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Early non-psychotic deviant behaviour as an endophenotypic marker in bipolar disorder, schizo-affective disorder and schizophrenia

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ABSTRACT
Objective: To determine and compare the incidence of early non-psychotic deviant behaviour (i.e. under the age of ten) in Afrikaner patients with bipolar disorder, schizo-affective disorder and schizophrenia. **Methods:** Patients with bipolar disorder, schizo-affective disorder and schizophrenia were interviewed using a structured questionnaire probing for early deviant childhood behaviour starting before the age of 10 years. Information from close family members was also obtained where possible. Seven areas of possible deviance were probed into: social dysfunction, unprovoked aggression, extreme anxiety, chronic sadness, extreme odd behaviours, attention impairment and learning difficulties. Demographic data included: age, marital status, gender, and years of formal education. The following clinical features were also recorded: age of onset of illness and suicide attempts. **Results:** A total of 74 patients diagnosed with bipolar disorder, 43 patients diagnosed with schizo-affective disorder and 80 patients diagnosed with schizophrenia were interviewed. Early deviant behaviour was statistically more prevalent in schizophrenia (65%) and schizo-affective disorder (60,5%), than in the bipolar group (21,6%). Deviant childhood behaviour was grouped into 3 clusters: social functioning impairment cluster (social isolation, aggression, extreme odd behavior), mood/anxiety cluster (extreme fears, chronic sadness) and a cognitive impairment cluster (attention impairment, learning disability). Bipolar patients showed significantly less social functioning and cognitive impairment compared to patients with schizo-affective disorder and schizophrenia. **Conclusion:** Our findings suggest that early deviant behaviour may be a possible endophenotypic marker in schizophrenia and schizo-affective disorder.

Keywords: Early non-psychotic deviant behaviour, Endophenotype, Bipolar disorder, Schizo-affective disorder, Schizophrenia

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Introduction

Schizophrenia genetic research has advanced greatly with the new tools that are currently available in molecular genetics. Gene identification, however, remains a task of extraordinary difficulty in part because of the heterogenous and imprecise definition of the clinical phenotype. A great deal of heterogeneity exists among the symptoms of individuals sharing a common clinical diagnosis, and many are not readily classifiable using standard criteria. Refinement of phenotypes by using endophenotypes should be extremely valuable and should increase the chances of discovering mechanisms of inheritance as well as susceptible genes. Endophenotypes provide a means for identifying the "downstream" traits or facets of clinical phenotypes, as well as the "upstream" consequences of genes. The endophenotype could mark the path between the

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genotype and the behavior of interest, in this case schizophrenia.[1]

Early deviant patterns of behaviour in children who go on to develop schizophrenia have been consistently reported in high-risk, prospective and retrospective behavioural studies of schizophrenia.[2] These aberrant behaviours could constitute valid endophenotypes for the disease indicating early neurodevelopmental abnormalities.

Founder populations, such as the Afrikaner population (Appendix 1), hold tremendous promise for mapping genes for complex traits, as they offer less genetic and environmental heterogeneity and greater potential for genealogical research.[3]

A previous comparison study examined the demographic, syndrome course, symptom and early deviant behavior history of 109 Afrikaner probands who met criteria for DSM schizophrenia and schizo-affective disorder, and compared them to 109 age- and gender-matched US probands. Approximately two thirds of both the Afrikaner probands (68%) and the US probands (67%) reported one or more forms of early non-psychotic deviance, including poor socialization, extreme fears/ chronic sadness, and/or attention/learning impairment.[2] The question was asked whether this early deviant behaviour was unique to subjects diagnosed with schizophrenia or schizo-affective disorder or if it also occurred in bipolar disorder subjects.

There have been several studies investigating premorbid intellectual and social functioning in bipolar, schizo-affective and schizophrenia patients. However, the majority of these studies have included the adolescent period in their assessment of premorbid functioning. None of the studies specified deviant behaviour occurring under the age of ten.

One comparison study of schizophrenia (N=536) , schizo-affective disorder (N=31) and non-psychotic bipolar disorder (N=68), demonstrated that impaired premorbid intellectual, language, and behavioural functioning were specific to future schizophrenia patients compared to future non-psychotic bipolar disorders.[4] In a large longitudinal population-based study of 50 087 male subjects over 27 years, lower premorbid IQ score was associated with increased risk for schizophrenia, severe depression, and other non-affective psychoses, but not for bipolar disorder. This finding indicated that at least some aspects of the neurodevelopmental etiology of bipolar disorder may differ from the other disorders that were investigated.[5]

Our aim with this study was to determine and compare the incidence of early non-psychotic deviant behaviour (i.e. under the age of ten) in Afrikaner patients with bipolar disorder, schizo-affective disorder and schizophrenia. We hypothesized that the prevalence of early non-psychotic deviant behaviour was less prevalent in bipolar patients when compared to schizophrenia and schizo-affective disorder patients.

