

Published in final edited form as:

*Schizophr Res.* 2010 July ; 120(1-3): 113–120. doi:10.1016/j.schres.2009.12.004.

## Avoidant Personality Disorder Symptoms in First-Degree Relatives of Schizophrenia Patients Predict Performance on Neurocognitive Measures: *The UCLA Family Study*

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### Abstract

Whether avoidant personality disorder symptoms are related to neurocognitive impairments that aggregate in relatives of schizophrenics is unknown. We report the relationship between avoidant personality disorder symptoms and neurocognitive performance in the first-degree relatives of probands with schizophrenia.

367 first degree relatives of probands with schizophrenia and 245 relatives of community controls were interviewed for the presence of avoidant personality symptoms and symptoms of paranoid and schizotypal personality disorders and administered neurocognitive measures. Relationships between neurocognitive measures and avoidant symptoms were analyzed using linear mixed models.

Avoidant dimensional scores predicted performance on the span of apprehension (SPAN), 3–7 Continuous Performance Test (3–7 CPT), and Trail Making Test (TMT-B) in schizophrenia relatives. These relationships remained significant on the SPAN even after adjustment for paranoid or schizotypal dimensional scores and on the TMT-B after adjustment for paranoid dimensional scores. Moreover, in a second set of analyses *comparing* schizophrenia relatives to controls there were significant or trending differences in the degree of the relationship between avoidant symptoms and each of these neurocognitive measures even after adjustments for paranoid and schizotypal

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dimensional scores. The substantial correlation between avoidant and schizotypal symptoms suggests that these personality disorders are not independent.

Avoidant and in some cases schizotypal dimensional scores are significant predictors of variability in these neurocognitive measures. In all analyses, higher levels of avoidant symptoms were associated with worse performance on the neurocognitive measures in relatives of schizophrenia probands. These results support the hypothesis that avoidant personality disorder may be a schizophrenia spectrum phenotype.

## Keywords

Avoidant Personality Disorder; Schizotypal Personality Disorder; Schizophrenia; Genetics; Paranoid Personality Disorder; Neurocognition

## 1. Introduction

Cognitive deficits aggregate in first-degree relatives of schizophrenia probands unaffected by schizophrenia and therefore reflect liability to schizophrenia (Snitz, MacDonald, & Carter, 2006) (Toulopoulou, et al., 2007). Some of these cognitive deficits may be related to schizophrenia-spectrum personality disorders. There is some direct evidence that spectrum personality disorders aggregate in relatives of schizophrenics suggesting that they also index a liability to schizophrenia (K S Kendler, McGuire, Gruenberg, & Walsh, 1995). In a previous study we found that first-degree relatives of probands with childhood-onset or adult-onset schizophrenia are at increased risk for avoidant personality disorder even when controlling for the presence of paranoid and schizotypal personality disorders (D.L. Fogelson, et al., 2007). We concluded that avoidant personality disorder is a schizophrenia-spectrum personality disorder and that symptoms of avoidant personality may represent a core expression of vulnerability to schizophrenia. In this study we extend our prior findings by determining whether avoidant personality symptoms in first-degree relatives are associated with performance on cognitive tests that index a liability to schizophrenia (namely, the Degraded Stimulus Continuous Performance Test (DS-CPT) (Nuechterlein, 1991; Nuechterlein, Parasuraman, & Jiang, 1983), the 3–7 Continuous Performance Test (3–7 CPT) (Nuechterlein, Edell, Norris, & Dawson, 1986), the Trail Making Test B (TMT-B) (Reitan, 1958), the Span of Apprehension Test (SPAN) (R F Asarnow, Granholm, & Sherman, 1991), and the Wechsler adult intelligence Vocabulary Subscale (WAIS Vocab) (Wechsler, 1955)

