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A comparison study of early non-psychotic deviant behavior in Afrikaner and US patients with schizophrenia or schizoaffective disorder

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Abstract

In a previous study early non-psychotic deviant behaviors in US adult schizophrenic patients recruited for a large-scale genetic study were examined (*Psychiatry Research*, 101, 101). Early deviance characterized a distinct subgroup of patients at rates that were consistent with earlier reports. In addition, specific early non-psychotic deviant behaviors were meaningfully associated with later disease outcomes. In the present study, we examined the demographic, syndrome course, symptom and early deviant behavior history of 109 Afrikaner probands who met criteria for DSM schizophrenia or schizoaffective disorder, and compared them to 109 age- and gender-matched US probands. Consistent with past findings, 68% of Afrikaner probands, as compared to 67% of age- and gender-matched US probands, reported one or more forms of early non-psychotic deviance, including poor socialization, extreme fears/chronic sadness, and/or attention/learning impairment. The remaining 32 and 33% of probands, respectively, were without behavioral deviance until the onset of schizophrenia or schizoaffective disorder. The frequency and distribution of individual deviant behaviors were strikingly consistent between the samples. However, logistic regression analyses revealed different patterns of associations between the early deviant behaviors manifested and disease outcome. Afrikaner participants with early fears/chronic sadness were 3 times more likely to attempt suicide, while among US participants, this form of early deviance conferred 3.5 times more risk for later schizoaffective disorder, and 3 times greater likelihood of later sensory (tactile and/or olfactory) hallucinations. Afrikaner participants with attention/learning impairment were 2.5 times more likely to experience later auditory hallucinations, while US participants with these early difficulties were 3 times more likely to experience thought disorder. We concluded that early non-psychotic childhood deviance in this independently collected Afrikaner population distinguished a distinct subtype of patients and that the forms of early deviance manifested were meaningfully linked to later disease outcome. Possible reasons for the association pattern differences in these two populations are considered.

Keywords

Schizophrenia; Schizoaffective disorder; Early onset

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1. Introduction

A convergence of evidence over the past decade from the medical (Geddes and Lawrie, 1995; Verdoux et al., 1997, reviews), anatomical (Green et al., 1994; O'Callaghan et al., 1991; Guy et al., 1983; Cannon et al. 1994) and neuroanatomical (e.g. Lewis, 1997; Waddington and Buckley, 1996) literature has suggested that schizophrenia is a neurodevelopmental disorder with roots in early childhood (e.g. Lieberman, 1999). Moreover, early deviant behavior patterns in children who go on to develop schizophrenia have been consistently reported in high-risk, prospective and retrospective behavioral studies of schizophrenia (Cannon and Jones, 1996, review). These aberrant behaviors have been linked to early neurodevelopmental anomalies (Cannon et al., 1997; Foerster et al., 1991; Guy et al., 1983) and likely reflect abnormalities in specific neural pathways. For example, prospective longitudinal studies of large cohorts have suggested that during infancy motor development is delayed and speech problems are more frequent among children who later develop schizophrenia (e.g. Jones et al., 1994). During the preschool and early school years, studies have reported preference for solitary play (Jones et al., 1994) and behavioral maladjustment in the classroom (Done et al., 1994), and cognitive impairment in verbal, non-verbal and math skills were reported at ages 8, 11 and 15 (Jones et al., 1994). Retrospective studies have provided findings consistent with these. An analysis of taped recordings of children revealed that abnormal social reactions, odd movement and anomalous posture reliably indicated to clinicians which children would later become schizophrenic (Walker and Lewine, 1990). Social and academic impairments during the first school-age years were more frequent among 45 future schizophrenic patients as compared to a psychiatric control sample (Foerster et al., 1991). In a clinic-referred population of 61 patients with schizophrenia onset between the ages of 7 and 17, social impairment, motor deficits and language learning disabilities were increased as compared to findings in matched non-psychotic psychiatric controls.

However, early behavioral deviance appears to occur in only a subgroup of patients (Sobin et al., 2001; Done et al., 1994; Torrey et al., 1994; Offord and Cross, 1969)—a distinction that has often gone unrecognized among those interested in describing a neurodevelopmental model of schizophrenia. That early behavioral deviance, and perhaps also the various neurodevelopmental anomalies that underlie these behaviors, may in fact be both a subtype and disease-onset marker, has important implications. Understanding the patterns and distribution of early deviant behaviors that in some patients long precede DSM schizophrenia may be fundamental to accurately characterizing its broad phenotypic heterogeneity. Moreover, for those patients whose histories include early deviant behavior, the behaviors themselves may provide important clues about brain development and, by extension, possible neurobiologic and neurogenetic underpinnings of schizophrenia.

In a previous study we described early non-psychotic deviance in a population of US participants who met lifetime criteria for schizophrenia or schizoaffective disorder. We found 67% of 205 patients reported marked behavioral abnormalities before age 10 and that the specific early behavioral abnormalities predicted later aspects of the disease course that were clinically consistent with the early behaviors, and also predicted family history of schizophrenia (Sobin et al., 2001). However, by necessity, the data were based on retrospective report of patients. School records were generally unavailable. (Even when available, school records only reflected the readily observable classroom behaviors spontaneously provided by teachers or aides.) Obtaining reports from parents and/or siblings was also problematic. Families of schizophrenic patients are often fragmented. At the same time, the perceptions of involved families are understandably influenced by lingering emotional reactions that can include guilt, disappointment, anger or fear. Parents are especially unwilling to remember or reveal painful details of a sick child's early experiences. Thus, while the approach is not without

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limitations, it seemed useful to further explore patient-reported non-psychotic early deviant childhood behaviors.

