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# Avoidant personality disorder is a separable schizophrenia-spectrum personality disorder even when controlling for the presence of paranoid and schizotypal personality disorders ☆
## The UCLA family study

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## Abstract

It is unresolved whether avoidant personality disorder (APD) is an independent schizophrenia (Sz)-spectrum personality disorder (PD). Some studies find APD and social anxiety symptoms (Sxs) to be separable dimensions of psychopathology in relatives (Rels) of schizophrenics while other studies find avoidant Sxs to be correlated with schizotypal and paranoid Sxs.

Rates of APD among first-degree Rels of Sz probands, attention-deficit/hyperactivity disorder (ADHD) probands, and community control (CC) probands were examined. Further analyses examined rates when controlling for the presence of schizotypal (SPD) and paranoid (PPD) personality disorders, differences in APD Sxs between relative groups, and whether APD in Rels of Szs reflects a near miss for another Sz-spectrum PD.

Three hundred sixty-two first-degree Rels of Sz probands, 201 relatives of ADHD probands, and 245 Rels of CC probands were interviewed for the presence of DSM-III-R Axis I and II disorders. Diagnoses, integrating family history, interview information, and medical records, were determined.

APD occurred more frequently in Rels of Sz probands compared to CC probands ($p < 0.001$) and also when controlling for SPD and PPD ($p < 0.005$). Two Sxs of APD were most characteristic of the Rels of Sz probands: "avoids social or occupational activities..." and "exaggerates the potential difficulties..." 65% of the Rels of Sz probands who had diagnoses of APD were more

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than one criterion short of a DSM-III-R diagnosis of either SPD or PPD. This indicates that APD is a separate Sz-spectrum disorder, and not merely a sub-clinical form of SPD or PPD.

## 1. Introduction

The detection of relatives of schizophrenia (Sz) probands who are affected by a schizophrenia-spectrum diagnosis allows delineation of an extended phenotype that may be helpful for establishing patterns of familial transmission. Accepted schizophrenia-spectrum disorders include: Sz, schizoaffective disorder, atypical psychosis, schizotypal personality disorder and paranoid personality disorder. Some family studies have also found a familial relationship of Sz with avoidant personality disorder which suggests that avoidant personality disorder is a schizophrenia-spectrum disorder (Asarnow et al., 2001; Baron et al., 1985; Kendler et al., 1993).

Meehl (1962) hypothesized that social anxiety is part of the schizotypy core, predisposing to Sz. We review below several other lines of research which support the association between symptoms of social anxiety and a liability to Sz: social anxiety symptoms in the relatives of schizophrenics, social anxiety in patients with Sz, examination of "high-risk" children for early predictors of psychosis, and factor analyses demonstrating that social anxiety is separable from other types of schizophrenia-spectrum related psychopathology. These studies offer mixed support for the hypothesis that symptoms of social anxiety may represent an extended phenotype that may be helpful in the delineation of the familial transmission of Sz.

### 1.1. Social anxiety in relatives of probands with schizophrenia

Family studies have found an increased prevalence of social anxiety personality traits in the family members of Sz probands (Torgersen, 1994). Studies of psychosis proneness in relatives (Lyons et al., 1995; Bailey et al., 1993) report that avoidant personality disorder in the relatives of patients with Sz explains a modest amount of variance in the perceptual aberration and social anhedonia scales completed by these relatives (Eckblad et al., 1982; Chapman et al., 1978). A study of "social closeness" and emotional blunting in first-degree relatives of probands with Sz shows that the relatives score poorly on a measure of social closeness which most likely reflects anhedonia, social anxiety, and odd behaviors (Berenbaum et al., 1994). These studies do not address whether social anxiety in the relatives is separable from other measures of psychosis proneness.