Methods

Approval for conducting this study was obtained from the Research Ethics Committee of the Faculty of Health Sciences of the University of Pretoria and from the Research Ethics Committee of 1-Military Hospital, Thaba Thswane. Afrikaner patients with schizophrenia or schizo-affective disorder who had multiple affected (two or more) family members had been recruited previously for an ongoing genetic project being conducted collaboratively by the Department of Psychiatry,University of Pretoria and the Laboratory for Human Genetics, Rockefeller University. These subjects were randomly recruited via the outpatient and inpatient departments of Weskoppies Hospital, Pretoria and interviewed using the Diagnostic Interview for Genetic Studies (DIGS) Modified for Genetics in Mental Function Initiative Laboratory of Neurogenetics Rockefeller University by two senior psychiatrists with more than 20 years clinical experience each. Afrikaner bipolar patients were also recruited randomly from the outpatient and inpatients departments of Weskoppies Hospital, Pretoria, as well as from the outpatient and inpatient departments of 1-Military Hospital, Thaba Thswane. The interviewers of the bipolar disorder patients were two registrars in Psychiatry who were supervised by one of the senior clinicians mentioned before. All clinicians are staff members of the Department of Psychiatry at the University of Pretoria.

All of the subjects had been diagnosed formally under supervision of an experienced consultant psychiatrist using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV). Their history, collateral history, clinical findings and diagnosis were recorded in their clinical files.

The criteria used for being an Afrikaner were : Afrikaans language, typical Afrikaans surnames of both parents and grandparents on the paternal and maternal side, and geneaological tracings by a geneaologist.[3]

Written informed consent was obtained from all patients taking part in the study. All participants were interviewed using a semi-structured questionnaire probing for early deviant childhood behavior beginning before the age of ten (Appendix 2). The age of ten was used as a cut-off to exclude behaviors that might be attributable to pre-pubertal hormonal changes.[2] Where possible, additional information was obtained from close family members with permission of the participants.

Regarding the mental state at the time of interview, all patients were stable and apsychotic during the interview and were, according to the judgement of the interviewer, a reliable source of relevant information at that time.

The early deviant behaviour questionnaire probed seven areas of possible deviance, including social isolation (avoidance of other children, inability to have friends, isolated play), unprovoked aggression, extreme anxiety, chronic sadness, extreme odd behaviours (unprovoked screaming fits, disorganized or irrational behaviour, inappropriate affect), attention 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 reported behaviour was a permanent feature or transient, and whether there was a likely environmental trigger for the reported behaviour (e.g. marital discord,

parental abuse or death of a loved one). Behaviours were considered present only if the behaviour was both of a more permanent nature and severe. If an environmental precipitant or other social circumstances could explain the deviant behaviour, it was coded as absent. The deviant behaviour had to be present before ten years of age. Learning disabilities and/or attention 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 noted in school reports.

Demographic data (age at interview, marital status, gender, number of years of education) and certain clinical features (age of onset of illness, suicide attempts) were recorded for every participant. Suicide attempts were only recorded as present or not present and were not quantified.

Data was entered and analyzed using the statistical program Stata (Release 8.0). Sociodemographic data and syndrome features were compared between the three diagnostic groups : bipolar disorder, schizo-affective disorder and schizophrenia. Continuous variables (age, age of onset of illness and years of education) were compared using a one way analysis of variance. Categorical variables (gender, marital status and suicide attempts) were compared using chi squared tests for contingency tables. Suicide attempts were explored further using the logistic regression model adjusting for age and gender, and the schizo-affective group were used as the baseline reference group.

Behaviours were compared between the three groups using chi squared tests. The 7 types of deviant behaviour were joined into three clinically logical clusters: social functioning impairment cluster (included social isolation, aggression and extreme odd behaviour); mood/anxiety cluster (included extreme fears and chronic sadness); and cognitive impairment cluster (included attention impairment and learning disability). The number of deviant behaviours exhibited in each cluster was compared between the 3 groups using chi squared tests. The relationship of the number of deviant behaviours to disease type was further investigated using ordinal logistic regression models which could also adjust for the effects of age and gender.