In this study, we compared childhood information obtained from 109 Afrikaner patients with schizophrenia or schizoaffective disorder to an age- and gender-matched subsample of patients from our US sample. We reasoned that if the early childhood deviance data were largely due to reporting error and reflected patients' fluctuating internal states, severity of illness or cognitive decline, the specific results would not replicate. Additionally, in our previous study, and consistent with other investigators' findings, gender was associated with specific symptom manifestation, and age at time of interview was associated with the report of early learning disabilities/attentional impairment (likely attributable to increased societal awareness of these difficulties). To control for these effects, an age- and gender-matched subsample of our US patients was selected for comparison to the Afrikaner population. We predicted that the gender differences found in the original US study would replicate in the Afrikaner population. Thus, specifically, we predicted that females would have a higher rate of marriage, and higher rates of schizoaffective disorder, and auditory, visual and sensory (tactile/olfactory) hallucinations. We predicted that the previous rates of early non-psychotic deviant childhood behaviors would replicate in the independently collected Afrikaner population. We also predicted that the associations previously reported between early deviant behaviors and later illness features would replicate. Specifically, we predicted that early poor socialization would predict earlier age of syndrome onset, early extreme fears/chronic sadness would predict later schizoaffective disorder, and attentional impairment/learning disability would predict increased likelihood of schizophrenia among probands' family members.

2. Methods

This study included participants from independently collected samples in South Africa and the US. All participants provided written informed consent before beginning the initial interview. Afrikaner participants were evaluated as part of a collaborative genetic project that began in November 1997 between the Laboratory of Human Neurogenetics at Rockefeller University in New York City and the Department of Psychiatry at the University of Pretoria. A total of 168 probands and their family members were recruited and diagnosed, and enrollment for the genetic study is ongoing. The subsample used in this study included 109 participants (78 males, 31 females) who completed a diagnostic interview, who met DSM-IV criteria for schizophrenia or schizoaffective disorder and were without co-morbid substance dependence or other confounding medical diagnosis, and who provided information regarding early deviant childhood behavior occurring before age 10. Fifty-nine unrelated proband participants did not meet these criteria. Participants were recruited from in patient, outpatient and follow-up clinics at a large psychiatric hospital in Pretoria, South Africa, or from its greater catchment area. Approximately 10% of participants were referred by local private psychiatrists or were self-referred in response to radio recruitment and notices by local support group leaders. The remaining participants were offered enrollment in the study by their treating psychiatrists.

A full description of the US sample was given in Sobin et al. (2001). Approximately 85% of the sample were recruited through advertisements in advocate newspapers, and the remaining 15% were recruited from area day treatment clinics. Potential differences in selection biases will be considered in Section 4.1. The same enrollment, assessment and interviewer-training procedures were used in both sites. Information on family history of mental disorders was obtained from parents, subjects and/or other family members just following enrollment and before the diagnostic interview. In the case of the Afrikaner participants, when previous admissions of family members to the psychiatric hospital where the study was based were reported, clinical records were obtained and diagnoses recorded. For approximately 75% of

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the US participants, report of family history of mental illness was obtained from participants' parents. The remaining information was obtained from the participants themselves.

All participants were interviewed using the Diagnostic Interview for Genetic Studies (DIGS) by a specially trained clinician with a minimum of 3 years of clinical experience in diagnosis (Nurnberger et al., 1994). In multi-site test-retest analyses, the DIGS was shown to be reliable for the major DSM diagnostic categories. In ongoing reliability studies between the two Afrikaner clinicians, the two US clinicians and the US investigator who trained all the clinicians, diagnostic agreement >90% for DSM-IV diagnoses was obtained. In cases where patients were unable to provide symptom or syndrome information, with the patients' permission, information was obtained from a family informant, typically the mother.

The clinical variables analyzed (Table 1) are largely self-evident. The variable 'family history of schizophrenia' indicated whether a first, second, and/or third degree relative of a subject had been diagnosed with and/or hospitalized for schizophrenia or schizoaffective disorder. The variables 'family history of other psychiatric disorder' indicated whether a first, second, and/or third degree relative of a participant had been diagnosed with, hospitalized for, and/or treated for any other major psychiatric disorder excluding schizophrenia or schizoaffective disorder.

History of early childhood deviance was obtained using a semi-structured questionnaire probing early deviant non-psychotic childhood behaviours (see Sobin et al., 2001, for a complete description). For approximately half of the subjects, the inquiry was conducted separately from the DIGS and by different interviewers who were blind to the results of the DIGS. For the other half, inquiry regarding childhood behaviors was completed before the diagnostic interview to prevent interviewer bias that might occur as a result of information obtained during the DIGS. The early childhood behavior questionnaire probed seven areas of possible deviance including social dysfunction (avoidance of other children, inability to have friends, isolated play), extreme odd behaviors (unprovoked screaming fits, disorganized or irrational behavior, inappropriate affect), unprovoked aggression, extreme anxiety, chronic sadness, attentional impairment and learning disabilities. Yes/no responses were recorded. In the case of a 'yes' response, examples were obtained and the interviewer determined whether the behavior reported was chronic or transient, whether there was a likely environmental trigger for the reported behavior (e.g. marital discord, parental abuse, death of a loved one), and whether the behavior began before age 10. Age 10 was used as a cut-off to exclude behaviors that might be attributable to pre-pubertal hormonal changes. Behaviors were considered present only if the behavior was both chronic and severe, if no environmental precipitant was present and if the behavior began before age 10. Learning disabilities and/or attentional impairment were considered present only if the child received a formal diagnosis, was provided with specific remediation, or if either of these were reported by teachers or school personnel or noted in records or school reports.

