWEEN THE MALE-MALE (67 PAIRS) AND MALE-FEMALE (32 PAIRS) SIB PAIR GROUPS

Differences between M-M and M-F groups (%)				
Confounding variables	M-M	M-F	z	P*
Age at interview	37.5 (8.8)	40.0 (10.8)	1.32	0.188
Age at onset	23.2 (5.4)	23.3 (6.8)	-0.04	0.969
Duration of illness	14.4 (8.0)	16.1 (10.2)	0.93	0.350
Years of schooling	6.6 (3.0)	6.9 (3.1)	0.50	0.620
Episodes	2.5 (1.9)	2.4 (1.1)	-0.77	0.441
Substance use	12.5	35.6	-3.72	0.0002
Mood	9.3	3.3	1.53	0.125
Anxiety	1.7	4.2	-0.99	0.321
Stress	21.4	3.4	3.14	0.002

Mean (SD) or percentages

**Significance levels*

The male-male and male-female groups differed significantly in terms of two variables: the abuse of or dependency on any substance (p=0.0002), and a history of a stressor prior to the onset of illness (p=0.002). The concordance analysis with the variable " any substance abuse or dependency" (categorised into concordance for the presence, concordance for the absence and disconcordance for " any substance abuse or dependency") revealed that eye contact, auditory hallucinations and global hallucinations did not have a higher than expected concordance for the presence of any substance abuse or dependency (Appendix 3). No concordance for the presence of any substance abuse or dependency was noted for delusions of control and thus no concordance analysis was necessary for this item.

The second covariate of interest namely presence of a stressor prior to the onset of illness showed similar results for eye contact, auditory hallucinations and global hallucinations. Delusions of control again did not show any concordance for the presence of the covariate.

The age of onset was, despite the lack of significant difference between the gender groups, evaluated in more detail given the conflicting findings of age of onset on symptomatology [1;7-9]. Only in the male-male group did concordance of the earlier age of onset (less than 23 years of age; dichotomised around the mean age of onset) showed significantly higher than

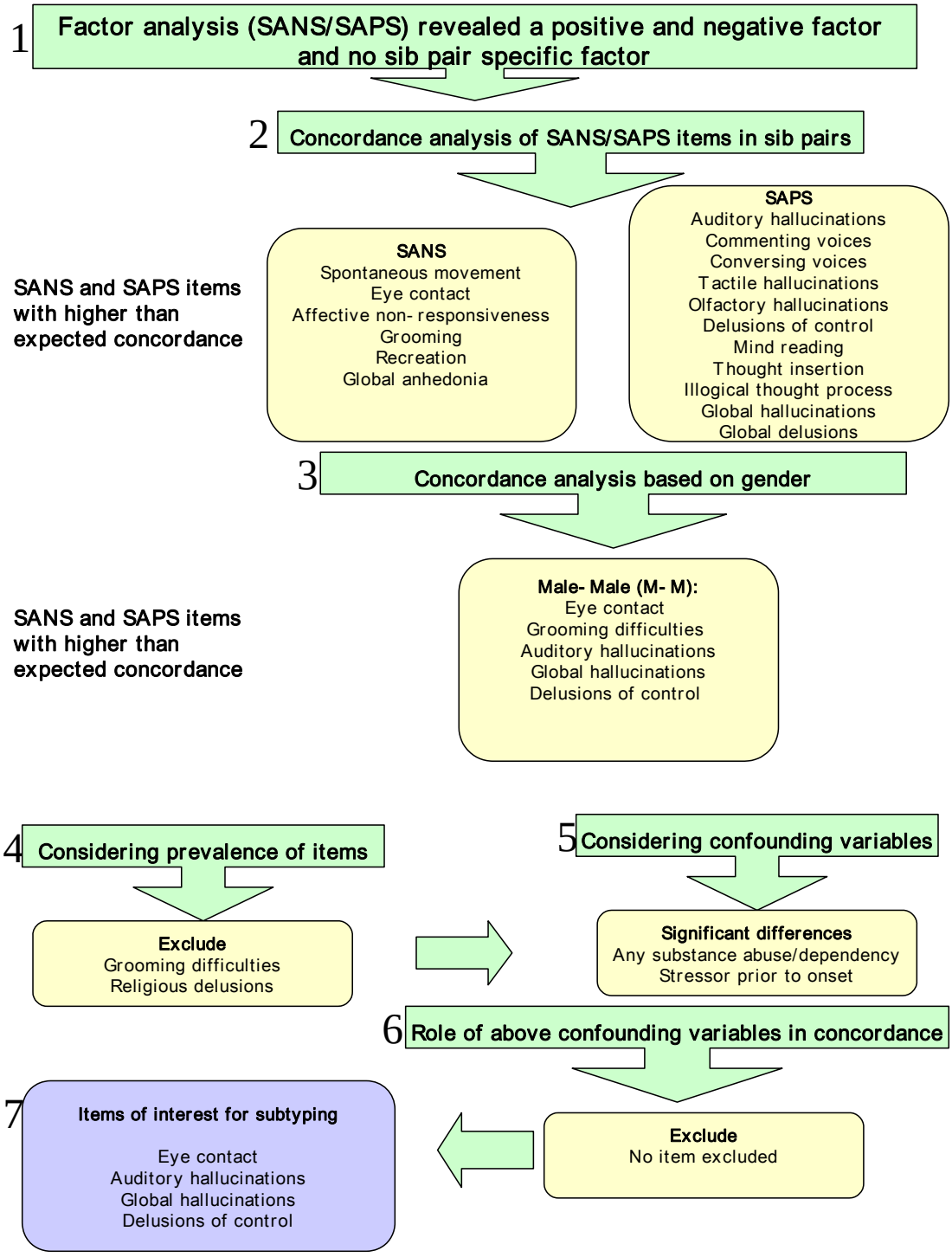
expected values (p=0.038). However, the concordance of the SANS and SAPS items namely eye contact (p=0.431), auditory hallucinations (p=0.629), global hallucinations (p=0.473) and delusions of control (p=0.917) were not higher than expected in the earlier age of onset group.

The final analysis compared the concordance rates of the DIGS life-time items with the SAPS and SANS items of interest to investigate whether life-time symptomatology are reflected in the concordance findings on the SANS and SAPS of the male-male group. The items on the life-time DIGS that had higher than expected concordance were conversing voices (p.0.002), delusions of jealousy (p=0.001), thought insertion (p=0.0001), thought withdrawal (p=0.01), delusions of reference (p=0.012) and delusions of control (p=0.0001). Global hallucinations had a one hundred percent concordance for lifetime symptomatology. Delusions of control and global hallucinations therefore seems to represent the only items that remained with a higher than expected concordance in both the lifetime and SANS/SAPS analysis.

7. SUMMARY OF FINDINGS

The factor analysis of the SANS and SAPS individual and global items identified the same symptom factors in the comparator and sib pair group.

The concordance analysis identified 3 global items (hallucinations, delusions and anhedonia) and 14 individual items from the SANS and SAPS with higher than expected concordance. However, only grooming difficulties, eye contact, auditory hallucinations, global hallucinations and delusions of control had a higher than expected concordance within the male-male sib pair group (chosen to factor out the possible confounding effect of gender). Grooming difficulties were excluded since the prevalence differences between the male-male and male-female groups may be responsible for the findings of higher than expected concordance. None of the tested confounding variables played a significant role on the higher than expected concordance detected for eye contact, auditory hallucinations, global hallucinations and delusions of control. The delusions of control item was the only item to have higher than expected concordance on the SAPS and the lifetime DIGS analysis. This item would therefore be of specific interest for a genotype-phenotype analysis. A visual summary of all the concordance findings is represented in the following figure.