Many studies have demonstrated that poor performance on the CPT, TMT-B, SPAN, and WAIS Vocab aggregate in first-degree relatives of probands with schizophrenia, reflecting a liability to schizophrenia. A meta-analysis of 43 cognitive test scores in the unaffected adult relatives of probands with schizophrenia examined the magnitude of the effect size for the CPT-X ( $d'$ ) (Cohen's  $d = .43$ ), TMT-B ( $d = .41$ ), SPAN ( $d = .23$ ), and WAIS Vocab ( $d = .21$ ). (Snitz, et al., 2006) All effect sizes were positive, indicating poorer performance for relatives of schizophrenics than controls, where a “ $d$ ” of .20 to .40 was considered small and a  $d > .40$  was considered medium. When studies controlled for age, the effect size increased for the CPT-X ( $d'$ ) ( $d = .56$ ), TMT-B ( $d = .50$ ), and WAIS Vocab ( $d = .44$ ) and decreased for the SPAN ( $d = .17$ ). Samples not matched on education were not excluded from the meta-analysis because controlling for education may over-control for liability to schizophrenia.

Far fewer studies have examined neurocognitive/neurophysiologic measures in relatives or individuals affected by schizotypal personality disorder or other schizophrenia-spectrum personality disorders. Relatives with DSM-III-R schizophrenia spectrum personality symptoms have antisaccade eye movement abnormalities, higher error rates and longer

antisaccade latency than unaffected relatives (American Psychiatric Association, 1987) (Thaker, et al., 1999). Patients with schizotypal personality disorder have poorer eye tracking and mean tracking accuracy (Siever, et al., 1990). A measure of disorganization schizotypy derived from the Structured Interview for Schizotypy-Revised was correlated with the CPT37 false alarm variable in 63 relatives of schizophrenia patients (K.S. Kendler, Lieberman, & Walsh, 1989) (Vollema & Postma, 2002). Some studies have examined neurophysiologic measures and avoidant symptoms in patients with schizotypy. Poorer quality eye tracking is associated with the deficit-like symptoms of social isolation, inadequate rapport, social anxiety, and odd speech in patients with schizotypal symptoms and schizotypal personality disorder (Siever, et al., 1994). In this study there was no differentiation made between the contribution of avoidant and schizotypal symptoms. Eye tracking accuracy is correlated with the presence of social isolation and limited desire for social contact (Bergman, et al., 1996). We could find no studies that have examined neurocognitive or neurophysiologic correlates of avoidant personality disorder. Herein we determine the relationship between avoidant personality disorder symptoms in the first-degree relatives of probands with schizophrenia and their performance on the DS-CPT, 3–7 CPT, TMT-B, SPAN, and the WAIS Vocab. If symptoms of avoidant personality disorder are correlated with neurocognitive deficits shown in prior studies to be associated with liability to schizophrenia this would provide additional support for the hypothesis that avoidant personality disorder is a schizophrenia-spectrum personality disorder and that symptoms of avoidant personality may represent a core expression of vulnerability to schizophrenia (D.L. Fogelson, et al., 2007).

## 2. Methods

### 2.1 Diagnosis of First-Degree Relatives

Three-hundred sixty-seven first degree relatives, age 18 and older, of probands with adult-onset schizophrenia (AOSz, n=275 relatives of 11 probands) and with childhood-onset schizophrenia (COSz, n=92 relatives of 51 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 selected DSM-III-R axis I and II disorders. All adult participants in this study provided written informed consent. Minor participants provided assent and their parents provided written consent for the minors study participation. Demographics of these participants are presented in Table 1.

Best estimate diagnoses, derived from an integration of direct interview, family history, and medical records, were used for the analyses (4, 18). Nine family interviewers were doctorate or master's degree-level clinicians, while one had a bachelor's degree and four years of experience in clinical interviewing. Training procedures and reliability of the interviewers has been described in prior publications of the UCLA Family Study (R.F. Asarnow, et al., 2001; D L Fogelson, Nuechterlein, Asarnow, Subotnik, & Talovic, 1991). The best estimate diagnoses were reviewed and confirmed by the study investigators at a weekly research meeting.