Data were entered and analyzed using Statview version 5.0 for PC and SAS version 6.1. *T*-tests for continuous variables and Fisher's exact tests for dichotomous variables were used to first determine possible associations between gender and the demographic, syndrome feature, and symptom history variables and to examine possible associations between early deviant variables. Logistic regression analyses were then used to determine the level of risk conferred for later disease outcomes by specific early deviant behaviors found to significantly differ in *t*-test and χ^2 analyses.

3. Results

The sample included a total of 218 patients with a lifetime history of either schizophrenia or schizoaffective disorder and for whom information regarding early deviant childhood behavior

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had been obtained. One hundred and nine participants were of Afrikaner descent, were unrelated at least up to the fifth degree, and included 78 males and 31 females. The remaining 109 were also unrelated and were age- and gender-matched to the Afrikaner sample, selected from our larger US database of schizophrenic patients. Preliminary to our main analyses, we compared the demographic, syndrome and symptom features of 109 Afrikaner participants included in these analyses with the remaining 59 probands for whom childhood information was not available to ensure that this subsample was in fact representative of the group as a whole.

Afrikaner participants with and without early childhood information did not differ with regard to current marital status, family history of schizophrenia, family history of psychiatric disorder not including schizophrenia, age of DSM schizophrenia/schizoaffective disorder onset, frequency of schizoaffective disorder, frequency of attempted suicide, or frequency of delusions, visual hallucinations, sensory hallucinations, thought disorder or alogia/flat affect. The subsamples differed with regard to three variables. The subsample with completed early deviant childhood behavior questionnaires had a higher frequency of left-handed participants (15.46% vs. 2.38%, χ^2=6.26, Fisher's exact *P*=0.039); a lower frequency of the auditory hallucinations (71.96 vs. 87.5%, χ^2=4.49, Fisher's exact *P*=0.040); and a lower frequency of the symptom disordered behavior (70.27% vs. 85.42%, χ^2=4.01, Fisher's exact *P*=0.048). We did not expect that the difference with regard to handedness would influence these findings. Differences with regard to the frequency of two isolated symptoms in the absence of differences on all of the remaining course and symptom variables suggested to us that the selected group of Afrikaner participants was largely representative of the entire sample recruited to date.

We compared the clinical profiles of the Afrikaner and US populations to determine their clinical similarity (Table 1). With regard to demographics, there were no differences between the samples in handedness, marital status, and family history of schizophrenia or family history of other psychiatric illness. The samples did differ with regard to the number of years of education achieved.

With regard to syndromal features, the Afrikaner population reported a later onset of DSM schizophrenia and a substantially lower rate of schizoaffective disorder and attempted suicide than in the US population. In terms of symptom history, the samples differed only with regard to lifetime history of thought disorder, which Afrikaner participants experienced at a substantially higher frequency than that reported by the US participants. Thus, the schizophrenia syndrome was found to be essentially equivalent in these two populations with greater heterogeneity indicated in the US sample by the substantially higher frequency of schizoaffective disorder.

In order to determine whether the same gender differences found among the US population also existed among the Afrikaner population, males and females were compared. If such differences were found, they would need to be statistically controlled in the subsequent analyses. Contrary to our predictions there were no differences between male and female Afrikaner patients on any of the demographic, syndromal feature or symptom variables assessed. (Among the US population, more males than females had never married, substantially more females than males reported a history of sensory hallucinations, and more males than females reported experiencing alogia/flat affect.)

Preliminary to the analysis of early childhood deviant behaviors and their association with later syndromal features, we compared the samples with regard to syndromal features alone. The difference between samples in the number of years of education obtained was attributable to the lower educational achievement of male rather than female Afrikaner participants. The differences between the Afrikaner and US males and not the females again accounted for the

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difference between samples with regard to age of syndrome onset. The frequency of reported schizoaffective illness was evident in both males and females, while only males differed significantly in the rates of attempted suicide, with substantially more US males than Afrikaner males attempting suicide. The frequency of sensory hallucinations reported by the US female participants was markedly higher than that reported by the Afrikaner females, but this difference was not significant when the populations were compared without regard to gender.

Table 2 compares the distribution of individual early deviant childhood behaviors in the two populations. Seventy-five (68.8%) Afrikaner participants reported experiencing one or more non-psychotic deviant behaviors beginning before 10 years of age. These included social withdrawal (*n*=16, 14.68%), odd behavior (*n*=12, 11.0%), extreme aggression (*n*=13, 11.9%), excessive fears (*n*=32, 29.4%), chronic sadness (*n*=12, 11.0%), attentional impairment (*n*=38, 34.9%), and learning disabilities (*n*=16, 14.7%). The populations were strikingly consistent in the number and type of early deviant behaviors endorsed. Our hypothesis regarding the similarity of these samples in the early deviant childhood behaviors reported was largely supported. The frequencies of any early deviant childhood behaviors and the distribution of the numbers of behaviors reported did not differ. An examination of the frequency of individual behaviors queried revealed that the Afrikaner participants reported a higher frequency of early extreme fears. In addition, the Afrikaner participants reported more attentional impairment.