1
Factor analysis (SANS/SAPS) revealed a positive and negative factor and no sib pair specific factor
2
Concordance analysis of SANS/SAPS items in sib pairs
SANS and SAPS items with higher than expected concordance
SANS
Spontaneous movement
Eye contact
Affective non- responsiveness
Grooming
Recreation
Global anhedonia
SAPS
Auditory hallucinations
Commenting voices
Conversing voices
Tactile hallucinations
Olfactory hallucinations
Delusions of control
Mind reading
Thought insertion
Illogical thought process
Global hallucinations
Global delusions
3
Concordance analysis based on gender
SANS and SAPS items with higher than expected concordance
Male- Male (M- M):
Eye contact
Grooming difficulties
Auditory hallucinations
Global hallucinations
Delusions of control
4
Considering prevalence of items
Exclude
Grooming difficulties
Religious delusions
5
Considering confounding variables
Significant differences
Any substance abuse/dependency
Stressor prior to onset
6
Role of above confounding variables in concordance
Exclude
No item excluded
7
Items of interest for subtyping
Eye contact
Auditory hallucinations
Global hallucinations
Delusions of control

8. REFERENCES

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APPENDIX 1. THE DEMOGRAPHIC CHARACTERISTICS OF THE SIB PAIR AND THE NON-SIB PAIR COMPARATOR GROUP

	Sib pair group (n=214)	Non-sib pair group (n=299)
Gender		
Male	173 (80.8%)	226 (75.6%)
Female	41 (19.2%)	73 (24.4%)
Marital status		
Single	162 (75.7%)	248 (82.9%)
Married	24 (11.2%)	24 (8%)
Separated/Divorced/ Widowed	14 (4%)	23 (7.7%)
*Residence		
Alone	7 (3.3%)	7 (2.3%)
With parents	160 (74.8%)	187 (62.5%)
Residential care	2 (0.9%)	1 (0.3%)
With other people	33 (15.4%)	46 (15.4%)
*Employment		
Disability grant	158 (73.8%)	218 (72.9%)
Unemployed	25 (11.7%)	45 (15.1%)
Employed	14 (6.5%)	15 (5%)
Student	3 (1.4%)	9 (3%)

Schooling		
Mean (SD)	6.7 (3.02) years	7.7 (3.16)
Range	0-13 years	0-16 years
Median	7 years	8 years
Age at interview		
Mean (SD)	37.8 (9.32) years	35 (10) years
Range	17-70 years	13-84 years
Median	37 years	34 years
Age of onset		
Mean (SD)	23.1 (5.78) years	22.5 (6.15) years
Range	14-42 years	11-53 years
Median	22 years	21 years

**Only selected categories.*

APPENDIX 2. SANS AND SAPS ITEMS: ORDINAL DIFFERENCES BETWEEN SIBS IN THE SIB PAIR GROUP

SANS items	Concordant (concordant for absence of symptom)	1 point difference	2 points difference	3 points difference	4 or 5 points difference
Unchanging facial expression	22 (3)	34	29	13	4
Decreased spontaneous movements	30 (17)	28	27	12	5
Paucity of expressive gestures	25 (7)	30	33	8	6
Poor eye contact	30 (10)	27	24	10	9
Affective non responsivity	25 (9)	34	27	9	7
Inappropriate affect	77 (74)	8	8	2	7
Grooming and hygiene	40 (24)	26	16	10	11
Impersistence	32 (1)	31	24	10	4
Physical anergia	27 (5)	30	29	10	5
Recreational interests	32 (1)	40	15	9	5
Intimacy and closeness	27 (4)	33	19	5	6
Relationships	30 (2)	30	22	11	6
SAPS items	Concordant (concordant for absence of symptom)	1 point difference	2 points difference	3 points difference	4/5 points difference

Auditory hallucinations	61 (51)	7	10	14	8
Voices commenting	78 (76)	2	9	4	6
Voices conversing	72 (67)	4	8	8	7
Somatic/tactile hallucinations	86 (84)	2	6	2	4
Olfactory hallucinations	85 (82)	3	6	2	3
Visual hallucinations	84 (81)	2	6	2	6
Persecutory delusions	58 (53)	5	13	11	14
Delusions of jealousy	96 (95)	3	2	1	0
Delusions of guilt or sin	92 (92)	3	6	1	1
Grandiose delusions	84 (84)	2	5	4	6
Religious delusions	83 (83)	3	7	7	3
Somatic delusions	85 (84)	3	8	7	9
Delusions of reference	76 (73)	5	12	8	9
Delusions of being controlled	80 (77)	3	4	4	0
Delusions of mind reading	81 (78)	3	9	4	5
Thought broadcasting	83 (81)	2	11	4	1
Thought insertion	86 (84)	3	8	0	2
Thought withdrawal	82 (81)	3	5	1	2
Clothing and appearance	79 (79)	3	8	4	7
Social and sexual behaviour	80 (80)	6	3	8	4
Aggressive, agitated behaviour	76 (76)	3	10	3	9
Repetitive behaviour	93 (93)	0	5	1	2

Derailment	73 (69)	2	19	3	4
Tangentiality	69 (67)	6	17	6	3
Incoherence	70 (68)	8	13	8	2
Illogicality	71 (68)	7	16	5	2
Circumstantiality	64 (61)	10	17	7	3
Pressure of speech	96 (94)	4	1	0	0
Distractible speech	98 (98)	1	1	1	0
Clanging	101 (101)	0	0	0	0

**Sibs only included if all variables rated (n=214)*

APPENDIX 3. THE INFLUENCE OF " ANY SUBSTANCE ABUSE OR DEPENDENCY" AND " STRESSOR PRIOR TO ONSET OF ILLNESS" ON CONCORDANCE FINDINGS IN THE SIB PAIR GROUP (N=214) (SELECTED ITEMS ONLY)

Items	Covariates	++	--	+-	++	+-	--	Chi-square	P value	
		Observed			Expected					
Eye contact	sub ++	3	5	6	2.57	4.57	6.86	0.219	0.640	
	sub --	27	10	21	24.25	7.25	26.51	2.505	0.114	
	sub +-	7	10	8	4.84	7.84	12.32	3.074	0.080	
	Stress++	2	3	3	1.53	2.53	3.94	0.454	0.501	
	Stress--	27	15	23	22.80	10.80	31.39	4.645	0.031	*
	stress+-	8	7	9	6.51	5.51	11.98	1.484	0.223	
Inappropriate affect	sub ++	1	13	1	0.15	12.15	2.70	5.947	0.015	*
	sub --	1	49	8	0.43	48.43	9.14	0.899	0.343	
	sub +-	1	16	8	1.00	16.00	8.00	0.000	1.000	
	stress++	1	7	0	0.13	6.13	1.75	8.000	0.005	**
	stress--	2	49	14	1.25	48.25	15.51	0.614	0.433	
	stress+-	0	22	3	0.09	22.09	2.82	0.102	0.750	
Global affect	sub ++	8	6	1	4.82	2.82	7.37	11.204	0.001	**
	sub --	40	2	16	39.72	1.72	16.55	0.064	0.800	
	sub +-	17	0	8	17.64	0.64	6.72	0.907	0.341	
	stress++	5	1	2	4.50	0.50	3.00	0.889	0.346	
	stress--	43	1	21	44.03	2.03	18.93	0.777	0.378	
	stress+-	17	1	7	16.81	0.81	7.38	0.066	0.797	
Global anhedonia	sub++	10	1	4	9.60	0.60	4.80	0.417	0.519	
	sub--	48	1	9	47.52	0.52	9.96	0.536	0.464	
	sub+-	18	2	5	16.81	0.81	7.38	2.600	0.107	
	stress++	5	2	1	3.78	0.78	3.44	4.022	0.045	*
	stress--	50	2	13	49.11	1.11	14.78	0.940	0.332	
	stress+-	21	0	4	21.16	0.16	3.68	0.189	0.664	
Auditory hallucinations	sub ++	1	8	6	1.07	8.07	5.87	0.008	0.930	
	sub --	8	27	17	5.24	24.24	22.53	3.132	0.077	
	sub +-	6	22	3	1.81	17.81	11.37	16.800	0.000	**
	stress++	1	5	2	0.50	4.50	3.00	0.889	0.346	
	stress--	5	38	21	3.75	36.75	23.49	0.720	0.396	
	stress+-	8	9	8	5.76	6.76	12.48	3.222	0.073	
Commenting voices	sub++	0	12	3	0.15	12.15	2.70	0.185	0.667	
	sub--	4	41	11	1.61	38.61	15.78	5.134	0.023	*
	sub+-	1	21	3	0.25	20.25	4.50	2.778	0.096	
	stress++	0	7	1	0.03	7.03	0.94	0.036	0.850	
	stress--	2	52	9	0.67	50.67	11.66	3.276	0.070	