Results

The patient groups participating in this study were : patients with bipolar disorder (n=74); patients with schizo-affective disorder (n=43); and patients with schizophrenia (n=80).

Sociodemographic characteristics

The average age at the time of the interview was 44,5 years for the bipolar group, markedly higher than the age of 33,7 years for the schizo-affective group and 31,3 years for the schizophrenia group. The results of marital status were as follows : In the bipolar group 27% of patients were divorced, 43,2 % were married, 24,3% were single and 5,4 % were widowed. In the schizo-affective group 23,3% of patients were divorced, only 16,3% were married, 55,8% were single and 4,6% were widowed. In the schizophrenia group 15% of patients were divorced, only 8,7% were married, 75% were single and 1,3% were widowed. The gender distribution in the bipolar group was 51,3 % male versus 48,6 % female, in the schizo-affective group 58,1 % male and 41,9 % female, while in the schizophrenia group 70% were males and 30% females. The bipolar group had on average 13,5 years of education, the schizo-affective group 12,2 years of education, and the schizophrenia group 11,5 years of education (Table I).

Clinical features

The average age of onset of illness was 28,4 years for the bipolar group, 23,5 years for the schizo-affective group and 22,9 years for the schizophrenia group. Suicide attempts occurred in 47,3 % of bipolar patients, 27,9 % of schizo-affective disorder patients and 12,5 % of schizophrenia patients. When the schizo-affective group was used as a reference group, it was found that the bipolar patients were about 3 times more likely to have attempted suicide than the schizo-affective group. The

Table I: Demographic characteristics of patients with Bipolar disorder, Schizo-affective disorder and Schizophrenia.

Characteristic		*Group*			
		Bipolar disorder n=74	*Schizo-affective disorder n=43*	*Schizophrenia n=80*	*(P-value)*
Age at interview (years)	Mean S.D.	44.5 13.6	33.7 12.1	31.3 11.4	F=22.9 P<0.001
Marital status n (%)	Divorced Married Single Widowed	20 (27%) 32 (43.2%) 18 (24.3%) 4 (5.4%)	10 (23.3%) 7 (16.3%) 24 (55.8%) 2 (4.6%)	12 (15%) 7 (8.7%) 60 (75%) 1 (1.3%)	x2=44.8 P<0.001
Gender n (%)	Male Female	38 (51.3%) 36 (48.6%)	25 (58.1%) 18 (41.9%)	56 (70%) 24 (30%)	x2=5.7 P=0.058
Numbers of years of education	Mean S.D	13.5 2.6	12.2 2.5	11.5 2.8	F=11.14 P<0.001

Table II: Clinical features and early deviant childhood behaviour of patients with Bipolar disorder, Schizo-affective disorder and Schizophrenia

Clinical Features		*Group*			
		Bipolar disorder n=74	*Schizo-affective disorder n=43*	*Schizophrenia n=80*	*P-value*
Selected clinical features					
Age of onset of illness	Mean S.D.	28.4 14.3	23.5 6.3	22.9 7.6	F=5.97 P=0.003
Suicide attempts	No attempts Attempts	39 (52.7%) 35 (47.3%)	31 (72%) 12 (27.9%)	70 (87.5%) 10 (12.5%)	x2=22.7 P<0.001

Table III: Clusters of deviant childhood behaviour < age 10

Clinical Features		*Group*			
		Bipolar disorder n=74	*Schizo-affective disorder n=43*	*Schizophrenia n=80*	*P-value*
One or more deviant behaviour	n(%) P<0.001	16 (21.6%)	26 (60.5%)	52 (65%)	x2=32.6
Social functioning impairment cluster (Social withdrawal/ aggression/ odd behaviour)	n(%) P<0.001	6 (8.1%)	14 (32.6%)	31 (38.7%)	x2=20.1
Mood/Anxiety cluster (Extreme fears/ chronic sadness)	n(%) P=0.195	8 (10.8%)	10 (23.3%)	12 (15%)	x2=3.3
Cognitive impairment cluster (Attention impairment/ learning disability)	n(%) P<0.001	12 (16.2%)	20 (46.5%)	41 (51.2%)	x2=22.3

schizophrenia group was less likely to have attempted suicide than the schizo-affective group (Table II).

One or more forms of deviant behaviour were present in 21,6 % of the bipolar group, 60,5 % of the schizo-affective group and 65 % of the schizophrenia group (Table III, Figure 1).