In order to increase and balance cell sizes for statistical analyses, these seven behaviors were clustered into three logical categories. Variables reflecting socially abnormal behaviors, including social withdrawal, aggression against others, and socially odd behavior, were grouped (*n*=33, 30.3%); mood-based variables, including extreme anxiety and chronic sadness, were combined (*n*=38, 34.9%); and variables reflecting cognitive dysfunction, including attentional impairment and learning disability, were combined (*n*=43, 39.5%). There were no differences in the proportions of males and females reporting childhood behavior problems including poor socialization, extreme fears/chronic sadness, or attentional impairment/learning disability (Table 1). The differences in the frequency of early fears and attentional impairment were not evident once the behaviors were clustered.

In order to assess possible associations between early deviant childhood behaviors and later syndromal characteristics single order analyses were completed (Tables 3-5) for all variables listed. Early social withdrawal, aggression and/or odd behavior were not related to any later syndrome outcomes in either population. Early extreme fears/chronic sadness in the Afrikaner population was associated with an increased frequency of attempted suicide and also with a lower frequency of later alogia/flat affect. In the US population this form of early deviant behavior was associated with a higher frequency of schizoaffective illness and an increased frequency of sensory hallucinations. Early attentional/learning impairment in the Afrikaner population was associated with a lower level of academic achievement and an increased frequency of auditory hallucinations. Among the US patients, early attentional impairment/ learning disability was associated with lower academic achievement and an increased risk of later thought disorder. An unexpected finding was a lower frequency of family members with manifest schizophrenia among Afrikaner participants who reported early attentional and/or learning impairment. This will be discussed further below.

The results of these single-order association tests were used to determine which early deviant childhood behaviors might pose a significant risk for particular syndrome outcomes, and thus which variables to include in a logistic regression model. As suggested by the above analyses, early social withdrawal, aggression and/or odd behavior was not associated with an increased risk of any syndromal features in either subsample. Among the Afrikaner population, patients with extreme fears/chronic sadness in early childhood were nearly 3 times more likely to attempt suicide (weight coefficient=1.00; S.E.=0.45; $\chi^2_{d.f.=1}=3.32$; *P*=0.03; odds ratio=2.72;

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95% CI=1.12-6.60). Among the US population, patients with this type of early deviance were almost 3.5 times more likely to report lifetime symptoms consistent with a diagnosis of schizoaffective disorder (weight coefficient=1.21; S.E.=0.54; $\chi^2_{d.f.=1}=3.99$; $P=0.02$; odds ratio=3.36; 95% CI=1.18-9.58). In addition, these US patients were nearly 3 times more likely to experience sensory hallucinations (weight coefficient=1.00; S.E.=0.50; $\chi^2_{d.f.=1}=3.99$; $P=0.05$; odds ratio=2.73; 95% CI=1.02-7.33).

With regard to attentional impairment/learning disabilities before age 10, Afrikaner patients with this early cognitive impairment were 2.5 times more likely to experience later auditory hallucinations (weight coefficient=0.895; S.E.=0.47; $\chi^2_{d.f.=1}=3.62$; $P=0.05$; odds ratio=2.72; 95% CI=0.96-6.16). US patients with early attentional impairment/learning disabilities were nearly 3 times more likely to experience thought disorder (weight coefficient=1.01; S.E.=0.41; $\chi^2_{d.f.=1}=6.07$; $P=0.01$; odds ratio=2.76; 95% CI=1.23-6.17).

Similar to our previous findings, early deviant childhood behaviors occurred in approximately 70% of participants with schizophrenia/schizoaffective disorder, suggesting that these early behaviors distinguish a meaningful subgroup of patients. The frequency distribution and rates of these early problems were remarkably consistent across the two samples. In addition, specific early deviant childhood behaviors were statistically associated with later clinically similar disease characteristics. However, the associations of these early deviant behaviors to later syndromal features was different in the two samples. The possible source of these differences are considered in Section 4.

4. Discussion

We attempted to replicate our previous findings with regard to early deviant non-psychotic behaviors in an independently collected sample of adult patients meeting lifetime diagnostic criteria for DSM schizophrenia/schizoaffective disorder. The compared samples were matched by gender and age, and they were evaluated using identical instruments and methods. In order to determine the clinical comparability of the samples, we first compared their demographic, syndrome and symptom characteristics. The one demographic difference found was in the number of years of education obtained by Afrikaner males, who completed fewer years of education than the US patients. While this suggested an earlier and more severe disturbance of cognitive functioning than among the US patients, it was not reflected in an earlier age of syndrome onset among Afrikaner males. Just the opposite was true; age of syndrome onset for Afrikaner participants was later than that of the US participants. This seemingly contradictory finding in a more genetically homogeneous sample may suggest that the recognition of symptoms and formal diagnosis of disorders is delayed in the Afrikaner culture. Moreover, compulsory military service in South Africa may pre-empt the completion of advanced education following high school.