	stress+-	3	15	7	1.69	13.69	9.62	1.854	0.173	
Tactile hallucinations	sub++	0	12	3	0.15	12.15	2.70	0.185	0.667	
	sub--	3	47	7	0.74	44.74	11.52	8.769	0.003	**
	sub+-	0	24	1	0.01	24.01	0.98	0.010	0.919	
	stress++	0	7	1	0.03	7.03	0.94	0.036	0.850	
	stress--	1	56	7	0.32	55.32	8.37	1.709	0.191	
	stress+-	2	20	3	0.49	18.49	6.02	6.292	0.012	**
Olfactory hallucinations	sub++	0	13	2	0.07	13.07	1.87	0.077	0.782	
	sub--	2	46	9	0.74	44.74	11.52	2.723	0.099	
	sub+-	1	23	1	0.09	22.09	2.82	10.413	0.001	**
	stress++	1	7	0	0.13	6.13	1.75	8.000	0.005	**
	stress--	0	57	7	0.19	57.19	6.62	0.214	0.644	
	stress+-	2	18	5	0.81	16.81	7.38	2.600	0.107	
Global hallucinations	sub++	1	8	6	1.07	8.07	5.87	0.008	0.930	
	sub--	9	27	21	6.67	24.67	25.66	1.879	0.171	
	sub+-	5	17	3	1.69	13.69	9.62	11.839	0.001	**
	stress++	1	5	2	0.50	4.50	3.00	0.889	0.346	
	stress--	5	38	21	3.75	36.75	23.49	0.720	0.396	
	stress+-	9	9	7	6.25	6.25	12.50	4.840	0.028	*
Delusions of control	sub++	0	15	0	0.00	15.00	0.00	No concordance		
	sub--	2	45	10	0.86	43.86	12.28	1.966	0.161	
	sub+-	1	24	0	0.04	23.04	1.92	25.000	0.000	**
	stress++	0	8	0	0.00	8.00	0.00	No concordance		
	stress--	2	57	5	0.32	55.32	8.37	10.365	0.001	**
	stress+-	1	19	5	0.49	18.49	6.02	0.718	0.397	
Mind reading	sub++	0	12	3	0.15	12.15	2.70	0.185	0.667	
	sub--	4	44	9	1.27	41.27	14.46	8.136	0.004	**
	sub+-	0	20	5	0.25	20.25	4.50	0.309	0.579	
	stress++	0	6	2	0.13	6.13	1.75	0.163	0.686	
	stress--	1	53	10	0.56	52.56	10.88	0.414	0.520	
	stress+-	3	17	5	1.21	15.21	8.58	4.352	0.037	*
Thought insertion	sub++	0	13	2	0.07	13.07	1.87	0.077	0.782	
	sub--	2	48	7	0.53	46.53	9.94	4.983	0.026	*
	sub+-	0	24	1	0.01	24.01	0.98	0.010	0.919	
	stress++	0	8	0	0.00	8.00	0.00	No concordance		
	stress--	0	59	5	0.10	59.10	4.80	0.106	0.745	
	stress+-	2	18	5	0.81	16.81	7.38	2.600	0.107	
Global delusions	sub++	1	8	6	1.07	8.07	5.87	0.008	0.930	
	sub--	9	30	19	5.90	26.90	25.20	3.509	0.061	
	sub+-	6	11	8	4.00	9.00	12.00	2.778	0.096	
	stress++	1	5	2	0.50	4.50	3.00	0.889	0.346	
	stress--	9	36	20	5.55	32.55	26.89	4.270	0.039	*
	stress+-	6	8	11	5.29	7.29	12.42	0.327	0.568	
Global bizarre behaviour	sub++	1	8	6	1.07	8.07	5.87	0.008	0.930	

	sub--	2	41	14	1.42	40.42	15.16	0.333	0.564	
	sub+-	3	16	6	1.44	14.44	9.12	2.926	0.087	
	stress++	0	5	3	0.28	5.28	2.44	0.426	0.514	
	stress--	6	44	14	2.64	40.64	20.72	6.730	0.009	**
	stress+-	0	16	9	0.81	16.81	7.38	1.205	0.272	
Incoherence	sub++	1	11	3	0.42	10.42	4.17	1.176	0.278	
	sub--	3	42	13	1.56	40.56	15.89	1.916	0.166	
	sub+-	1	19	5	0.49	18.49	6.02	0.718	0.397	
	stress++	1	7	0	0.13	6.13	1.75	8.000	0.005	**
	stress--	2	48	15	1.39	47.39	16.22	0.369	0.543	
	stress+-	2	17	6	1.00	16.00	8.00	1.563	0.211	
Illogical thought process	sub++	1	11	3	0.42	10.42	4.17	1.176	0.278	
	sub--	3	40	15	1.90	38.90	17.20	0.948	0.330	
	sub+-	2	19	4	0.64	17.64	6.72	4.096	0.043	*
	stress++	1	7	0	0.13	6.13	1.75	8.000	0.005	
	stress--	3	47	15	1.70	45.70	17.61	1.426	0.232	
	stress+-	2	16	7	1.21	15.21	8.58	0.848	0.357	
Global thought disorder	sub++	1	9	5	0.82	8.82	5.37	0.070	0.791	
	sub--	5	29	23	4.78	28.78	23.45	0.021	0.885	
	sub+-	2	14	9	1.69	13.69	9.62	0.104	0.747	
	stress++	1	7	0	0.13	6.13	1.75	8.000	0.005	**
	stress--	4	34	26	4.52	34.52	24.97	0.109	0.741	
	stress+-	3	11	11	2.89	10.89	11.22	0.010	0.922	

**Sub any substance use*

Stress stressor prior to onset if illness

++ Concordant for presence of the symptom

+- Disconcordant for the presence of the symptom

-- Concordant for the absence of the symptom

CHAPTER 8

DISCUSSION AND CONCLUSION

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1. CLINICAL FINDINGS

This chapter is organized into a number of sections. Section 1 deals with the demographic features, symptom patterns, treatment, and comorbid conditions of the sib pairs. In section 2, the factor analysis results are discussed. Sections 3 to 5 discuss the findings pertaining to concordance analysis and the implications of these findings for further targeted genetic studies. The final section deals with incidental but important issues arising from the study. These include the ethical implications of research in indigenous populations and procedural challenges for future research.

1.1 DEMOGRAPHIC VARIABLES

The mean age at interview (38 years) and the mean duration of illness (14 years) were similar to those of other sib pair study populations (range 28.7 to 47.75 years and 9 to 19.9 years respectively). As expected, some impairment in social and occupational functioning can be inferred from the small proportion of individuals who were married (13.6%) and the high rate of work disability (78%). Of major concern was the impact of the socio-political history of the Xhosa people on their levels of education, as a low educational status may affect the legitimacy of informed consent and the reliability of the

information obtained. However, our subjects had attained an average of nearly 7 years of schooling, and fewer than 1% had never attended school.

1.2 PRODROMAL SYMPTOMS AND TRIGGERING EVENTS

Prodromal symptom duration varied considerably, with a quarter having experienced an acute onset of psychosis. However, a history of prodromal symptoms (when assessed retrospectively) is a difficult variable to evaluate accurately because it is prone to recall bias and furthermore, symptoms may be difficult to identify by the patient or family members [1].

Surprisingly few participants reported a triggering event, although the occurrence of gestational and post-partum triggers in some of our cases lend support to the importance of this vulnerable period in the life of female participants [2]. The triggering events that did occur did not reflect a clear predominance of cultural influences, as would have been expected from the importance attached to supernatural phenomena by the Xhosa population. The patients could have been reticent about revealing their traditional beliefs because they wanted to accommodate the " Western" biological framework of the researchers. In any event, no structured assessment tool exists for capturing ethnic-specific trigger events, and further research along these lines is necessary.