### 1.2. Social anxiety in schizophrenia patients

Social anxiety is highly prevalent in outpatients with Sz and is unrelated to clinical psychotic symptoms (Pallanti et al., 2004). Social anxiety comorbid with Sz is associated with higher risk for suicide attempts, greater lethality of suicide attempts, more substance abuse, lower social adjustment, and lower overall quality of life (Bayle et al., 2001; Blanchard et al., 1998; Pallanti et al., 2004; Taiminen et al., 2001). The rate of social anxiety ranges from 13% to 39% in patients with Sz (Bermanzohn et al., 2000; Cassano et al., 1999; Cosoff and Hafner, 1998; Kendler et al., 1995a). "Shyness" as a personality trait is greater in schizophrenics than in controls (Flanagan, 1992). Social anxiety and shyness have been studied in the interactions of schizophrenic patients with others (Fingeret et al., 1985; Heinssen and Glass, 1990; Monti et al., 1984; Morrison and Bellack, 1987; Penn et al., 1994; Pilkonis et al., 1980). These studies were not designed to determine whether social anxiety was an independent factor from positive or negative symptoms. However, one study that examined this question directly found social anxiety to be unrelated to clinical psychotic symptoms (Pallanti et al., 2004). More recently, studies have shown that avoidant personality scores were highly intercorrelated with all DSM cluster A personality disorder (Spitzer et al., 1990) dimensional scores and that avoidant personality disorder is highly prevalent in outpatients with schizotypal personality disorder (Keshavan et al., 2005; Battaglia et al., 1995). These latter studies are at odds with the finding that social anxiety symptoms are unrelated to other dimensions of psychosis (Pallanti et al., 2004).

### 1.3. Social anxiety in individuals at heightened risk for schizophrenia

Studies of children at high risk for developing Sz have examined the prevalence of social anxiety related

symptoms. These subjects score poorly on measures of peer relations, adaptation to school, hobbies, interests, and social–sexual adjustment (Dworkin et al., 1993), which may reflect high levels of social anxiety. Two studies with similar findings (Auerbach et al., 1993; Hans et al., 2000) support the conclusion that adolescents at risk for Sz have social deficits that are independent of early-onset schizotypal personality disorder and paranoid personality disorder and may reflect a vulnerability indicator to Sz. A prospective study found that premorbid social phobia was associated with more than a 3.5 times increased odds of developing Sz (Tien and Eaton, 1992). Prospective studies found that during childhood, early adolescence and adolescence, poor social competence is more characteristic of children at risk for Sz than children at risk for affective disorder (Dworkin et al., 1991, 1994). These studies are unable to sort out whether social anxiety in the relatives is separable from other measures of psychosis proneness.

### 1.4. Social anxiety is a separable dimension of psychopathology

Factor analytic studies have found that avoidant personality disorder and avoidant/social anxiety symptoms are a separable dimension of psychopathology found in normals, individuals who are at heightened risk for developing schizophrenia-spectrum disorders, individuals with schizotypal personality disorder, and the first-degree relatives of probands with Sz (Bentall et al., 1989; Fogelson et al., 1999; Kendler et al., 1995b; Raine et al., 1994; Tyrka et al., 1995; Vollema and van den Bosch, 1995).

These studies have left unresolved whether avoidant personality disorder and social anxiety in first-degree relatives of Sz probands overlap with other Sz-spectrum disorders. Deciphering the relationship between avoidant personality disorder and other schizophrenia-spectrum disorders requires blind evaluation of relatives of patients with Sz compared to community control relatives. (Keshavan et al., 2005) To address these concerns we examined if avoidant personality disorder shows heightened rates among first-degree relatives of Sz probands compared to relatives of control groups and shows heightened rates even when controlling for the presence of schizotypal and paranoid personality disorders. We also examined whether some individual avoidant personality disorder symptoms are more characteristic of relatives of schizophrenics compared to relatives of community controls and if avoidant personality disorder when present in the first-degree relatives of Sz probands mainly reflects a near miss for a diagnosis of another schizophrenia-spectrum personality disorder. We examined the specificity of these familial relationships by comparing these rates and characteristics in the relatives of the Sz probands to the relatives of CCs as well as to the relatives of ADHD probands, another disorder with prominent cognitive features.