The difference in the frequency of suicide attemptors was striking, with the US sample double that of the Afrikaner population. In fact many of the patients in this study had access to or were housed in a long-term care facility that provided a protected environment for those with unremitting illness. Such facilities no longer exist in the US, regardless of need. These supervised living circumstances for the chronically ill in this study perhaps provided greater protection from suicide attempts.

Our analyses of early non-psychotic deviant behaviors broadly replicated our previous findings. The overall frequencies of behaviors and their distributions were strikingly consistent in the two samples, with 68.8% of Afrikaners compared to 67.0% of US participants reporting early deviance. With regard to the frequencies of individual early deviant behaviors reported,

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Afrikaners reported more early extreme fears and more attentional impairment, but the frequencies reported did not differ when individual symptoms were clustered. Moreover, early deviant behaviors in both populations were meaningfully linked to later disease outcome. However, the populations differed with regard to the specific associations found. Among Afrikaner participants, early extreme fears/chronic sadness were associated with an increased risk of later suicide attempts in the absence of schizoaffective disorder, suggesting greater severity of the schizophrenia symptoms manifested. Among US participants early, extreme fears/chronic sadness were associated with an increased risk of schizoaffective disorder, and not suicidality, as well as sensory hallucinations, suggesting greater clinical heterogeneity in the US sample. It is interesting to note that in the Afrikaner population, early extreme fears/chronic sadness were associated with a reduced frequency of later alogia/flat affect. We could speculate that in this population early emotional reactivity might represent a relatively stable trait that becomes beneficial in the course of later disorder. Also interesting to consider, though not possible to interpret on the basis of these data, is the finding among Afrikaner participants that early attention and learning problems were associated with later risk of auditory hallucinations—a severe symptom of schizophrenia related to a specific perceptual system (McGuire et al., 1995). Among US participants, this form of early deviance was associated only with thought disorder—a more cognitively diffuse form of intellectual impairment. Whether this reflects a concordance between genetic endowment (more vs. less homogeneous) and clinical syndrome manifestation awaits further investigation.

One seemingly contradictory finding was that early attentional/learning impairment was associated with a significantly decreased frequency of family members with manifest schizophrenia. In the original US sample, this form of early deviance was strongly associated with an increased frequency of family schizophrenia. (The overall rates of family history of schizophrenia did not differ in the two subsamples; Table 1.) In a genetically heterogeneous population, the association between early attentional/learning impairment and family history of schizophrenia broadly suggested that those with this form of early deviance might carry a more familial subtype. However, the absence of this association does not necessarily indicate the reverse.

It is important to note that the findings in this subsample of US patients differed in some regards from our previous full sample analyses (Sobin et al., 2001), which included a more balanced gender distribution (59% males as opposed to 72% males in the current study). In the original study, patients with a history of early social impairment were 2.5 times more likely to experience schizophrenia onset before age 17. In the US subsample examined for the purposes of this study, early social impairment was not significantly associated with age of onset in either the US or Afrikaner subsamples. However, differences were all in the expected direction and the absolute values closely approximated our original findings. In the first report, the (statistically significant) onset age difference in US patients with early social impairment was 1.76 years earlier. In this smaller subsample, the absolute difference was 1.59. In Afrikaner patients with early social impairment, onset of schizophrenia was 1.96 years earlier than, Afrikaner patients without this form of early deviance. Thus, in a larger sample with a more even gender distribution, the difference here reported would likely have reached statistical significance.

Also in our earlier report, patients with attentional/learning impairment were 2 times more likely to have 1°, 2° or 3° relatives with schizophrenia. In the subsample here considered, this difference was minimal. This is likely attributable to the reduced number of females in the matched subsample whose family history of schizophrenia was greater than that of the males in the original sample. (In all three groups—the original US sample, *N*=205; the Afrikaner subsample, *N*=109; and the US subsample, *N*=109—family history of schizophrenia among females was higher than that among males, though not substantially so.)

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A finding that was consistent across the full sample and the subsample of US patients but was not found in the Afrikaner subsample was the association between early extreme fears/chronic sadness and later sensory hallucinations. The substantially higher rate of sensory hallucinations among US participants accounted for by females, and not males, may suggest that this symptom is associated with more heterogeneous forms of schizophrenia.

To summarize, as suggested in previous reports (Done et al., 1994; Torrey et al., 1994; Offord and Cross, 1969), early childhood deviance in the subsamples here examined were reported by approximately 68% of patients who met lifetime criteria for schizophrenia/schizoaffective disorder, and thus differentiated a large but distinct subgroup of patients whose disorder may begin decades before the onset of full syndromal illness, as indicated by behaviors that are not included in the current nosology. These forms of early deviance are meaningfully linked to later logically related syndrome features, perhaps substantiating their validity as precursors of the full disease syndrome. Indeed, initial molecular findings support a genetic basis for this subtype (Liu et al., 2002). At the same time, the value and the significance of these symptoms appear to differ in these two populations. These differences may be related to the different genetic background of a given patient population. In our large heterogeneous US sample, these behaviors indicated earlier onset age and increased family history of schizophrenia (Sobin et al., 2001). In the more genetically homogeneous Afrikaner population, these behaviors seemed to indicate increased syndrome severity as suggested by the association with markedly increased risk of suicide, poor school achievement and increased auditory hallucinations. While the specific associations differed, they were all clinically consistent and meaningful. Early fears predicted later syndromal features associated with extreme mood disturbance (suicide or schizoaffective disorder), and early attentional/learning impairment was associated with increased risk of specific types of cognitive disturbance (auditory hallucinations or thought disorder).