1.3 PSYCHOTIC SYMPTOMS

Consistent with international data, many of the participants in this study reported repeated hospitalizations, most displayed residual symptoms and psychotic features were present in a substantial number. Lifetime paranoid delusions were the most common delusions (88%). Grandiose delusions, delusions of reference and religiose delusions were found in 55%, 51% and 47% of subjects, respectively. Cassano et al. (1998) also reported persecutory delusions to be the most common (58%), closely followed by reference (54.8%), grandiose (19%), guilt (16%), somatic (13%) and control type delusions (13%) in a first episode sample of patients with schizophrenia [3]. Thought broadcasting was present in only 10% of their sample. Koen et al. (2004) found paranoid delusions in 44 (61.9%) out of six African and 65 mixed ethnic origin South African schizophrenia inpatients [4]. Grandiose delusions were found in 42.3% and control delusions in 60.6% of this sample. Although the Xhosa sibling pairs showed a higher overall rate of delusions than the study by Koen et al. (2004), paranoid and grandiose delusions were also the most common [4].

Of interest is that delusions of a religious nature most commonly had traditional healing practices as a central theme, and although the concern was that it would be difficult to separate culture-bound themes from psychotic themes, family members distinguished between what they accepted as " normal" cultural beliefs and what they perceived as psychosis. This is in

keeping with the viewpoint of delusions being beliefs that are not shared within the specific cultural context of the patient. The challenge for future studies would be to delineate the divisions between normality and pathology on the spectrum of religious (traditional) beliefs and religious delusions in the Xhosa population.

Auditory hallucinations were very common in the Xhosa sample. This was also the most common symptom (61%) in the Cassano et al. (1998) first episode sample [5], followed by visual (16%), gustatory (6%) and tactile (3%) hallucinations. The South African sample of Koen et al. (2004) likewise reported similar rates of auditory (70.4%) and visual (12.7%) hallucinations [4]. Gustatory and olfactory hallucinations are classically associated with an organic lesion such as an epileptic focus, and it was therefore not surprising to find these two perceptual changes to be the least common in this sample, especially considering the low rate of significant neurological or developmental difficulties reported by the patients. There was no significant relationship between a history of physical illness and any of these hallucinations.

1.4 BEHAVIOURAL SYMPTOMS AND THOUGHT DISORDER

The high rate of reported aggressive behaviour (78%) might be a reflection of the way in which we defined this term. The DIGS does not specify any specific criteria for aggression. Thus, for the purpose of this study, any verbal or physical abuse linked to the illness was reported as positive for aggression. This may have led to the over-reporting of aggressive incidents. Nevertheless, in the light of these results, it seems that families and health care workers are at an increased risk for violence. Further support for this is provided by a study by Koen et al. (2004) that showed a high incidence of violence associated with specific delusions and substance abuse in a South African inpatient sample [4].

The catatonic subtype was of interest, given that previous reports [6] have suggested the existence of a gene specific for catatonic schizophrenia. Very few patients (n=8) were classified as having catatonic subtype, and none of the sibling pairs were concordant for this subtype. The prevalence of catatonia seems to be in keeping with other studies that also reported a low prevalence (6%) [3].

Thought disorder was common, as expected, with circumstantiality, incoherence, derailment and/or tangential thinking occurring in between 15% and 25% of subjects. Loosening of associations was less common (fewer than 5% of subjects) and lower than that reported by Cassano et al (1998) [3].

Negative symptoms, such as affective flattening, alogia and anhedonia, were common, with over 78% of the sample rated as mildly to markedly affected. Inappropriate affect, ranging from mild to marked, was found in only one out of every five patients.

1.5 TREATMENT IN THE XHOSA SCHIZOPHRENIA SIB PAIR SAMPLE

The majority of patients (96%) were using medication at the time of the interview and, as expected from clinical experience, depot medications were the treatment of choice. Although the high level of medication use could be explained by an over-representation of medication compliant recruits in this sample, another South African sample (Mbanga et al. (2003) [7]) reported a high rate of medication use and belief in the combined use of traditional and western medication. This suggests that the high rates of compliance found in our Xhosa sample are not unusual. Whether the high compliance rates are an authentic finding or are due to selection bias will have to be addressed in a follow-up study on this sample. Such a study can, however, be complicated by the migratory patterns of patients as they move between the Eastern and Western Cape. A possible solution would be to involve multiple clinics to tract patients across this migration.

The low rate of clozapine use (<5%) was of concern in view of the presence of ongoing psychotic symptoms in 67 (> 10%) of the patients. In a few cases clozapine was used together with depot antipsychotic medication, a combination known to increase the risk for significant morbidity from agranulocytosis. The medication requirements of these cases needed reassessment. Despite these concerns, it was obvious that monotherapy was most often reported, with only 11 patients receiving mood altering drugs.

Nearly a quarter of subjects (24%) received anticholinergic drugs. Since the DIGS does not allow for a detailed analysis of movement disorders, we could not draw any practical conclusions regarding associations between specific extrapyramidal symptoms and medication use history. Future studies wishing to examine such associations should make use of rating instruments designed to assess specific movement disorders.

This investigation found an alarming lack of specific knowledge of the drugs used (e.g. a participant would know that he or she was using a depot preparation, but knew neither the name nor the dose) and poor record keeping and access to records in the rural communities. Future studies should consider performing objective measurements rather than relying on the patients' history. An example of such an approach would be a morphological evaluation of the participants. The results of such a study

could shed light on the possible role of developmental factors on schizophrenia with minimal dependence on historical data.

1.6 COMORBID CONDITIONS AND SYMPTOMS

Comorbid conditions form an integral part of the complexity of schizophrenia. Thirty-six percent of the sample had confirmed or suspected comorbid depression, anxiety, substance abuse or substance dependency. This is significantly lower than the 93% comorbidity reported by Kendler et al. (1996) in a community sample [8] and the 58.1% comorbidity reported by Cassano et al 1998 [3], but in line with the reported life-time comorbidity for first admission psychosis (affective and non-affective) of 40.2% [9].

The comorbidity of schizophrenia with specific disorders varies widely. Substance and alcohol abuse rates range from 6.5% in non-affective psychosis [3;9] to 43.2% in alcohol dependence and 37.7% in drug dependence, in community samples [8].

This study relied on patient and collateral reports of drug use and this may possibly have led to underreporting of substance abuse and dependency. However, family members and health professionals were able to provide reliable collateral information. Koen et al. (2003) [10] interviewed fifty Xhosa

schizophrenia patients to determine the prevalence of comorbid substance abuse or dependency. Sixty percent of the total sample admitted to cannabis use at some time, with only 10% occasionally using other drugs. Thirty two percent of the sample was considered to be ongoing cannabis users. Of the total sample, 5 patients (11%) gave an inaccurate self-report (4 denied use and 1 falsely admitted use). The majority (71%) of patients gave a history of tobacco smoking, which is in line with international data [11].

Our findings of a lower rate of substance abuse than that observed in the foregoing studies may be attributable to methodological and population specific differences between our study and the others, including first versus multiple admissions, gender and race differences, differences in education, differences in mean age of onset, inclusion of patients using atypical antipsychotics - which may potentially increase comorbid anxiety disorders and the use of community samples, that might have included untreated patients with high affective disorder comorbidity (74%) [8]. We did not formally evaluate subjects for the presence of all anxiety disorders or for mixed depression and anxiety.

The substance abuse comorbidity may also have been influenced by the implementation in the Eastern Cape of a new disability allowance policy,

which stipulates that patients would be denied disability allowances should they test positive for cannabis at their regular clinic appointments.

It was already obvious early in the study that the mood section of the DIGS elicited few positive responses, although subclinical depressive symptoms were noted. To allow for a degree of uncertainty in the diagnosis of mood disorders, a category, " possible mood disorders" (defined as any depressive symptom that had led to impairment, independent of the time period) was included in the analysis. Nevertheless, the observed rate of 16.2% of possible and confirmed mood disorders is low relative to previous studies, which have shown rates ranging from 40% to 93% [3;8;9].