Specifically, the distribution of the 7 different categories of deviant behaviour that we probed for was as follows (Table IV) : Social isolation: 6,8 % in the bipolar

Figure 1: The frequency of deviant behaviour in bipolar disorder, schizo-affective disorder and schizophrenia patients.

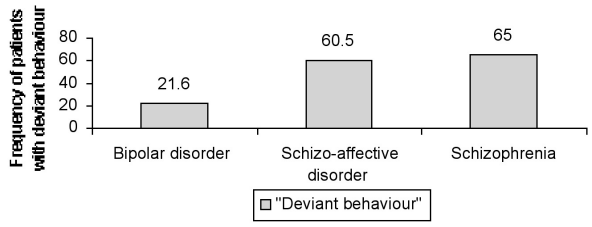

Table IV: Distribution and frequency of individual early deviant behaviours

	Bipolar disorder (n=74)		*Schizo-affective disorder (n=43)*		*Schizophrenia (n=80)*	
	Freq.	*%*	*Freq.*	*%*	*Freq.*	*%*
Type of deviant behaviour						
Social isolation	5	6.8	7	16.3	16	20
Extreme agression	3	4	2	4.6	10	12.5
Odd behaviour	1	1.3	6	13.9	16	20
Extreme fears	7	9.5	7	16.3	7	8.7
Chronic sadness	3	4	8	18.6	6	7.5
Learning disability	4	5.4	17	39.5	24	30
Attention impairment	11	14.9	17	39.5	37	46.2

group, 16,3 % in the schizo-affective group and 20 % in the schizophrenia group; Aggression: 4 % in the bipolar group, 4,6 % in the schizo-affective group and 12,5 % in the schizophrenia group; Extreme odd behaviour: 1,3 % in the bipolar group, 13,9 % in the schizo-affective group and 20 % in the schizophrenia group; Extreme fears: 9,5 % in the bipolar group, 16,3 % in the schizo-affective group and 8,7 % in the schizophrenia group; Chronic sadness: 4 % in the bipolar group, 18,6 % in the schizo-affective group and 7,5 % in the schizophrenia group; Learning disability: 5,4 % in the bipolar group, 39,5 % in the schizo-affective group and 30 % in the schizophrenia group; Attention impairment: 14,9 % in the bipolar group, 39,5 % in the schizo-affective group and 46,2 % in the schizophrenia group.

The 7 domains of early deviant behaviour were then grouped into 3 clusters, namely social functioning impairment cluster, mood/anxiety cluster and cognitive impairment cluster. The social functioning impairment cluster included social isolation, aggression and extreme odd behavior. The mood/anxiety cluster included extreme fears and chronic sadness, while the cognitive impairment cluster combined attention impairment and learning disability. While in the bipolar group 8,1 % showed social functioning impairment, in the schizo-affective group this figure was 32,6 % and in the schizophrenia group it was 38,7 %. Mood and anxiety problems were present in 10,8 % of the bipolar group, in 23,3 % of the schizo-affective group and in 15 % of the schizophrenia group. Cognitive dysfunction was reported in 16,2 % of bipolar patients, but in 46,5 % of schizo-affective patients and 51,2 % of schizophrenia patients.

Discussion

Our study comparing 7 domains of early deviant behaviour before the age of ten across 3 different diagnostic entities produced results which strongly support the possible use of early deviant behaviour as an endophenotypic marker in schizophrenia/schizo-affective disorder. The frequency of these behaviours in 65 % of schizophrenic patients and 60 % of schizo-affective patients is statistically significantly higher than the frequency of 21% found in bipolar patients. This result supports our hypothesis that early non-psychotic deviant behaviour is specific to schizophrenia and schizo-affective disorder and therefore may be a valid and useful endophenotype for genetic studies of these disorders. Of note are the findings that bipolar patients were much less likely to show social functioning impairment and also much less likely to show cognitive impairment than the other two diagnostic groups. As mentioned earlier, there have been several previous studies that compared childhood/premorbid intellectual and social functioning in bipolar, schizo-affective and schizophrenia patients. However, none of these studies had excluded the adolescent period. Our study specifically probed for early deviant behaviour occurring before the age of ten across 3 diagnostic groups. Our findings are nevertheless in line with those of some previous studies with regard to childhood premorbid intellectual and behavioral functioning: One study, comparing subjects with schizophrenia (N=536), schizo-affective disorder (N=31) and non-psychotic bipolar disorder (N=68) demonstrated that impaired intellectual, language, and behavioral functioning were specific to future schizophrenia patients relative to future non-psychotic bipolar patients.[4] In a large longitudinal study of 50 087 male subjects, lower premorbid IQ score was associated with increased risk for schizophrenia, severe depression, and other non-affective psychoses, but not bipolar disorder.[5]