4.1. Limitations

The participants in this study were all Euro-Caucasian, albeit of varying descents. While these analyses help extend our previous findings from the US to a cross-national population, the findings may not apply to other races. In order to maximize comparability and reduce confounding effects of age and gender on symptoms and early deviance behaviors reported, we matched the US patients to the Afrikaner patients by age and gender. However, in the Afrikaner sample, the genders were not equally represented. Unequal cell sizes (males 78, females 31) diminished the statistical likelihood of detecting differences between the genders. While we compared the genders in both the main (Afrikaner) and comparison (US) sample and found no differences among the Afrikaners and only symptom differences among the US participants, in samples with large balanced cell sizes, differences between the genders might be more readily identified and subsequently controlled. It is also important to note that matching in this manner altered some of the results obtained in our original study of 205 US patients where the distribution of males to females was more even (120 males, 85 females).

The participant-selection processes in these two samples differed. In the US population, a large majority of participants enrolled at the suggestion of an unaffected family member who had contacted the study recruiter for details regarding participation. In the Afrikaner population, the study enrollment was explained and offered by the treating physician. While one might expect that the method used in South Africa might have yielded a more severe patient population, the marked similarity in frequency of symptoms reported does not support this notion. Nonetheless, it is a potential limitation and deserves further consideration in future studies.

As in the previous study, the preponderance of information regarding early deviant childhood behaviors was obtained from the patients themselves and the validity of this approach can be

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questioned. In particular patients, current states may significantly influence their report of past experience, and thus this issue is most relevant to the finding of an association between early anxiety/chronic sadness and schizoaffective disorder, but may also apply to current perception of social relatedness and early childhood social difficulties. The current states of patients, who met lifetime criteria for schizoaffective disorder were not analyzed for the purposes of this study, but such analyses would be valuable in future studies. The striking similarity of findings in these two independently collected samples may provide support for this approach. Early records are likely to be superior to retrospective report for some of the behaviors queried, but only to the extent that teachers or school personnel recognized and had the opportunity to record information regarding a child's deviant behavior and/or school problems. It is likely that teachers and even parents would be unaware of the inner experiences of their children. We are currently in the process of comparing and contrasting parent and patient reports of early childhood deviance and later clinical outcome. These results should help to suggest which sources are likely to be most informative with regard to specific behavioral experiences.

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Table 1

Demographic and clinical characteristics of 109 Afrikaners and 109 age- and gender-matched US participants with a lifetime history of DSM schizophrenia or schizoaffective disorder

	Afrikaner population (*n*=109)		**US population (*n*=109)**		**Afrikaner males (*n*=78)**		**US males (*n*=78)**		**Afrikaner females (*n*=31)**		**US females (*n*=31)**	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Demographics												
Interview age	30.94	8.49	30.74	8.09	30.01	7.81	30.03	7.67	33.26	9.78	32.55	8.94
No. years education	**11.90**	**2.10**	**13.46**	**1.99****	**11.68**	**1.98**	**13.50**	**1.95****	12.45	2.29	13.36	2.14
	%	(*N*)	%	(*N*)	%	(*N*)	%	(*N*)	%	(*N*)	%	(*N*)
Left-handed	13.76	(15)	12.84	(14)	14.10	(11)	12.82	(10)	12.90	(4)	12.90	(4)
Single (never married)	79.82	(87)	85.32	(93)	83.33	(65)	*92.31*	(*72*)	70.97	(22)	*67.74*	(*21*)††
Fam hx/schiz	31.19	(34)	34.91	(37)	29.49	(23)	33.33	(25)	35.48	(11)	38.71	(12)
Fam hx/other psych dx	68.81	(75)	61.32	(65)	67.95	(53)	62.69	(42)	70.97	(22)	58.06	(18)
Syndrome features	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Age DSM schiz onset	**22.55**	**5.47**	**19.84**	**4.37****	**22.77**	**5.60**	**19.54**	**3.88****	22.00	5.16	20.58	5.42
	%	(*N*)	%	(*N*)	%	(*N*)	%	(*N*)	%	(*N*)	%	(*N*)
Schizoaffective	**24.77**	**(27)**	**48.62**	**(53)****	**24.36**	**(19)**	**46.15**	**(36)****	**25.81**	**(8)**	**54.84**	**(17)***
Attempted suicide	**27.52**	**(30)**	**50.46**	**(55)****	**25.64**	**(20)**	**48.72**	**(38)****	32.26	(10)	54.84	(17)
Symptom history	%	(*N*)	%	(*N*)	%	(*N*)	%	(*N*)	%	(*N*)	%	(*N*)
Delusions	98.17	(107)	95.28	(101)	97.44	(76)	92.31	(72)	100	(31)	93.55	(29)
Auditory hallucinations	70.64	(77)	64.76	(68)	70.51	(55)	57.69	(45)	70.97	(22)	74.19	(23)
Visual hallucinations	36.70	(40)	43.40	(46)	37.18	(29)	38.46	(30)	35.48	(11)	51.61	(16)
Sensory hallucinations	22.94	(25)	33.94	(37)	23.08	(18)	*26.92*	(*21*)	**22.58**	**(7)**	***51.61***	***(16)****†
Disordered behavior	69.72	(76)	65.14	(71)	70.51	(55)	65.38	(51)	67.74	(21)	64.52	(20)
Thought disorder	**77.06**	**(84)**	**50.46**	**(55)****	**78.20**	**(61)**	**48.72**	**(38)****	74.19	(23)	54.84	(17)
Alogia/flat affect	70.64	(77)	75.00	(81)	71.80	(56)	*80.77*	(*63*)	67.74	(21)	*58.06*	(*18*)†
Deviant childhood behav <age 10	%	(*N*)	%	(*N*)	%	(*N*)	%	(*N*)	%	(*N*)	%	(*N*)
Social withdrawal/aggression/odd behav	30.28	(33)	40.37	(44)	28.20	(22)	42.31	(33)	35.48	(11)	35.48	(11)
Extreme fears/chronic sadness	**34.86**	**(38)**	**20.18**	**(22)***	32.05	(25)	17.95	(14)	41.94	(13)	25.81	(8)
Attentional impairment/learning disability	39.45	(43)	37.62	(41)	41.03	(32)	39.74	(31)	35.48	(11)	32.26	(10)