## 2. Methods

### 2.1. Diagnosis of first-degree relatives

Three hundred sixty-two first-degree relatives, age 18 and older, of probands with adult-onset schizophrenia (AOSz, $n=111$ probands) and with childhood-onset schizophrenia (COSz, $n=51$ probands), 201 relatives of probands with attention-deficit/hyperactivity disorder (ADHD, $n=113$ probands), and 245 relatives of adult and child community control (CC) probands ($n=48$ adult probands; $n=71$ child probands) were blindly and directly interviewed for the presence of DSM-III-R axis I and II disorders. All participants in this study provided written informed consent or assent (if a minor). Demographics on these participants are presented in Table 1.

Best estimate diagnoses, derived from an integration of family history, direct interview, and medical records, are used for the analyses. The best estimate diagnoses were reviewed and confirmed by the UCLA authors at a weekly research meeting.

Nine family interviewers were doctorate or master's degree-level clinicians, while one had a bachelor's degree and four years of clinical experience in clinical interviewing. Training procedures and reliability of the interviewers has been described in prior publications of the UCLA Family Study (Asarnow et al., 2001; Fogelson et al., 1991).

### 2.1.1. Direct interview

Axis I diagnoses were assessed with the Diagnostic Interview Schedule (DIS) (Robins et al., 1981) augmented with the Present State Exam (PSE) psychosis section (Wing et al., 1974) and a timeline of psychotic and affective symptoms. We have modified the DIS with supplemental items from the Expanded PSE to allow for in-depth probing of possible psychotic symptoms after the standard DIS is completed. The time line of affective and psychotic episodes allows temporal judgments that are critical for diagnostic decisions. These modifications insure that information for determining Research Diagnostic Criteria (RDC) (Spitzer et al., 1978) and DSM-III-R diagnoses is requested and clarified. Although the DIS has been used in epidemiological studies and has been found to have acceptable reliability and validity (Regier et al., 1984; Robins et al., 1984), our

Table 1
Demographics of first-degree relatives of proband groups

| Characteristic | Schizophrenia proband relatives (N=362) | | Community control proband relatives (N=245) | | ADHD proband relatives (N=201) | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD |
| Age (years) | 42.4 | 14.0 | 43.1 | 12.0 | 39.1 | 8.0 |
| Gender | N | % | N | % | N | % |
| Male | 162 | 45 | 107 | 44 | 86 | 43 |
| Female | 200 | 55 | 138 | 56 | 115 | 57 |
| Race/ethnicity | | | | | | |
| American Indian/Alaskan Native | 2 | 1 | 1 | 1 | | 0 |
| Asian/Pacific Islander | 21 | 6 | 13 | 5 | 5 | 3 |
| Black/African American | 25 | 7 | 21 | 9 | 11 | 5 |
| Hispanic | 51 | 14 | 24 | 10 | 22 | 11 |
| Caucasian | 242 | 67 | 177 | 72 | 155 | 7 |
| Other | 21 | 6 | 9 | 4 | 8 | 4 |

modifications were made to offset concern about the sensitivity of this instrument for diagnosing Sz.

Axis II disorders were assessed with the Structured Clinical Interview for DSM-III-R: Personality Disorders (SCID-II) (Spitzer et al., 1990). Our assessment of personality disorders included two "narrow" Sz-spectrum disorders (paranoid and schizotypal) (Asarnow et al., 2001; Kendler et al., 1993), and schizoid, avoidant, and borderline personality disorders. Criteria were rated on a three point scale.

To further improve the diagnostic accuracy of the DIS and SCID-II all diagnoses of a psychotic or schizophrenia-spectrum disorder were discussed at a weekly research meeting attended by the UCLA authors. After the discussion, as necessary, further information was obtained from subjects and medical records, and diagnostic revisions were made to reflect any new pivotal information.

### 2.1.2. Family history

After the systematic delineation of a genealogy, family history information was elicited to evaluate Axis I disorders using a modified version of the National Institute of Mental Health Relative Psychiatric History (RPH) interview format (Gershon, 1985). Diagnostic status was determined for three psychotic disorders (schizophrenia, schizoaffective-manic/depressed-mainly schizophrenic subtype, atypical psychosis) using Family History-RDC diagnostic criteria (Andreasen et al., 1977).