Data regarding a history of psychosis was not collected at the initial interview. In retrospect however, psychosis is an important part of the history in the context of this study, since the argument could be built that early deviant behaviour may be related to psychosis per se and not necessarily to schizophrenia or schizo-affective disorder. Going back to the clinical files, we were only able to obtain data about psychosis in 61 of the 74 bipolar disorder subjects who participated in the study. Of these 61 subjects, 39 (63,9%) suffered from bipolar I disorder and 22 (36,0 %) from bipolar II disorder. Of these bipolar subjects (n=61), 22 subjects (36,0%) had a history of psychosis. These 22 subjects with a history of psychosis all suffered from bipolar I disorder and they comprised 56,4% of the bipolar I subjects. With just over one third of bipolar patients having had a history of psychosis, one could argue that the higher prevalence of early non-psychotic deviance found in schizophrenia and schizo-affective disorder, may be related to psychosis per se, and not to the disorders themselves. Future comparison studies with larger samples of bipolar patients, using only bipolar I patients with histories of psychosis, will be needed to clarify this issue.

Our analysis of the demographics of the three patient groups revealed some noteworthy differences. Patients with bipolar disorder were significantly older (more than 10 years) at the time of interview compared to those in the other two groups. This finding may be a reflection of the later onset of illness found in the bipolar group. Three quarters of our schizophrenia patients had remained unmarried during their lifetime, possibly reflecting the devastating effect of schizophrenia on social functioning.

The number of years of education was significantly higher in bipolar than in schizophrenia and schizo-affective patients. Bipolar patients had on average completed approximately one and a half years tertiary education and schizo-affective patients on average less than three months tertiary education. It is, however, important to note that the average schizophrenia patient had not completed grade 12 at school, reflecting schizophrenia's adverse impact on school performance. This finding supports those of previous studies. Patients with schizophrenia have been shown to have poor school adjustment, even when differences in premorbid IQ are taken into account.[6] Bipolar patients, on the other hand, have demonstrated relative preservation of premorbid school functioning despite deterioration of social functioning in adolescence[6], and significantly better academic performance than schizophrenia patients in the

premorbid period.[7]

The only two clinical features that we investigated were age of onset of illness and the presence or absence of suicide attempts. Our findings suggest that bipolar disorder tends to have its onset at a significantly later age than schizophrenia and schizo-affective disorder. Although this study was based mostly on subjective reporting by the patients themselves, their estimate of the age of onset of illness might still give us an indication of when their symptoms started, or at least at what age their symptoms started to have a significant impact on their lives.

Suicide attempts was significantly more frequent in the bipolar group (47,3%) compared to the schizo-affective group (27,9%) and the schizophrenia group (12,5%). Bipolar subjects were at least three times more likely to attempt suicide than schizophrenia or schizo-affective subjects. These findings are slightly inconsistent with those of a previous comparison study which showed that suicide attempts occurred in 28% of bipolar patients, 42,8% of schizo-affective patients and 27,3% of schizophrenia patients.[8]

Previous studies estimated that 25-50 % of patients with bipolar disorder attempt suicide during their lifetimes.[9] The bipolar subjects in our study fell near the upper end of this range.

Limitations

It could be argued that the higher prevalence of early non-psychotic deviance found in schizophrenia and schizo-affective disorder may be related to psychosis per se, and not the disorders themselves. We did not collect this data at interview. As explained earlier, we suggest that future studies have larger samples of bipolar subjects, all of them with a history of psychosis.

Information regarding early deviant behavior was obtained from the patients themselves. The validity of this method may be questioned. The current mental state of the patients may have influenced the accuracy of their accounts of their early lives. Early school records and interviews with close family members are likely to have improved the accuracy and reliability of information. However, school records were unavailable in the vast majority of cases, and parents and other close family members were seldom available for interviews, especially in the older patients. One can also argue that teachers and even parents were not necessarily aware of the inner experiences of the children, and that subjective accounts of behaviors may be as accurate as objective accounts.