### 2.2 Direct Interview

Axis I diagnoses were assessed with the Diagnostic Interview Schedule (DIS) (L N Robins, Helzer, Croughan, & Ratcliff, 1981) augmented with the Present State Exam (PSE) psychosis section (Wing, Cooper, & Sartorius, 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 ensure that information for determining Research Diagnostic Criteria (RDC) (Spitzer, Endicott, & Robins, 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; L.N. Robins, et al., 1984), our modifications were made to offset concern about the sensitivity of this instrument for diagnosing Sz.

We made a determination at the symptom level as to whether the symptoms were secondary to substance use and if they were, we re-rated the symptom as not present. This insured that axis I and II diagnoses were not made if due primarily to substance abuse.

Axis II disorders were assessed with the Structured Clinical Interview for DSM-III-R: Personality Disorders (SCID-II) (Spitzer, Williams, Gibbon, & First, 1990). Our assessment of personality disorders included two “narrow” Sz-spectrum disorders (paranoid and schizotypal) (R.F. Asarnow, et al., 2001; K S Kendler & Diehl, 1993), and schizoid, avoidant, and borderline personality disorders. Items were rated on a three point scale and a diagnosis of a personality disorder was made using DSM-III-R diagnostic criteria. Dimensional scores were constructed for each personality disorder by adding together each item’s scaled score.

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.

### 2.3 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, Endicott, Spitzer, & Winokur, 1977).

Family history information was also elicited to evaluate five Axis II personality disorders (paranoid, schizotypal, avoidant, schizoid, & 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, preferably the proband’s parents. Collecting data from two informants has been shown to raise sensitivity without loss of specificity (Roy, Walsh, & Kendler, 1996). For a complete description of the family history interview see our prior publication (D. L. Fogelson, Nuechterlein, Asarnow, Payne, & Subotnik, 2004).

### 2.4 Ascertainment and Diagnosis of Probands

The family members came from three proband groups: child and adult onset schizophrenia (COSz & AOSz) and community controls (CC). Because the probands were not the subjects in the present study, they are only briefly discussed. For a complete description of the ascertainment of the schizophrenia and community control probands, see our previous publications (R.F. Asarnow, et al., 2001; Nuechterlein, et al., 1992).

All AOSz probands had 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. AOSz probands also met DSM-III-R criteria for Sz or schizoaffective disorder. The AOSz probands meeting study criteria came from admissions to four local public psychiatric hospitals and from referrals to the UCLA

Adult Psychiatry outpatient department. COSz probands were screened and selected from 12 Los Angeles County facilities including the UCLA 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. Family history of psychiatric disorders was not considered in AOSz or COSz proband selection. Potential schizophrenia probands were excluded for current drug and alcohol dependence, or for having a history of abuse that made the diagnosis of Sz ambiguous. 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.

## 2.5 Neurocognitive Testing of First Degree Relatives

Directly interviewed first degree relatives were administered the DS-CPT, 3-7 CPT, SPAN, TMT-B, and the WAIS Vocab. These measures represent three neurocognitive domains that have detected subtle deficits in sustained, focused attention, early perceptual processes, and sequential visual tracking in unaffected relatives of schizophrenia patients as well as an index of general verbal ability level (R F Asarnow, et al., 1991; Braff, 1993; Kremen, et al., 1994; K. H. Nuechterlein, et al., 1998; Nuechterlein & Dawson, 1984). The literature-supporting selection of these measures has been summarized in a previous paper (K. Nuechterlein, et al., 1998).

The DS-CPT, a measure of sustained, focused visual attention, involves detection of each occurrence of a highly blurred target digit within a quasi-random series of blurred, single-digit stimuli presented at 40 ms each at a pace of 1/s over an 8-min period (Nuechterlein, et al., 1983). Blurring (degradation) of stimuli enhances the role of early perceptual encoding in performance. Details of stimulus characteristics and projector equipment were given in a prior paper (Nuechterlein, et al., 1986). The signal/noise discrimination index,  $d'$ , from signal detection theory was the primary DS-CPT variable.