Comparisons between Afrikaners and US participants are indicated in bold and:

*Fisher's exact test (two-tailed) *P*=0.05 or *t*-test *P*=0.05;

**Fisher's exact test (two-tailed) *P*=0.01 or *t*-test *P*=0.01. Comparisons between Afrikaner males and females or US males and females are indicated in italics and:

†Fisher's exact test (two-tailed) *P*=0.05 or *t*-test *P*=0.05;

††Fisher's exact test (two-tailed) *P*=0.01 or *t*-test *P*=0.01.

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Table 2

Distribution and frequency of individual early deviant behaviors

	Afrikaner population (*n*=109)		US population (*n*=109)	
	Freq.	**%**	**Freq.**	**%**
No. of deviant behaviors				
None	34	31.19	36	33.03
Any	75	68.81	73	66.97
1	39	52.00	36	43.32
2	19	25.33	25	34.25
3	11	14.67	12	16.44
4	1	1.33	0	0.00
5	5	6.67	0	0.00
Type of deviant behavior				
Social withdrawal	16	14.68	26	23.85
Extreme aggression	13	11.93	13	11.93
Odd behavior	12	11.01	13	11.93
Extreme fears	**32**	**29.36**	**12**	**11.01****
Chronic sadness	12	11.01	11	10.09
Learning disability	16	14.68	23	21.10
Attentional impairment	**38**	**34.86**	**24**	**22.02***

* Fisher's exact test (two-tailed) P=0.05.

** Fisher's exact test (two-tailed) P=0.01.

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Table 3

Single-order associations of social withdrawal/aggression/odd behavior and demographic, syndrome and symptom features

	Social withdrawal/aggression/odd behavior							
	Afrikaner probands (*N*=109)				**US probands (*N*=109)**			
	No (*n*=76)		**Yes (*n*=33)**		**No (*n*=65)**		**Yes (*n*=44)**	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Demographics								
Age at interview	31.50	8.58	29.64	8.28	31.34	8.20	29.86	7.94
No. of years of education	11.84	2.07	12.03	2.20	13.66	1.98	13.16	2.00
	%	(*N*)	%	(*N*)	%	(*N*)	%	(*N*)
% Female	26.32	(20)	33.33	(11)	30.77	(20)	25.00	(11)
Single (never married)	77.63	(59)	84.85	(28)	80.00	(52)	93.18	(41)
Left-handed	11.84	(9)	18.18	(6)	10.77	(7)	15.91	(7)
	(*n*=76)		(*n*=33)		(*n*=69)		(*n*=37)	
Family hx of schizophrenia	30.26	(23)	33.33	(11)	33.33	(21)	37.21	(16)
Family hx of other psychia dx	65.79	(50)	75.76	(25)	61.90	(39)	60.46	(26)
Syndrome features	(*n*=76)		(*n*=33)		(*n*=65)		(*n*=44)	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Schizophrenia onset age	23.14	5.59	21.18	5.00	20.46	4.01	18.87	4.76
	%	(*N*)	%	(*N*)	%	(*N*)	%	(*N*)
Attempted suicide	26.32	(20)	30.30	(10)	55.38	(36)	43.18	(19)
Schizoaffective	25.00	(19)	24.24	(8)	47.69	(31)	50.00	(22)
Symptom history								
Delusions	97.37	(74)	100	(33)	**96.92**	**(63)**	**86.36**	**(38)** *
Auditory hallucinations	68.42	(52)	75.76	(25)	60.00	(39)	65.91	(29)
Visual hallucinations	32.90	(25)	45.46	(15)	40.00	(26)	45.46	(20)
Sensory hallucinations	22.37	(17)	24.24	(8)	35.38	(23)	31.82	(14)
Disordered behavior	68.42	(52)	72.73	(24)	70.77	(46)	56.82	(25)
Thought disorder	77.63	(59)	75.76	(25)	44.62	(29)	59.09	(26)
Alogia/flat affect	67.10	(51)	78.79	(26)	73.85	(48)	75.00	(33)

* Fisher's exact test (2-tailed) *P*=0.05 or *t*-test *P*=0.05.