The average age at interview was more than ten years higher in the bipolar group compared to the schizophrenia and schizo-affective groups. One can only speculate about the influence of this difference on our results. One might expect that older patients would have a poorer recall of the details of their early life, but this would be difficult to verify.

Sample sizes were relatively small and we would suggest larger samples for future studies.

The study was limited to one ethnic group and the generalizability of the results is unknown. However, the schizophrenic and schizo-affective patients from this study have been previously compared with schizophrenic and schizo-affective patients from another ethnic group (US) with remarkably similar results.[2]

Our study investigated early deviant behaviour in three major mental illnesses only, namely bipolar disorder, schizo-affective disorder and schizophrenia. Similar comparison studies which include other mental disorders, as well as a control group of healthy subjects, are suggested.

Conclusion

This comparison study supported our hypothesis that early non-psychotic deviant behaviour was less prevalent in bipolar disorder patients when compared to schizophrenia and schizo-affective disorder patients. Early non-psychotic deviant behavior may therefore be a possible endophenotypic marker in schizophrenia and schizo-affective disorder. Furthermore, bipolar patients had significantly less impairment in social and cognitive functioning compared to schizophrenia and schizo-affective patients. In the interpretation of our demographic data, we found bipolar patients to be much older at the time of interview, a finding which may represent the later onset of illness also found in bipolar patients in this study. The high prevalence of unmarried subjects in schizophrenia emphasized the devastating effect of schizophrenia on social functioning. The adverse effect of schizophrenia relative to schizo-affective disorder and bipolar disorder on school functioning was also reflected in our results, with the average schizophrenia patient having never completed school. Bipolar patients in our study were significantly likelier to attempt suicide in their lifetimes than those with schizophrenia and schizo-affective disorder. We suggest that future studies have larger sample sizes, include other mental disorders and healthy control groups, and make use of school records and family interviews in addition to subjective patient reports.

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APPENDIX 1 :

Definition of an Afrikaner as used in the study : Early non-psychotic deviant behavior as an endophenotypic marker in bipolar disorder, schizo-affective disorder and schizophrenia.
The Afrikaner population owe their origin to the first European Settlement led by the Dutchman Jan van Riebeeck in 1652. These people were servants of the Dutch East India Company and were Protestants. Afrikaners also originate from settlers who arrived in later years : nine free burghers of Dutch and German origins in 1657 (pioneer farmers of which only two remained) and less than 200 French Huguenots who arrived during the years from 1688 to 1689.
The language spoken by this group is Afrikaans. The slow emergence of Afrikaans as a cultural language developed late in the 19th century. Afrikaner terminology was used for the first time in the 17th century to differentiate between children who, born from parents of European origin, were born in Africa as opposed to those who were born in Europe.
Lists are available of the most important Dutch, German and immigrant surnames from other countries. Important French Huguenot surnames are also listed.

Probands in our study met the following criteria for an Afrikaner :
1. Afrikaans language
2. Typical surnames of both parents and grandparents (paternal and maternal)
3. Genealogical tracings by a geneaologist.[1]

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APPENDIX 2: Questionnaire used to probe for early non-psychotic deviant behavior:

1. How did you get along with other children? Did you have friends? Did you enjoy playing with other children? (IF SUBJECT INDICATES ISOLATION OR PROBLEMS). What problems did you have? When (at what age) did these difficulties begin?
2. Did you have a lot of fears before the age of 10? Do you think you had more fears than other children? (IF YES) Why do you say that? What were you afraid of? (IF FEARS ARE REPORTED) When (at what age) did these fears begin?
3. Did you have any problems with attention or daydreaming before the age of 10? (IF YES) Could you describe the problems? Did anyone else notice and comment on this? Did you have problems in school because of attention? When (at what age) did you or others notice the problems?
4. As a child before age 10, were you ever diagnosed with a learning disability or did you have trouble completing schoolwork? (IF YES) What kind of problems did you have e.g. reading delay, speech impediment, and poor concentration? Were you ever placed in a special class or were you ever given special tutoring to help with your schoolwork? (IF YES) Could you describe the kind of help you received? When (at what age) did these problems begin?
5. Were you aggressive as a child, compared to others? (IF YES) Did you have any problems related to this? Could you describe the problems to me? Did anyone ever comment on this? (IF YES) When (at what age) did these problems begin?
6. Did you ever go through periods of extreme sadness? (IF YES) More so than other children? Could you describe this? When (at what age) did this begin?
7. As a child before age 10, did you do things that you or others thought were odd or unusual? (IF YES) What were they? When (at what age) did this begin?