The 3-7 CPT, a successive discrimination visual vigilance task that requires sustained working memory processes, involves responding to each successive sequence of a "3" followed by a "7" in a quasi-random series of clearly focused single digits. Additional processing load was presented in the form of auditory distraction, using a recording of a male voice reading rapidly the same quasi random series of digits. The  $d'$  measure of signal/noise discrimination was the primary variable.

The SPAN, a measure of rapid perceptual encoding and efficient covert visual search, involves detection of target letters (T or F) within briefly presented arrays of 0, 2, or 9 other letters (R F Asarnow, et al., 1991; R F Asarnow & MacCrimmon, 1981). The partial-report, forced-choice format limits the role of short-term memory and enhances the role of early encoding and search processes. Stimulus characteristics and projector equipment for this version were described by Nuechterlein et al. (Nuechterlein, et al., 1986). The accuracy of target detection in 10-letter arrays was the dependent variable.

The TMT-B, a measure of sequential visual conceptual tracking, involves connecting numerals and letters on a sheet of paper as quickly as possible (Reitan, 1958). The need to alternate between a number series and a letter series (1, A, 2, B, 3, C, etc.) entails demands on maintenance of task set over time, working memory for position in the two sequences, and organized visual scanning. An adolescent version was used to accommodate the age range of subjects in the overall study from which this report is drawn. The number of seconds required to complete Part B was used as the dependent variable. A reciprocal transformation was used to normalize the distribution of scores, resulting in a variable reflecting Trails B speed.



## 2.6 Statistical Methods

Relationships between avoidant symptoms and neurocognitive performance (SPAN, 3–7 CPT, DS-CPT, TMT-B or WAIS Vocab) were assessed via mixed effects regression models with main effects for avoidant symptoms and group (SZ or control), a symptom by group interaction (in combined models) and age and gender as covariates (as appropriate). To account for the inclusion of multiple relatives of a single proband, we included a random effect for family with a variance components structure (Littell, Milliken, Stroup, & Wolfinger, 1996). Additional analyses were conducted to determine whether relationships between avoidant symptoms and neurocognitive performance persisted after the effects of schizotypal and paranoid symptoms were covaried. We chose to conduct the primary analyses using dimensional scores for all three personality disorders both because continuous measures provided greater power both for detecting associations between symptoms and for capturing overlap among the disorders and because there were so few diagnoses of avoidant personality disorder in the controls that it was not possible to assess its relationship to the neurocognitive measures except on a symptom level. However, we conducted secondary analyses using diagnostic categories to see to what extent they captured the same effects observed with more sensitive dimensional scores. We included three groups of subjects in these analyses: SZ relatives who met criteria for avoidant personality diagnosis, SZ relatives who did not meet avoidant personality criteria, and CC probands who did not meet avoidant personality disorder criteria. To be conservative, all analyses used two-tailed significance tests with cutoff  $\alpha=5\%$ , despite the fact that our hypotheses were clearly directional, with higher avoidant personality disorder symptoms expected to be associated with worse neurocognitive performance. In each model we included only subjects who had valid neurocognitive data on the measure being assessed. All analyses were performed in SAS Proc Mixed.

## 3. Results

Table 1 shows the demographics for the schizophrenia relatives and control relatives. They were comparable in age and gender but differed on education (schizophrenia relatives = 13.8 years, controls = 15.0 years;  $p < .0001$ ). Note that the means and standard deviations reported in this table are raw sample values but the p-values comparing the groups do adjust for correlations within families. Our previous finding that avoidant personality disorder aggregates in the first-degree family members of schizophrenia probands (D.L. Fogelson, et al., 2007) is represented again in Table 1

Age is an important predictor for the neurocognitive measures used in this study with the degree of the effect potentially depending on the proband group. We therefore fit mixed effects regressions of cognitive performance on age, and in the combined sample include both group and an age by group interaction. Overall, performance decreases significantly with age on all neurocognitive measures except WAIS Vocab where it increases. For the DS-CPT, SPAN and WAIS Vocab there is no evidence of an age by group interaction, but there are significant age effects ( $p$ -values .0005,  $< .0001$  and  $< .0001$  respectively). Thus for the DS-CPT, SPAN and WAIS Vocab, we adjusted for age in models relating the neurocognitive measures to symptoms. For the 3–7 CPT, there is a significant age by group interaction ( $p$ -value .0016) and for the TMT-B, there is a trend towards an age by group interaction ( $p$ -value .0651). Thus, for the 3–7 CPT and the TMT-B we created age-adjusted versions of the variables (3–7 CPTageadj and TMT-Bageadj) by partialing out the control age effect to preserve the “illness related” age effect.