Family history information was also elicited to evaluate five Axis II personality disorders (paranoid, schizotypal, avoidant, schizoid, and borderline) using the SCID-II adapted to a third person format. DSM-III-R criteria were used to determine diagnostic status for the five personality disorders.

Family history information was usually obtained from two first-degree relatives, when possible the proband's parents. Collecting data from two informants has been shown to raise sensitivity without loss of specificity (Roy et al., 1996). For a complete description of the family history interview see our prior publication (Fogelson et al., 2004).

### 2.2. Ascertainment and diagnosis of probands

The family members came from four proband groups: child and adult-onset schizophrenia (COSz and AOSz), attention-deficit/hyperactivity disorder (ADHD), and community controls (CC). Because the probands were not the subjects in the present study, they are only briefly described here. For a complete description of the selection of the schizophrenia probands see our previous publications (Asarnow et al., 2001; Nuechterlein et al., 1992a).

All AOSz probands have a diagnosis of Sz or schizoaffective disorder, mainly schizophrenic by RDC, with the first psychotic episode occurring less than two years prior to study entry. A period of at least two weeks of active psychosis was required. These probands also met DSM-III-R criteria for Sz or schizoaffective disorder. The AOSz probands meeting the study criteria came from consecutive admissions to four local public psychiatric hospitals and from referrals to the UCLA Adult Psychiatry outpatient department. Family history of psychiatric disorders was not considered in proband selection. Adult-onset probands were excluded for current drug and alcohol abuse, or for having a history of use that made the diagnosis of Sz ambiguous.

COSz probands were screened and selected from 12 Los Angeles County facilities including the UCLA

Table 2
Rates of personality disorders in relatives

| | Schizophrenia proband relative (N=362) | | Community control proband relatives (N=245) | | ADHD proband relatives (N=201) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Diagnosis | | | | | | |
| Avoidant personality disorder | 34 | 9.4 | 5 | 2.0 | 11 | 5.5 |
| "Only APD" [a] | 24 | 6.6 | 4 | 1.6 | 9 | 4.5 |
| Paranoid personality disorder | 13 | 3.6 | 4 | 1.6 | 3 | 1.5 |
| Schizotypal personalitydisorder | 14 | 3.9 | 1 | 0.4 | 3 | 1.5 |

[a] "Only APD" refers to avoidant personality disorder but no other concurrent Axis I or Axis II schizophrenia-spectrum disorder.

Neuropsychiatric Hospital and school-based programs. All child probands were required to have a diagnosis of DSM-III-R (American Psychiatric Association, 1987) Sz with an onset before 13 years of age.

ADHD probands were recruited from pediatric clinics and patient support groups. All ADHD probands met the criteria for DSM-III-R ADHD.

Names of potential CC probands living in the same zip codes as the other probands were obtained from a scientific survey research firm (Survey Sampling Inc., Fairfield, Conn.). CC probands were only excluded if they had a diagnosis of Sz or ADHD.

## 3. Statistical methods

Because members of the same family cannot be treated as independent observations due to shared genetics and shared social environment, family membership was included in all statistical models as a random effect. Analyses were conducted using SAS 9.1 PROC MIXED for linear models with random effects, or PROC GLIMMIX for logistic regression with random effects.

Denominator degrees of freedom were calculated using the "containment method" as specified in SAS, and thus the *df* reported below may vary somewhat among similar analyses. To be conservative, significance levels for all analyses were set at alpha equal to 0.05 despite strong a priori directional hypotheses.

## 4. Results

There were 34 (9.4%) cases of avoidant personality disorder in the Sz relatives, 5 (2.0%) in the CC relatives, and 11 (5.5%) in the ADHD relatives (see Table 2). The differences between the Sz group and the CC group were statistically significant ($F=11.28$, $df=1,325$, $p<0.001$), whereas those between the Sz and ADHD groups were not ($F=2.65$, $df=1,288$, $p=0.11$). The odds ratio is 5.0 for the Sz and CC relatives and 1.8 for the Sz and ADHD relatives.