** Fisher's exact test (2-tailed) *P*=0.01 or *t*-test *P*=0.01.

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Table 4

Single-order associations of extreme fears/chronic sadness and demographic, syndrome and symptom features

	Extreme fears/chronic sadness							
	Afrikaner probands (*N*=109)				**US probands (*N*=109)**			
	No (*n*=71)		**Yes (*n*=38)**		**No (*n*=87)**		**Yes (*n*=22)**	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Demographics								
Age at interview	31.61	8.20	29.68	9.00	30.66	7.99	31.09	8.65
No. of years of education	12.10	2.37	11.53	1.45	13.48	2.14	13.36	1.26
	%	(*N*)	%	(*N*)	%	(*N*)	%	(*N*)
% Female	25.35	(18)	34.21	(13)	26.44	(23)	36.36	(8)
Single (never married)	76.06	(54)	86.84	(33)	83.91	(73)	90.91	(20)
Left-handed	84.51	(60)	89.47	(34)	10.34	(9)	22.73	(5)
	(*n*=71)		(*n*=38)		(*n*=69)		(*n*=37)	
Family hx of schizophrenia	30.99	(22)	31.58	(12)	35.71	(30)	31.82	(7)
Family hx of other Psychia dx	70.42	(50)	65.79	(25)	57.14	(48)	77.27	(17)
Syndrome features	(*n*=71)		(*n*=38)		(*n*=87)		(*n*=22)	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Schizophrenia onset age	23.01	5.41	21.68	5.54	19.92	4.43	19.46	4.22
	%	(*N*)	%	(*N*)	%	(*N*)	%	(*N*)
Attempted suicide	**19.72**	**(14)**	**42.10**	**(16)***	50.58	(44)	50.00	(11)
Schizoaffective	25.35	(18)	23.68	(9)	**42.53**	**(37)**	**72.73**	**(16)****
Symptom history								
Delusions	97.18	(69)	100	(38)	93.10	(81)	90.91	(20)
Auditory hallucinations	71.83	(51)	68.42	(26)	63.22	(55)	59.09	(13)
Visual hallucinations	39.48	(28)	31.58	(12)	37.93	(33)	59.09	(13)
Sensory hallucinations	21.13	(15)	26.32	(10)	**28.74**	**(25)**	**54.54**	**(12)***
Disordered behavior	69.01	(49)	71.05	(27)	68.97	(60)	50.00	(11)
Thought disorder	73.24	(52)	84.21	(32)	51.72	(45)	45.46	(10)
Alogia/flat affect	**77.46**	**(55)**	**57.90**	**(22)***	71.26	(62)	86.36	(19)

* Fisher's exact test (2-tailed) *P*=0.05 or *t*-test *P*=0.05.

** Fisher's exact test (2-tailed) *P*=0.01 or *t*-test *P*=0.01.

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Table 5

Single-order associations of attentional/learning impairment and demographic, syndrome and symptom features

	Attentional impairment/learning disability							
	Afrikaner probands (*N*=109)				**US probands (*N*=109)**			
	No (*n*=66)		**Yes (*n*=43)**		**No (*n*=68)**		**Yes (*n*=41)**	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Demographics								
Age at interview	30.88	8.81	31.02	8.09	31.07	8.25	30.20	7.89
No. of years of education	**12.23**	**2.22**	**11.40**	**1.83***	**13.75**	**1.96**	**12.98**	**1.97***
	%	(*N*)	%	(*N*)	%	(*N*)	%	(*N*)
% Female	30.30	(20)	25.58	(11)	30.88	(21)	24.39	(10)
Single (never married)	80.30	(53)	79.07	(34)	82.35	(56)	90.24	(37)
Left-handed	12.12	(8)	16.28	(7)	10.29	(7)	17.07	(7)
	(*n*=66)		(*n*=43)		(*n*=69)		(*n*=37)	
Family hx of schizophrenia	**39.39**	**(26)**	**18.60**	**(8)***	34.85	(23)	35.00	(14)
Family hx of other psychia dx	71.21	(47)	65.12	(28)	63.64	(42)	57.50	(23)
Syndrome features	(*n*=66)		(*n*=43)		(*n*=68)		(*n*=41)	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Schizophrenia onset age	23.09	5.70	21.72	5.05	20.02	4.70	19.51	3.82
	%	(*N*)	%	(*N*)	%	(*N*)	%	(*N*)
Attempted suicide	25.76	(17)	30.23	(13)	54.41	(37)	43.90	(18)
Schizoaffective	22.73	(15)	27.91	(12)	50.00	(34)	46.34	(19)
Symptom history								
Delusions	98.48	(65)	97.67	(42)	95.59	(65)	87.80	(36)
Auditory hallucinations	**63.64**	**(42)**	**81.40**	**(35)***	57.35	(39)	70.73	(29)
Visual hallucinations	40.91	(27)	30.23	(13)	36.77	(25)	51.22	(21)
Sensory hallucinations	27.27	(18)	16.28	(7)	32.35	(22)	36.58	(15)
Disordered behavior	72.73	(48)	65.12	(28)	61.76	(42)	70.73	(29)
Thought disorder	78.79	(52)	74.42	(32)	**41.18**	**(28)**	**65.85**	**(27)****
Alogia/flat affect	68.18	(45)	74.42	(32)	76.47	(52)	70.73	(29)

* Fisher's exact test (2-tailed) *P*=0.05 or *t*-test *P*=0.05.

** Fisher's exact test (2-tailed) *P*=0.01 or *t*-test *P*=0.01.

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