Gender was a significant predictor of performance on the SPAN ( $p$  values around  $< .05$  in combined sample models and around  $< .005$  in Sz relatives alone), with women performing worse than men. Gender was not a significant predictor of performance on any of the other

neurocognitive measures. We therefore report gender effects only for the SPAN in the subsequent analyses.

Overall means for the dimensional avoidant scores with their distribution and range were calculated for the relatives of schizophrenics vs. controls. The possible range of scores is 7 to 21. The mean score was 9.54 (SD 3.11; minimum score 7, median 9, third quartile 11, max 21) in the relatives of the Sz probands vs. 8.22 (SD 2.01; minimum score 7, median 7, third quartile 9, max 17) in the relatives of the control probands. The effect size for the group difference in avoidant symptoms is  $d = .48$  and the corresponding  $p$  value, taking into account the correlations within families, is  $< .0001$ . In the controls there are a range of symptoms although slightly restricted compared to the schizophrenia relatives.

Models were first fit separately for relatives and controls. In each model we examined the relationship between avoidant dimensional scores and neurocognitive performance, variously adjusting for age, gender, and either paranoid personality quantitative dimensional scores or schizotypal dimensional scores (see Models 1 – 4 in Tables 3 & 5). Model 1 examines this relationship making no adjustments. Model 2, our primary model, adjusts for age and gender for reasons discussed in the previous paragraph. The secondary analyses, Models 3 and 4, adjust for paranoid personality quantitative dimensional score or schizotypal dimensional score respectively, as well as for age and gender. These secondary models are probably an overly-conservative test of the effect of avoidant symptoms on neurocognitive performance because of the significant positive relationships among the dimensional scores.

There was no evidence of a relationship between avoidant dimensional scores and any of the neurocognitive performance measures in controls. There was no relationship between avoidant dimensional scores and performance on the DS-CPT and WAIS Vocab in Sz relatives. However we did see significant results for Sz relatives on the SPAN, 3–7 CPT, and TMT-B as shown in Table 2. For each variable in a given model (row of the table) we indicate the  $p$ -value and significance level or indicate that the variable was not included in the model (NA). Avoidant dimensional scores consistently predicted performance on the SPAN, surviving adjustments for age, paranoid dimensional scores (trending), and schizotypal dimensional scores. Avoidant dimensional scores predicted performance on the 3–7 CPT, surviving adjustments for age and paranoid dimensional scores (trending), but not for schizotypal dimensional scores. Avoidant dimensional scores predicted performance on the TMT-B, surviving adjustments for age and paranoid dimensional scores, but not for schizotypal dimensional scores.

Based on the above results it is apparent that the effect of avoidant dimensional scores on cognitive performance cannot be fully interpreted without reference to the correlations between avoidant, paranoid, and schizotypal dimensional symptom scores. We examined these correlations in the Sz relatives, the control relatives, and the combined sample (Table 3). The dimensional scores are highly correlated with one another:  $p$ -values for the significance of all the correlation are  $< .0001$  and range from .33 to .66. In combination with the mixed models, this suggests that the overlapping characteristics of these disorders are crucial to neurocognition although there is evidence that avoidant symptoms explain additional variability beyond what is explained by the shared variance on the SPAN.