Interpretation of the results relating to mood and anxiety disorders in the sib pair study is, subject to a number of limitations. The criterion for recruitment into the study (diagnosis of schizophrenia in the proband and lack of significant mood symptoms) have biased the sample against the inclusion of mood symptoms. Caution should therefore be exercised in extrapolating these findings to the general schizophrenic population. Patient ratings were cross-sectional since the diagnosis of mood and anxiety disorders was based on a single interview. Important historical information may therefore have been missed. This may be specifically important in this context since the symptom dimensions of depression (or anxiety) and schizophrenia may have different

patterns of exacerbation and remission during the course of the illness [12]. Another limitation is that assessment instruments were translated into Xhosa orally by the Xhosa nurse. While the majority of patients were conversant in English, and every attempt was made to ensure equivalence when questions relating to mood and anxiety symptoms were put to Xhosa-speaking patients, cross-cultural adaptation of instruments is preferable in multilingual research. Determining and ensuring equivalence across primary and secondary language tools is often problematic and will remain a significant consideration in the design of research protocols in this population.

Further work is needed to characterize mood and anxiety symptom profiles in patients with schizophrenia across different ethnic populations. Cross-national comparative studies suggest that cultural factors may affect the symptom expression of mood and anxiety symptoms, although the exact reasons for the wide variation in prevalence (e.g. much lower rates of OCD in some Asian countries) are not known [13]. Should the low prevalence of mood and anxiety disorders be replicated in other studies of patients with schizophrenia who are of Xhosa descent or mixed race, it may well suggest that cultural or genetic factors play a role in protecting against comorbid conditions in these persons. However, proper assessment of this hypothesis requires a follow-up study designed to avoid the recruitment biases of the present study.

Further work is needed to develop culturally sensitive instruments to screen and diagnose mood and anxiety disorder in patients with schizophrenia and other psychotic disorders. While it is recognized that specific biological mechanisms, including genetic and auto-immune mechanisms, may play a role in the pathogenesis of mood and anxiety disorders, ethnic variations in these underlying factors are likely to be protective in certain groups. Further comparative studies to delineate these putative factors are warranted.

This study [14] found the lifetime prevalence of suicide attempts in this group of Xhosa patients with schizophrenia to be at the lower end of the spectrum (19.8%), but still comparable to studies in other patient populations [15;16]. The low rate of mood symptoms and the pre-requisite of having at least one first degree family member may have contributed to the slightly lower rate of attempts [17].

Separation, divorce or unmarried status significantly increased the risk of suicide attempts in this schizophrenia population and are consistent with the role of social support systems and the stress diathesis model in predicting suicidal behaviour. Factors that were not significantly associated with attempted suicide included religious affiliation, level of schooling, occupational status (specifically disability support), living arrangements and parenthood.

The presence of an affected sibling seems to be protective in this group of patients with schizophrenia. One explanation might be that the presence of affected siblings lowers the expectations of the patient and family, lessening the emotional stress linked to failure to achieve an expected level of functioning. However, these findings, together with the very low concordance rate, may reflect a delineation between the underlying pathophysiology of schizophrenia and suicidal behaviour.

In summary this study highlights the universality of suicide attempts (although the most common suicide methods varied from some other studies [18;19]) in schizophrenia patients. Furthermore, these findings raise the possibility that affected sib pair status may be protective in nature and supports ongoing efforts to understand the complex pathophysiological processes underlying suicidal behaviour in schizophrenia.

2. FACTOR SOLUTIONS

Similar two and five factor solutions for the global items of the SANS and SAPS were found in both the sibling pair and the non-sibling pair groups of Xhosa schizophrenic subjects. These accounted for more than 90% of the variance. A forced five-factor solution was used to allow comparisons with earlier studies, but the two-factor solution was the appropriate approach when eigenvalues larger than one were the minimum criterion. This was also found

to be the case by Dolfus et al. (1998) [20]. The forced 5-factor solution concurred with previous reports in Caucasian populations [21];[22]. The previously reported positive, negative and " disorganized" dimensions were again reflected in the global item solution of the Xhosa population (in both sib and non-sib pair groups). The positive dimension did not separate into separate delusions and hallucinations factors. The " disorganized" and negative symptom dimensions separated into " thought disorder" and " bizarre behaviour" factors and " affective changes" and " avolition/anhedonia" components, respectively.

Emsley et al. (2001)[23], in an article describing a smaller cohort of schizophrenic subjects from the pool from which these subjects were drawn, showed no separation between the negative symptom and the disorganization domain [24]. However, the differences between the original report by Emsley et al. (2001) and the current analysis may reflect the expansion and stratification of the sample. Alogia and concentration difficulties were excluded in this study, based on the findings of Emsley et al. (2001) [25].

The findings of this study correlated well with factor analysis findings on schizophrenic sib pair samples [26-28], despite the use of different assessment scales. Kendler et al. (1997) also reported a negative and positive symptom factor. Their affective/manic symptom factor included

thought disorder [29]. Similarly, Burke et al. (1996) found a positive, negative and disorganized symptom factor. SANS and SAPS instruments do not include mood symptoms as a separate item and thus this study cannot comment on mood symptoms [30].

Nevertheless, the core finding remains that very little difference exists between the Caucasian and Xhosa factor solutions, even in a sib pair sample. This despite the fact that the SAPS and SANS have proven validity in a factor analysis approach to subtyping schizophrenia [20] and the assumption that the ethnic homogeneity of this African population (the Xhosa) contributes to limiting the confounding cultural and genetic factors (so-called " background noise") associated with heterogeneous groups. In addition, the large number of single sets (two affected siblings per family) lessened the impact of large sibships on the statistical analysis.

Furthermore, our study represents a more homogenous clinical sample with very few schizo-affective patients relative to other studies and a broad recruitment basis with both urban (1/5) and rural participants (4/5), hospitalized subjects and outpatients. The predominance of male patients (4:1) is slightly higher than that of most previous studies (mostly 2:1) and may limit the generalizability of this study. Conceivably, a predominantly female group might demonstrate other unique shared familial factors. The power of

this study is not sufficient to address this issue and it should be the focus of an extended sample of patients with schizophrenia. The specific underlying reason for the more pronounced gender effect in the South African sample remains unknown since no specific criteria unduly discriminated against the recruitment of female participants. Whether this gender difference reflects different health seeking pathways by male patients with schizophrenia in the Xhosa population remains to be studied.

3. CONCORDANCE ANALYSIS

Since no factor specific to the sib pair group could be found and the negative and positive symptom factors did not reveal higher than expected concordance in the total sib pair group, the possibility exists that the structured symptoms as depicted by the SANS and SAPS may not be a valuable tool for genetic subtyping in the Xhosa population. However, concordance analysis of the SANS and SAPS (after dichotomising the values into presence or absence of the symptom), did reveal higher than expected concordance for forty individual items, mostly from the SAPS. In addition, the global items of hallucinations ($p=0.002$), delusions ($p=0.01$) and anhedonia ($p=0.037$) had higher than expected concordance.

It was therefore necessary to limit the number of items in order to increase the likelihood of identifying a specific subgroup large enough and specific enough to allow for a reasonable hypothesis and subsequent candidate gene studies.

Stratification by gender, and more specifically, the use of male only sib pairs, neutralized the gender effect, and thus concordant factors were more likely to represent shared familial factors because male siblings were more likely to share genetic variation within, for example, the pseudo-autosomal region [31-36]. Only five items remained concordant between sib pairs, and only in the male-male group, after this process, namely eye contact (p=0.027), grooming (p=0.003), auditory hallucinations (p=0.010), global hallucinations (p=0.017) and delusions of control (p=0.001).

Four of these five items (eye contact, auditory hallucinations, global hallucinations and delusions of control) were shown, by statistical means, to be independent of the prevalence differences between the gender groups. The nine confounding variables tested for independence against the remaining four items found that only the confounders “any substance abuse or dependency” and “a stressor prior to onset of illness” had some differential influence in the male-male and male-female sib pair groups. None of these confounders had a significant influence on the higher than expected

concordance found for the four items, eye contact, auditory hallucinations, global hallucinations and delusions of control.