When examining for the presence of avoidant personality disorder when there is no other comorbid Axis I or Axis II Sz-spectrum disorder ("Only APD," see Table 2), again the Sz group was greater than the CC

Table 3
Individual avoidant personality disorder symptoms in schizophrenia and control relatives

| | Schizophrenia proband relatives (N=362) | | Community control proband relatives (N=245) | | F-value [a] | p-value | Odds ratio |
|---|---|---|---|---|---|---|---|
| | N [b] | % | N [b] | % | | | |
| Avoidant personality disorder symptom | | | | | | | |
| 1. Is easily hurt by criticism… | 79 | 22 | 24 | 10 | 12.4 | 0.0005 | 2.5 |
| 2. Has no close friends… | 86 | 24 | 21 | 9 | 16.4 | 0.0001 | 3.3 |
| 3. Is unwilling to get involved… | 48 | 13 | 10 | 4 | 18.7 | 0.0001 | 3.4 |
| 4. Avoids social or occupational activities… | 49 | 14 | 8 | 3 | 10.1 | 0.0016 | 4.6 |
| 5. Is reticent in social situations… | 56 | 15 | 17 | 7 | 9.3 | 0.0025 | 2.5 |
| 6. Fears being embarrassed… | 31 | 9 | 8 | 3 | 2.5 | 0.116 | 2.8 |
| 7. Exaggerates the potential difficulties… | 13 | 4 | 2 | 1 | 5.4 | 0.021 | 4.5 |

[a] *df* for all seven analyses is 1324.
[b] *N* is the number of relatives rated at threshold level for the symptom.

Table 4
Frequency distribution of the number of paranoid and schizotypal personality disorder symptoms present in the 34 schizophrenia relatives with avoidant personality disorder

| Number of endorsed paranoid personality disorder symptoms | | | Number of endorsed schizotypal personality disorder symptoms | | |
|---|---|---|---|---|---|
| Number of symptoms | Number of relatives | % | Number of symptoms | Number of relatives | % |
| 0 | 9 | 26 | 0 | 2 | 6 |
| 1 | 9 | 26 | 1 | 2 | 6 |
| 2 | 10 | 29 | 2 | 12 | 35 |
| 3 | 2 | 6 | 3 | 8 | 24 |
| 4 | 1 | 3 | 4 | 4 | 12 |
| 5 | 1 | 3 | 5 | 2 | 6 |
| 6 | 1 | 3 | 6 | 2 | 6 |
| 7 | 1 | 3 | 7 | 1 | 3 |

group ($F=6.94$, $df=1,326$, $p<0.01$) but did not differ from the ADHD group ($F=1.07$, $df=1,287$, $p=0.30$). The odds ratios are 4.3 for the Sz and CC relatives and 1.5 for the Sz and ADHD relatives.

We extended our analysis by examining whether avoidant personality disorder shows heightened rates in relatives of Sz probands even when controlling for the presence of schizotypal and paranoid personality disorders. Using PROC GLIMMIX with schizotypal and paranoid personality disorder entered as covariates, avoidant personality disorder was again greater in Sz relatives than in CC relatives ($F=9.73$, $df=1,323$, $p<0.005$) but there were no differences between the Sz relatives and ADHD relatives ($F=1.71$, $df=1,286$, $p=0.19$). Thus, controlling for other Axis II Sz-spectrum disorders, avoidant personality disorder shows significantly greater presence in the Sz relatives than the CC relatives but not the ADHD relatives.

To provide a detailed description of the differences in avoidant traits exhibited by Sz relatives versus CC relatives, using PROC MIXED, analyses were conducted at the individual symptom level while controlling for the presence of paranoid and schizotypal personality disorders. Symptoms were analyzed using their SCID-II rating (coded 1=not present, 2=subthreshold, and 3=threshold). Six of the seven symptoms were statistically higher in the Sz group (see Table 3 for a list of results). Odds ratios were 2.5 or greater for all symptoms. The symptoms with the largest odds ratio were "avoids social or occupational activities..." (OR 4.6) and "exaggerates the potential difficulties..." (OR 4.5). Odds ratio is the relative frequency of a symptom in the relatives of Sz probands compared to relatives of CC controls. For example the symptom, "avoids social or occupational activities that involve significant

interpersonal contact, because of fears of criticism, disapproval, or rejection," is 4.5 times more likely to be present in the Sz relatives.