The findings above suggest that the relationship between neurocognitive performance and avoidant symptoms differs between Sz and control relatives with the former group exhibiting significant associations and the latter group exhibiting none. To formally test this hypothesis we fit mixed effects regressions of neurocognitive performance on avoidant symptom scores and group (schizophrenia relatives and controls) with an interaction term in the combined sample. Significance of the interaction term confirms a difference in the degree of impact of avoidant symptoms. After fitting this basic model to each neurocognitive measure we also

examined adjustments for age, gender, paranoid dimensional symptoms and schizotypal dimensional symptoms. (Table 4) There were no significant differences between the Sz relatives and control relatives on performance of the DS-CPT and WAIS Vocab as predicted by avoidant quantitative dimensional scores. There were significant differences (group by avoidant symptoms interactions) between the schizophrenia relatives and control relatives on the SPAN, 3–7 CPT, and TMT-B (trending) (Table 4). Avoidant dimensional scores were consistently a stronger predictor of performance on the SPAN, 3–7 CPT, and the TMT-B for the schizophrenia relatives compared to the control relatives with the results remaining the same after adjustments for age, gender (for the SPAN), paranoid dimensional scores, and schizotypal dimensional scores. Increased symptoms were associated with poorer performance in all cases.

We more simply contrasted neurocognitive performance of schizophrenia relatives with a diagnosis of avoidant personality disorder with that of schizophrenia relatives without a diagnosis of avoidant personality disorder, with adjustments for age, schizotypal and paranoid personality disorder diagnoses. The P values corrected for age for these comparisons were .04 for the SPAN, .002 for the 3–7 CPT, .03 for the DS CPT, .003 for the TMT-B, and .36 for WAIS Vocab. When we made corrections for the other personality disorders the significance did not change. However, it should be noted that the number of subjects whose symptoms met full diagnostic criteria for paranoid or schizotypal personality disorder was very small, and thus this analysis probably does not adequately account for the overlap in symptoms with avoidant personality disorder.

We also compared schizophrenia relatives with a diagnosis of avoidant personality disorder to community control relatives without a diagnosis of avoidant personality disorder. The P values corrected for age for these comparisons were .002 for the SPAN, <.0001 for the 3–7 CPT, <.0001 for the DS-CPT, <.0001 for the TMT-B, and .009 for WAIS Vocab. As before, when we made corrections for the presence of paranoid and schizotypal personality disorders the significance did not change, but as noted above this is not unexpected since the numbers of subjects achieving diagnostic criteria were not large enough for these variables to significantly affect the models.

#### 4. Discussion

The results of this study extend our previous findings that avoidant personality disorder symptoms may represent a core expression of vulnerability to schizophrenia. We found that performance of first-degree relatives of schizophrenia probands on the SPAN, 3–7 CPT, and TMT-B is predicted by dimensional scores of avoidant personality disorder symptoms in our primary model (Table 2, model 2). The relationship of avoidant symptoms with impaired performance of neurocognitive tasks in relatives of schizophrenics would be unremarkable if the same patterns existed in the relatives of community controls. In controls, however, there was no evidence that avoidant symptoms predicted cognitive impairment, suggesting specificity of the relationships to the liability to schizophrenia. This group difference in the impact of avoidant symptoms was statistically significant. Avoidant dimensional scores were consistently a stronger predictor of poor performance on the SPAN, 3–7 CPT, and the TMT-B for the schizophrenia relatives compared to the control relatives in our primary model (Table 4, model 2). Schizophrenia relatives have poorer cognitive performance than relatives of normal controls with the size of the discrepancy increasing with the degree of avoidant symptoms.

When we controlled for paranoid and schizotypal scores, avoidant symptoms lost some of their predictive power. We attribute this to the high correlation between dimensional scores of avoidant, paranoid and schizotypal symptoms (see Table 3). Even after adjustments for age,



paranoid dimensional scores (trending), and schizotypal dimensional scores, avoidant symptoms did predict deficits in one prominent neurocognitive vulnerability index, the span of apprehension. Given that the five included neurocognitive measures were selected to index several distinct cognitive constructs, it is not clear that a correction for multiple comparisons is appropriate here. While it is possible that some of our results represent false positives, the overall pattern of findings (significant results in 3/5 measures in the most informative group of relatives) is quite unlikely to occur by chance. We interpret this to mean that both avoidant dimensional scores and schizotypal dimensional scores are useful predictors of performance on these neurocognitive measures, but with the exception of the SPAN may not be statistically independent predictors of neurocognitive function. These analyses and the ones in our prior paper suggest that avoidant, schizotypal, and paranoid personality disorders are moderately related but not wholly redundant indicators of an underlying spectrum phenotype. The relationship to neurocognitive deficits is more evidence that this is the case.