4. HIGHER THAN EXPECTED CONCORDANCE: A REFLECTION OF CLINICAL SUBTYPES?

These four remaining items (eye contact, auditory hallucinations, global hallucinations and delusions of control) appear to be likely candidates for closer scrutiny in the genetic analysis of the Xhosa sample. These results will be evaluated individually, and discussed in the light of other published schizophrenia sib pair studies (see chapter 3). It is imperative to note that these studies, not counting that of Cardno et al. (1998) [37], used diagnostic assessment tools other than the SANS/SAPS and DIGS. Comparisons across studies should therefore be approached with the necessary caution.

4.1 EYE CONTACT

Eye contact has not previously been reported to have a higher than expected concordance between sib pairs. Troisi et al. (1991) showed that reduced eye contact and an increased rate of eye closures were linked to poor prognosis in a schizophreniform group. However, those exhibiting a poor prognosis also

demonstrated higher affective flattening and alogia. In line with these findings, Davison et al. (1996)[38] showed that no single measurement of facial communication could reliably distinguish between patients with schizophrenia, depressed patients, demented patients and patients with Parkinson's disease. Although it seems unlikely that eye contact as a single item should be diagnostic for schizophrenia, Pitman et al. (1987)[39;39] found that non-paranoid schizophrenic patients had significantly less eye contact than a normal control group, while the paranoid schizophrenic group differed only in that they showed fewer eyebrow and lower facial movements. It is possible that subgroups of patients with schizophrenia might differ as regards single items of facial expression, but it remains to be proven whether this is indeed the case. Eye contact might merely serve as a proxy marker for other phenotype markers. Indeed, it seems plausible that eye contact abnormalities may be linked to the occurrence of delusions as part of a distorted appreciation of complex stimuli [40]. From the inconsistent results in the literature and a paucity of genetic association studies on eye contact it seems that eye contact as a single item will need further research to more clearly define whether this item will be useful in the investigation of genotype-phenotype relationships in the Xhosa population.

4.2 AUDITORY AND GLOBAL HALLUCINATIONS

Loftus et al. (2000)[41] reported significant intra-pair concordance for auditory hallucinations in sib pairs, based on a chi-square approach. However, DeLisi et al. (1987)[42], Cardno et al. (1998)[43] and Loftus et al. (1998)[44] failed to show significant intra-pair concordance for this item. Kendler et al. (1997)[45] reported a higher than expected concordance for global hallucinations.

Hallucinatory phenomena form an integral part of schizophrenia and associations have been reported between these and specific anatomical structures and their functions in schizophrenia. For example, an event-related PET paradigm design demonstrated that hallucinations and delusions of persecution were associated with increased mesotemporal and ventral striatal activity [46].

Rosa et al. (2002)[47] also suggested linkage of the reality-distortion syndrome of schizophrenia spectrum disorders to chromosome 1. More specific to auditory hallucinations, Wei and Hemmings (1999) [48] reported a significant excess of the A1-A1 and A1-A2 allele of the cholecystokinin type A receptor gene in patients with schizophrenia with auditory hallucinations compared to a group of patients with schizophrenia without auditory hallucinations. Autosomal dominant partial epilepsy with auditory features also provides some clues as to the genetic basis of auditory phenomena. In this rare form of temporal lobe epilepsy 67-100% of the affecteds have

associated auditory phenomena. This disease has been linked to chromosome 10q24 and thus the overlap between this disorder and schizophrenia may represent a shared genetic mechanism.

Despite the promising results, the high rate of auditory hallucinations in both the sib pair and non-sib pair groups makes it more likely that the underlying disease mechanism is shared by most patients with schizophrenia. A case-control design based subtyping on the basis of the presence of these items will unfortunately require significantly larger sample sizes than ours to acquire a significantly large group without auditory hallucinations.

4.3 DELUSIONS OF CONTROL

Our findings are in keeping with Loftus et al. (2000) who found significant correlation between sib pair status and delusions of control [49]. This was also the only item to show similar concordance in the SAPS/SANS and lifetime symptom evaluation. The question is whether a plausible model exists for a possible genotype-phenotype relationship for a subgroup of Xhosa patients with schizophrenia with delusions of control.

The aim of the current study was not to elucidate a biological basis for schizophrenia, but rather to identify a genetic mechanism for a specific

subgroup. An item such as delusions of control should thus show specific properties, in addition to having higher than expected concordance, to make it suitable for the genotype-phenotype evaluation. Firstly, a neurocognitive model specific to delusions of control would be of particular value. Althought some disagreement exists, it has been suggested that delusions of control might be related to problems in motor control and feedback mechanisms that involve efference copy and comparators [50;51]. To understand this concept it is helpful to compare delusions of control with the neurological sign known as " anarchic hand" . Anarchic hand results from damage to the supplementary motor area and/or the anterior corpus callosum. The hand contralateral to the lesion will perform unintended goal-directed activities and may interfere with activities performed by the " good" hand. Although the anarchic hand is not under the patient' s control, the individual still recognizes the unintended activities of the hand and does not conclude that it is under alien control. On the other hand, in delusions of control the individual carries out intentional activities, but lacks the awareness of his own control over his hand or body. Differences between these entities suggest the possibility of abnormalities in the motor system and feedback mechanisms. In the case of the anarchic hand the feedback mechanism is faulty and the hand responds only to the current context. For example, it will reach for a pencil if it appears within the patient' s field of vision, even if this activity does not form part of the current goals of the individual (also described as impairment of the

inverse modeling of motor movement). In delusions of control, the part of the motor system involved in the awareness of the predicted state of the hand is abnormal (also described as a " forward" model abnormality). The individual hand therefore seems to move from the desire to move to the actual movement in one step. The person therefore does not have the sensation that the motor system has selected and checked the appropriate movement. A feeling of lack of control therefore exists.

It is thus not surprising that patients with schizophrenia, particularly those with delusions of control, have been reported to have a reduced ability to make rapid motor error corrections [52].

The anatomical basis for the control of the motor system seems to be situated in the prefrontal cortex (formulation of plans and goals), the medial premotor cortex (responsible for the development of appropriate sequences of motor commands and initiates the actions without external cues) and the superior parietal cortex (refining the reaching and grasping movements based on visual input). It seems likely that the parietal lobe is also responsible for the representation of the current and predicted limb position. Frith et al. (2000) [53] strongly suggest that the inverse and " forward" modeling takes place in the cerebellum. In keeping with this proposed defect in central monitoring [54;55]. Blakemore et al. (2003)[56] used hypnosis in normal controls to

induce delusions of control. These individuals then underwent a positron emission tomography and the results suggested abnormalities in the cerebellar-parietal network. Spence et al. (1997)[57] also found hyperactivation of the parietal and cingulate cortices in schizophrenic patients with delusions of control when compared to normal controls and patients with schizophrenia without the delusions of control. This hyperactivation remitted as the delusions ameliorated [58]. The physiological abnormality is therefore likely to be situated in the area responsible for the inhibition of the parietal and cingulate cortices, assuming that the motor control model described above is accurate. Prefrontal cortical under-activity may be the mechanism of reduced inhibition. However this would not explain why only 30% of our sample developed delusions of control. One possible explanation is that different disconnections between the prefrontal cortex and other brain areas may lead to different symptomatology. In delusions of control, the disconnection would involve the parietal cortex, while in hallucinations the temporal cortex may be involved [59].

Ceccherini-Nelli et al. (2003)[60] furthermore suggested that auditory hallucinations and delusions of control may differ in their relationship to linguistic deviations found in schizophrenia. Delusions of control seemed to be associated with speech poverty while auditory hallucinations were associated with sematic or phonemic paraphasias.