Table 4 displays the frequency distribution of the number of symptoms of paranoid personality disorder and schizotypal personality disorder in those 34 Sz relatives with avoidant personality disorder diagnoses. Eighty-two percent ($n=28$ of 34) of the Sz relatives were more than one symptom away from a threshold diagnosis of paranoid personality disorder, and 71% ($n=24$ of 34) were more than one symptom away from a threshold diagnosis of schizotypal personality disorder. Sixty-five percent ($n=22$ of 34) were more than one symptom away from a threshold diagnosis of either paranoid or schizotypal personality disorder.

## 5. Discussion

We find that first-degree relatives of probands with COSz or AOSz are at increased risk for avoidant personality disorder compared to first-degree relatives of CC probands, but not compared to first-degree relatives of ADHD probands. This finding holds for avoidant personality disorder that is present in the absence of other schizophrenia-spectrum personality disorders. Even when controlling for the presence of paranoid and schizotypal personality disorders, the analysis demonstrated that avoidant personality disorder is more prominent in first-degree relatives of Sz probands compared to CC relatives. This pattern suggests that avoidant personality disorder should be included as a Sz-spectrum disorder. Our findings replicate and extend the findings of other family studies (Asarnow et al., 2001; Baron et al., 1985; Kendler et al., 1993).

Two individual symptoms of avoidant personality disorder had the highest odds ratios in the Sz relatives when compared to the CC relatives: avoids social or occupational activities..." (OR 4.6) and "exaggerates the potential difficulties..." (OR 4.5) these are the symptoms most characteristic of avoidant personality disorder when it lies on a Sz spectrum. These symptoms are similar to the symptoms found in children at high risk for developing Sz (Auerbach et al., 1993).

Since 71% (24 of 34) of the time, avoidant personality disorder appears outside the presence of other Sz-spectrum disorders in first-degree relatives of Sz probands, it may detect additional relatives with liability to schizophrenia. These are not simply cases that are a "near miss" for either schizotypal or paranoid personality disorder, since more than 92% (22/24) of these cases were 2 or more criteria below the threshold

for a diagnosis of either schizotypal or paranoid personality disorder, further supporting avoidant personality disorder's putative role as a separable Sz-spectrum disorder.

Our findings are a continuation of Bleuler's observations of the prominence of social dysfunction in Sz, referred to as autism in his writings (Bleuler, 1950). Our findings are also supportive of Gottesman's hypothesis of the epigenetic transmission of Sz wherein the diathesis of Sz is dependent upon subtle disruptions in processes critical to forming and maintaining social relationships (Gottesman and Shields, 1982). Studies of normal social development find that these processes include being able to adroitly monitor and adjust to the demands of social relationships, which requires monitoring one's own affective state while recognizing how this is impacting other persons. Deficiencies in these processes early in development lead to a vicious cycle, whereby children are less likely to have successful peer relations, and as a consequence have less opportunity to acquire social skills through peer interactions (Garmezy, 1987). When deficiencies in social development derive from a vulnerability to Sz, they may be represented by avoidant personality disorder.

Social functioning has typically been treated as if it were a dimension independent of core Sz pathology. Level of social functioning in adults prior to the onset of psychosis is one of the best predictors of the level of functional adaptation after the onset of psychosis, a better predictor than type and severity of acute symptoms, and may represent a core aspect of Sz pathology (Liddle, 1987; Strauss and Carpenter, 1977). An emotional atmosphere of criticism is a risk factor for subsequent relapse of psychotic symptoms in Sz, and may be dependent upon avoidant personality disorder symptomatology (Nuechterlein et al., 1992b; Subotnik et al., 2002). The results of the present study suggest that sensitivity to criticism is associated with the liability to Sz, not just secondary to the development of a psychotic disorder. Avoidant personality symptoms may represent a core expression of vulnerability to Sz.

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