When we more simply contrasted neurocognitive performance of schizophrenia relatives with a diagnosis of avoidant personality disorder with that of schizophrenia relatives or community control relatives without a diagnosis of avoidant personality disorder, we found that all the comparisons were significant except for WAIS Vocab. All these comparisons remained significant even when controlling for the presence of paranoid and schizotypal personality disorders. This may seem surprising given the high correlation between avoidant symptoms and paranoid and schizotypal symptoms, Table 3. However, the small number of relatives with a diagnosis of paranoid/schizotypal personality disorder (D.L. Fogelson, et al., 2007) means that much of the overlap captured by the dimensional scores is not accounted for in the purely diagnostic models. We believe that the dimensional approach is more sensitive to the relationship between the three personality disorders and therefore present it as our primary model.

There are several methodological strengths to this study that bolster our conclusions. The relatives of schizophrenics were comparable to control relatives on age and gender. While control relatives attained a higher education level, we did not control for this difference in our analyses because we believe this difference preserves illness-related variance of interest between these groups (Snitz, et al., 2006). Relatives were interviewed and rated blind to the diagnosis of the proband. Diagnoses and ratings were derived from a synthesis of multiple sources of information: direct interview, family history, and medical records. Inter-rater reliability was established (D L Fogelson, et al., 1991). A limitation of this study is that we were unable to control for present state anxiety or depression because we did not have rating scales for anxiety or depression at the time of testing and we did not distinguish between a lifetime history of major depression and a current state of major depression. We do not know to what extent avoidant personality disorder is a surrogate for these other symptoms.

In a previous study the increased aggregation of avoidant personality disorder in first degree relatives of schizophrenia probands provided evidence that avoidant personality disorder is an endophenotype of schizophrenia (D.L. Fogelson, et al., 2007). The evidence included finding that avoidant personality disorder occurred more frequently in relatives of schizophrenia probands compared to community control probands and also when controlling for schizotypal and paranoid personality disorders. The evidence also showed that 65% of the relatives of schizophrenia probands with avoidant personality disorder were more than one criterion short of schizotypal or paranoid personality disorder. This indicated that avoidant personality disorder is a separable schizophrenia spectrum disorder, and not merely a subclinical form of schizotypal or paranoid personality disorder.

In this study we strengthened our finding that avoidant personality disorder is a separable schizophrenia spectrum disorder by observing that avoidant personality symptoms are related

to neurocognitive endophenotypes implicated in schizophrenia (Greenwood, et al., 2007). We also found evidence that some of the relationship of avoidant symptoms with neurocognitive performance is shared with paranoid and schizotypal symptoms, but some is not (particularly notable for the SPAN). We believe this means that avoidant personality disorder is neither independent of nor wholly a part of schizotypal personality disorder as a component of the schizophrenia spectrum. Our data here and in prior studies indicate this (D.L. Fogelson, et al., 2007). Furthermore, factor analyses provide further evidence that the avoidant and schizotypal dimensions are neither independent of nor wholly a part of schizotypal personality disorder (D L Fogelson, et al., 1999) (Nuechterlein, et al., 2002).

Linking two endophenotypes (clinical symptoms and neurocognitive performance) may allow us to better identify specific neurobiological functions and structures underlying schizophrenia. Their genetic determinants and anatomical expression may be simpler and more circumscribed than those for the heterogeneous construct of schizophrenia. In future studies we will examine the underlying genetic and neural substrates of avoidant symptoms in relatives of schizophrenics.