Previous studies have also suggested that delusions of control might represent a specific genetic vulnerability. Catalano et al. (1993)[61] compared a 12 base pair repeat polymorphism in the dopamine 4 receptor gene in two groups of patients, namely a delusions disorder group (n=59) and a schizophrenic patient group (n=79) against a control group of 75 individuals. They found that significantly more of the delusional group (27%) carried the rarer A2 allele compared to the control and schizophrenic groups (8%). This suggests that delusions may have a specific genetic underpinning that is not necessarily causative for schizophrenia as a whole.

This item will most likely be the best candidate for an investigation of the genotype-phenotype relationship in the Xhosa schizophrenia population, given the occurrence rate of ±30% and the higher than expected concordance on both the SAPS and lifetime DIGS assessment tools.

This study specifically used the SANS and SAPS to subtype schizophrenia in the Xhosa population in order to find a genotype-phenotype relationship. However, the SAPS and SANS may not necessarily reflect life-time symptomatology, since conversing voices, delusions of jealousy, thought insertion, thought withdrawal, delusions of reference and auditory hallucinations findings differed between the DIGS life-time and SANS/SAPS analysis. The items that differed were restricted to the SAPS and this fits in with Arndt et al. (1995) who illustrated that the negative component of the SANS seems stable over time while there seems to be some variation in the other positive domains, albeit independent from one another [62]. Possibly

the other dimensions may be influenced by the time-period demanded by the SAPS. Conceivably, the SANS items might more closely correlate with life-time negative symptoms, suggesting state rather than trait characteristics, as is the case with the thought disorder component of the SAPS. Hallucinations and delusions may be more aptly considered state markers in the context of factor analysis of the SAPS/SANS and lifetime symptomatology. This would not, however, explain our findings regarding delusions of control. Could delusions of control represent a positive domain symptom that independently remains a trait marker within the SAPS items?

5. SUMMARY OF DEMOGRAPHIC, CLINICAL, FACTOR ANALYSIS AND CONCORDANCE ANALYSIS

This study constitutes the third largest reported collection of affected sibling pairs with schizophrenia and the only one in an African population. As such, the information gathered may contribute significantly to our understanding of schizophrenia in this population and offer unique future research opportunities. To optimize the contribution of this study, a critical evaluation of the clinical data and research process will be presented in order to offer suggestions for developing effective protocols for further studies in this population.

In short, the factor analysis approach to the SANS and SAPS failed to identify specific " familial" symptom factors. Concordance analysis however, did identify symptoms that could be investigated further for possible candidate gene areas and delusions of control seem the most logical candidate. However, these factors may merely represent peripheral manifestations of underlying pathology or symptoms not considered in this analysis. In addition, the identified items are limited to the male-male subgroup as the mixed and female-female group sizes were too small to draw sufficient conclusions regarding the items identified in those groups. The low incidence of OCD and the concordant items on the SANS and SAPS raises possibilities that unique genetic loci may be present in the Xhosa population.

6. ETHICAL AND PROCEDURAL CHALLENGES

Psychiatric genetic research studies raise many ethical issues that are compounded when the relevant study involves more than one culture. It would be foolish to negate the ethical and methodological challenges we encountered during this study. In particular, those caused by the different ways in which different cultures conceptualize the family, value communal interests rather than individual autonomy, and view mental disorders.

We became aware of the ethical problems involved in cross-cultural genetic studies of psychiatric disorders when we assembled this sample of Xhosa-speaking subjects with schizophrenia and their family members. The study design complied with international ethical and practical guidelines, based on the Nüremberg paradigm for clinical research, and was approved by the relevant internal review boards. To ensure optimal communication with participants, the team included an experienced Xhosa-speaking psychiatric nurse as a core member of the team.

6.1 THE PROCEDURAL CHALLENGES

In common with genetic research projects of this nature, the design of this study required the collection of extensive and detailed psychiatric, family and genealogical information. A blood sample was also taken from which material for DNA analysis could be extracted in the follow-up study.

The research protocol further specified that the researchers should interview, and obtain blood samples, from at least one parent and one healthy sibling. We consequently invited probands to nominate relatives who would be willing to co-operate. The researchers then approached the nominated relatives and requested their assistance. In many instances, the relatives lived in remote rural communities, and reaching them was in itself a difficult task. Informed

consent was then obtained from each of the relatives for collection of a blood sample and participation in a structured diagnostic interview.

6.2 THE CONCEPT OF FAMILY IN TRADITIONAL XHOSA CULTURE

The researchers were aware that the distinction between the nuclear family, extended family and the community in the Xhosa culture differs from that of Western cultures. As an example, in the Xhosa culture there exists a custom of substitution of close relatives. If a close relative is absent, another relative will act as a substitute for the absent family member. For instance, in the absence of a biological father a male relative will act as a substitute father. The substitute, who could be an uncle, nephew or cousin, is regarded as the father of the relevant person. He is also referred to, and addressed, as father. The substitute father is, for all practical purposes, considered the biological father, and it is impolite to imply that he is not the actual father.

While inquiring about the proband' s family and obtaining information about the nominated parent and sibling the researchers had to consider two things. First, we had to ensure that the people involved were in fact biological parents and siblings, and not substituted relatives. Second, it was necessary to make these inquiries without transgressing cultural restraints. The researchers

therefore took care not to differentiate between family members based on their genealogical distance from the proband. In an attempt to distinguish between biological and culturally nominated substitutes, the researchers used terms such as " blood brother" as synonym for a biological brother.

However, despite great care in trying to obtain accurate information, the researchers found, upon receipt of the results of the DNA analysis (in the follow-up study), that some of the nominated people were in fact not the biological parents or siblings of the proband.

6.3 INDIVIDUAL AUTONOMY VERSUS COMMUNAL INTERESTS

This emphasis on the extended family is a manifestation of the emphasis that many African cultures traditionally place on communal interests, rather than individual autonomy. We came across another demonstration of this when we interviewed the nominated parent or sibling. We found that members of the extended family, and even community members, considered it their right to attend these interviews. The willingness of participants to share confidential information in the presence of extended family and community members struck us as notable. Only on one occasion did a subject, suspected to have

schizophrenia and paranoid delusions, insist that a member of the family leave the interview.

This had important implications because the research protocol reflected the emphasis placed by Western ethical committees on privacy and confidentiality. However, at first sight this appears to be a surmountable problem because subjects can waive their right to privacy and confidentiality. The principle of autonomy provides that participants can do this provided that they are fully informed about their rights, of the implications of such a waiver, and that they make the decision freely and without any coercion. Furthermore, even in the absence of such consent it may have been possible to justify a deviation from the research protocol based on cultural relativism. The researchers could argue that the expectations of the members of the community were in accordance with their culture, and that we as researchers should therefore accept the decision of subjects to relax guidelines, especially since these guidelines were put in place to protect the rights of the subjects.

However, we believed that a number of factors made such relaxation unwise. First, when interviewing the nominated parent and sibling, confidential information was sometimes revealed about the proband who was not present, and whose consent had not been obtained for the release of information. Second, the principle of beneficence imposed on the researchers the

obligation to prevent harm to subjects. We believed that there was a potential of harm to the subjects if extended family and community members attended the interviews. We took into account the very personal questions we had to ask, the pathology involved, and the mental status of some of the participants. Third, there is a general belief that private interviews produce more accurate information [63]. Fourth, we were alert to the danger that we could be using culture as an unjustifiable excuse to lower ethical standards. As was mentioned above, cultural relativism is not widely accepted as an ethical theory [64;65] and its use to obviate ethical rules is controversial. Finally, the question arose as to whether the subjects really had the freedom to exclude extended family and community members. Or, was this a form of " cultural" coercion where cultural pressures were forcing participants to accept a lesser degree of privacy than they would ideally like themselves?

We decided that we had a duty to protect vulnerable patients who may want the interviews to take place in private, away from peer, community and cultural pressure. We therefore had to find a way to ensure that subjects were not coerced into accepting a lesser degree of privacy and confidentiality than they wished to have. The researchers consequently made sure that the initial interview with the potential participant took place in private. While informing potential participants about the nature of the study, the researchers suggested to them that the rest of the interview should also take place in

private, with the possible exception of immediate family members. Participants usually accepted the researchers' suggestion, although it often caused substantial dissent from outsiders. While extended family and community members allowed the interviews to take place in private, they were clearly displeased by their exclusion.