We conclude that performance of first-degree relatives of schizophrenic probands on the SPAN, 3–7 CPT, and TMT-B is predicted by dimensional scores of avoidant personality disorder symptoms and that this supports the hypothesis that avoidant personality disorder is a useful phenotype that probably reflects unique aspects of the underlying liability to schizophrenia not captured by “better-known” schizophrenia-like personality traits.

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**Table 1**

## Demographic Variables

Variable/Level	Sz Relatives N=367	Controls N=245	Difference Sz vs. Control <sup>1</sup>
	mean with SD in parentheses		
Age (years)	42.41 (14.02), range 18–79	43.07 (12.00), range 18–69	P=.69
Education (yrs)	13.77 (2.91)	15.01 (2.32)	P< .0001
Gender	number with % in parentheses		
Male	163 (44.41%)	107 (43.67%)	P = .86
Female	204 (55.59%)	138 (56.33%)	
Avoidant Personality Disorder	34 (9.4%)	5 (2%)	P<.001

<sup>1</sup>Significance levels for group comparisons are adjusted for within family correlations



Table 2

**Analysis of Avoidant Quantitative Dimensional Scores as a Predictor of Performance on the SPAN, 3-7 CPT, and TMT-B in Sz Relatives.** {This analysis was performed in SAS Proc Mixed using a mixed effects regression of SPAN performance on avoidant symptoms in the Sz relatives and with random effect for family. Variance components structure was used for random effect (Littell, et al., 1996)}.

Model	Response	Avoidant Sum	Age	Paranoid Sum	Schizotypal Sum	Gender
1	SPAN	.03**	NA	NA	NA	NA
2	SPAN	.03**	<.0001**	NA	NA	.0016**
3	SPAN	.07*	<.0001**	NS	NA	.0016**
4	SPAN	.04**	<.0001**	NA	NS	.0016**
2	3-7 CPT+	.03**	+	NA	NA	NA
3	3-7 CPT+	.06*	+	NS	NA	NA
4	3-7 CPT+	NS	+	NA	.0574*	NA
2	TMT-B+	.003**	+	NA	NA	NA
3	TMT-B+	.04**	+	NS	NA	NA
4	TMT-B+	NS	+	NA	.0286**	NA

\* trending to significant,

\*\* significant,

NS = variable not significant, NA = variable not included in the model, + = age adjusted version of the variable.

**Table 3**

Correlations between dimensional symptom scores; all correlations are  $P < .0001$ .

Variable Pair	Relatives	Controls	Relatives+Controls
	N=367	N=245	N = 612
Avoidant/Paranoid	.51	.33	.49
Avoidant/Schizotypal	.62	.49	.51
Paranoid/Schizotypal	.63	.66	.65

**Table 4**

**Analysis of Avoidant Quantitative Dimensional Scores as a Predictor of Performance on the SPAN, 3-7 CPT, and TMT-B comparison between the Sz and Control Relatives.** {This analysis was performed in SAS Proc Mixed using a mixed effects regression of SPAN performance on avoidant symptoms and group (schizophrenia relatives vs. controls) with an interaction term and with random effect for family. Variance components structure was used for random effect (Littell, et al., 1996)}.

Model	Response	Avoidant Sum, control and Sz relatives	Avoidant X Grp	Age	Paranoid Sum	Schizotypal Sum	Gender
1	SPAN	NS	.02**	NA	NA	NA	NA
2	SPAN	NS	.03**	<.0001**	NA	NA	.04** Male > Female
3	SPAN	NS	.03**	<.0001**	NS	NA	.04** Male > Female
4	SPAN	NS	.03**	<.0001**	NA	NS	.04** Male > Female
2	3-7 CPT+	NS	.045**	+	NA	NA	NA
3	3-7 CPT+	NS	.048**	+	NS	NA	NA
4	3-7 CPT+	NS	.046**	+	NA	.02**	NA
2	TMT-B+	NS	.055*	+	NA	NA	NA
3	TMT-B+	NS	.077**	+	.0705*	NA	NA
4	TMT-B+	NS	.07*	+	NA	.008**	NA

\* trending to significant,

\*\* significant,

NS = variable not significant. NA = variable not included in model, + = age adjusted version of the variable.