As one might expect, the Xhosa people's concept of mental illness differed from that of Western mental health professionals. Many Africans' perception of mental illness is influenced by the belief that ancestors play an important part in their lives [66-68]. The appeasement of the ancestors is a protective measure and if the ancestors are displeased they will withdraw their protection, and this can lead to the onset of mental illness [69].

While not all Xhosas believe in supernatural powers, preliminary analyses of an attitude questionnaire demonstrated that about 90% of participants in this study believed that schizophrenia is caused by supernatural powers. In comparison Angermeyer and Matschinger [70] found that less than 12% of lay people in Europe believe this to be the case.

As a consequence of this belief, one family withdrew from the study after the death of a relative (a child) who had been run over by a car. The family

members construed this incident as an indication that their ancestors were displeased with their involvement in the study, and had cast a spell over them. The fact that healthy members of the family also supported this opinion, excludes the possibility of folie a deux.

The validity of the research hinged on the accurate diagnosis of schizophrenia. The diagnostic criteria of the DSM IV were used. The Xhosa belief system includes two conditions that are relevant here, viz. “ amafufunyana” and “ thwasa” . [71]. The researchers found that patients regarded as having “ amafufunyana” , satisfied the DSM-IV criteria for a number of disorders such as schizophrenia, other psychotic disorders, conversion disorders and mood disorders.

We found, furthermore, that there were traditional healers in a number of participating families and that parents and siblings who where described as healthy by the proband also often reported psychotic symptoms to the researchers.

The entities “ amafufunyana” and “ thwasa” provide a clear illustration of the distinction made by Kleinman (1978) [72] between disease, as a biomedical construct, and illness, as a sociocultural experience. While Western diagnostic categories are clearly useful for the various analyses

undertaken in modern genetic studies, it is crucial for interviewers to be aware of the impact of cultural understandings of mental illness on disease presentation, experience, and subsequent course.

Indeed, the distinction between cultural and non-cultural influences on the research procedure may not always be clear. This was brought to light when the seasonality of birth was assessed. Considerable evidence exists that suggests that a greater than expected number of schizophrenic births occur in winter and spring [73], suggesting that intra-partum factors might be at play in the genesis of schizophrenia. In our study, an excess of birth dates on specific days (1 January, 6 June) strongly suggested the introduction of artifactual data resulting from the procedural management of missing birth dates by Government institutions. It seems unlikely that reliable conclusions can be drawn from data relying on this data management system. It would be of interest to investigate the birth date frequencies of other seasonality studies, to find out if the same problem, albeit attenuated, may have occurred and whether this unique to the Xhosa population.

6.4 PROBLEMS ASSOCIATED WITH INFORMED CONSENT

The different ways in which people from different cultures conceptualize mental illnesses also influenced the acquisition of informed consent from

subjects. As already mentioned consent for participation in a research project is ethically and legally acceptable only if participants understand the information presented to them. It follows that subjects must understand the concepts used. In this study the protocol and instruments used Western concepts of mental disorders and Western nomenclature, de-emphasizing Kleinman' s (1978) [72] warning that while there exists a universal biophysical condition, culture shapes the final presentation of disorders. It was therefore a major challenge to us to ensure that when we explained the condition and symptoms we used appropriate Xhosa terminology and were sensitive to the sociocultural meaning participants may give to the symptoms they described.

Researchers who undertake cross-cultural genetic studies of psychiatric disorders must expect to come across problems not covered by existing guidelines. Our experiences in this study illustrate some of the complications in cross-cultural research situations, and the need for researchers to be attentive to the cultural context in which they will operate.

We believe that for psychiatric genetics to achieve the same success as that found in other areas of human genetics, researchers who undertake cross-cultural studies will have to pay more attention to the intersection between

nosology and medical anthropology [74] . Researchers must appreciate that culture is fundamental to the understanding of mental disorders. In this regard, Western trained mental health researchers must apply the DSM IV criteria with care and sensitivity when they deal with people from different cultural groups. Ensuring that research protocols are appropriate for all the cultures to be included in a study may be daunting. When preparing these documents, researchers should take into consideration the innumerable cultural variations in respect of mental disorders. One way of doing this may be to include terms such as " amafufunyana" as a descriptive term in the information document, and to specify the symptomatology.

Culture also influences communication between people and determines how people view aspects such as privacy, confidentiality and autonomy. Westernized study guidelines may arguably be inappropriate in certain cultures. However, for a researcher who has a Western training it may be difficult to decide what course to follow. The researchers' decision to recommend private interviews in this study can be used to demonstrate this. At one level this decision was driven by the principle of beneficence; the researchers wanted to prevent subjects from the harm that may follow an interview in the presence of community members. But, this can also be described as paternalistic and insensitive to the culture of their Xhosa subjects. Nevertheless, if the researchers had decided to heed community

demands it may have been dangerous as well. Public interviews may theoretically have triggered a psychotic episode with negative consequences for both the subject and the researchers. People who do not support cultural relativism might have argued that the public interviews would have compromised ethical standards to the detriment of participants from non-Western cultures. Finding a balance may be difficult for researchers who embark on this type of research, and there may not always be a ready answer to some of the dilemmas that confront them.

Patients with schizophrenia of Xhosa origin, and more specifically affected sib pairs, can contribute significantly to the current knowledge base, but inherent difficulties related to research in this population necessitate careful consideration of study protocols. We further consider the need for such researchers to be attentive to the cultural context within which they operate, as culture is fundamental to the understanding of mental disorder.

7. CONCLUSION

Despite the fact that the factor analysis approach did not reveal unique genetic subtypes, concordance analysis did bring to light three items or symptoms of interest for future genetic research. Research in this population

will challenge the researcher to consider confounding ethnic, ethical and methodological factors.

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APPENDIX A. LIST OF TERMS AND ABBREVIATIONS USED IN TEXT

Terms or abbreviations	Definition
Affected sibling pairs	Two siblings affected with a disorder. For the purposes of this study both siblings suffered from schizophrenia
Affected sibship	Two or more siblings affected with a disorder. For the purposes of this study all siblings suffered from schizophrenia
Affective changes	Changes in the pattern of observable expression of subjective emosional experience
Alogia	Decreased production of speech (not linked to motor aphasia)
Anhedonia/Asociality	Impaired ability to enjoy activities and decreased socialization
Avolition	Impairment of conation
Catatonic symptoms	Motor abnormalities such as negativism, rigidity, posturing, stupor and waxy flexibility
Concordance	Refers to the presence of a symptom or disease or other variable in both sibs
Delusions	A false unshakeable personal belief based on incorrect conclusions drawn from external reality. The belief falls outside

	of the belief system of the sub culture of the person.
DIGS	Diagnostic Interview for Genetic Studies
Familial	Refers to any condition which is commoner in relatives of an affected individual than in the general population
Genotype	The genetic constitution of the individual
Hallucinations	A sensoric observation without external stimulation of the specific sensory organ
Heritability	A statistical measure of the degree to which a trait is genetically determined
Linkage	Linked genes have their loci within measurable distance of one another on the same chromosome
Locus	The precise location of a gene on a chromosome
Microdeletion	Chromosomal deletion whose size is close to the limit of resolution using the light microscope
Negative symptoms	A group of symptoms that include affective changes, alogia, avolition, apathy, anhedonia and asociality
OCD	Obsessive compulsive disorder
Oligogenic model	In an oligogenic model a few genes of moderate effect is needed to cause the disease
Penetrance	The frequency of expression of the genotype
Phenotype	The observable characterstics of an individual

Poligenic model	In a poligenic model several genes of small effect is needed to cause the disease
Positive symptoms	A group of symptoms that include hallucinations, delusions, thought disorder and behavioural abnormalities
SANS	Schedule for the assessment of negative symptoms
SAPS	Schedule for the assessment of positive symptoms
SCID	Structured Clinical Interview for DSM-IV
Thought disorder	An abnormality in the form of thought and includes loose associations, incoherence and illogical thought processes
Variance	A quantity equal to the square of the standard deviation