Published in final edited form as:

Psychiatry Res. 2008 July 15; 160(1): 30–37. doi:10.1016/j.psychres.2007.04.024.

Elevated nailfold plexus visibility aggregates in families and is associated with a specific negative symptom pattern in schizophrenia

John P. Vuchetich^{a,*}, Jennifer L. Liska^b, Daphne P. Dionisio^a, John J. Stanwyck^c, Kathryn A. McGuire^c, and Scott R. Sponheim^{a,c}

^aDepartments of Psychiatry and Psychology, University of Minnesota, Minneapolis, MN

^bMinnesota Department of Corrections, Rush City, MN

^cVeterans Affairs Medical Center, Minneapolis, MN

Abstract

Twenty-four individuals with schizophrenia and 28 of their first-degree biological relatives were studied using clinical scales, functional ratings, and neuropsychological tests. An assessment of Nailfold Plexus Visibility (NPV) was also performed on these individuals. In keeping with the literature, we found an increased prevalence of high NPV in our schizophrenia subjects relative to controls and community norms, and also found that high NPV patients had significantly more negative symptoms and poorer social functioning. Measures of negative symptoms indicative of the deficit syndrome did a better job of distinguishing high from low NPV subjects than did more broadly defined negative symptom indices. As predicted, the prevalence of high NPV in first-degree relatives of high NPV schizophrenia subjects was increased compared to relatives of low NPV schizophrenia subjects. These two relative groups did not differ on overall level of schizotypy symptoms or on negative symptom schizotypy indices. However, relatives of low NPV patients scored significantly higher on scales of positive symptom schizotypy. Overall, these results support the hypothesis that high NPV is a marker of risk for a distinct subtype of schizophrenia.

Author Keywords

Plexus Visibility Scale; Schizotypy; Deficit Syndrome; Endophenotype

1. Introduction

The nailfold plexus in humans consists of the network of capillaries under the skin just proximal to the fingernail. Since the 1940's, researchers have investigated the relationship

*Corresponding Author – Email: vuche002@umn.edu; Address: University of Minnesota Psychiatry Department, F282/2A West Building, 2450 Riverside Ave, Minneapolis, MN 55454-1495. Telephone: (612) 273-9761; Facsimile: (612) 273-9779.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

between the plexus and conditions such as mental retardation, epilepsy, rheumatoid arthritis, low body weight, and mental illness (Hauptman and Myerson, 1948; Maricq, 1964; Maricq et al., 1970; Pokorney et al., 1970; Jones and Whitson, 1971; Granier et al., 1986; Hamilton, 1994; Cirillo, 1997). The nailfold plexus has frequently been studied in relationship to schizophrenia. Initial investigations focused on the structure of the capillaries themselves (Hauptman and Myerson, 1948; Wertheimer and Wertheimer, 1955). Subsequent research suggested, however, that it is the visibility of the vessels and not their structure that relates to liability to the development of schizophrenia (Norris and Chowning, 1964).

Nailfold plexus visibility (NPV) has the characteristics of an endophenotype, or marker related to genetic risk for schizophrenia (Gottesman and Shields, 1972; Iacono, 1985, Gottesman and Gould, 2003). A high level of plexus visibility is rare in the general population (occurring in 3–7% of healthy adults) while the rate of high NPV ranges from 20–70% in populations with schizophrenia (Poole et al., 1991, Curtis et al., 1999). NPV is stable over time following adolescence (Iacono, 1985). High NPV occurs more frequently in schizophrenia than in other psychiatric disorders, including the affective psychoses (Norris and Chowning, 1964, Clementz et al., 1992). Family studies have illustrated that nailfold plexus visibility is heritable in the normal population (Maricq and Jones, 1976) as well as in families segregating for schizophrenia (Clementz et al., 1992). Relatives of high NPV schizophrenia patients who themselves have greater plexus visibility tend to have higher levels of schizotypy than family members with low plexus visibility (Buchanan and Jones, 1969). Furthermore, college students with schizotypy identified by psychometric scales rather than family history have been shown to exhibit elevated rates of high NPV (Gooding and Miller, 1998). Finally, schizophrenia patients with high NPV are more likely to have a positive family history of schizophrenia (Maricq, 1963; Maricq et al., 1968; Poole, 1993).

In addition to being a putative endophenotype for schizophrenia, high NPV appears to identify liability for a distinct clinical subtype of schizophrenia. Poole et al. (1991) note that in studies of schizophrenia, rates of high NPV are more elevated in chronic and severely affected patient populations. Studies have also shown that schizophrenia patients with high NPV tend to have more negative symptoms (Poole et al., 1991, 1993; Curtis et al., 1999) and lower ratings of occupational functioning (Curtis et al., 1999). If confirmed, the ability of noninvasive assessment of plexus visibility to identify a specific subtype of schizophrenia would make high NPV an especially valuable trait by which to select more homogeneous groups of schizophrenia probands for genetic linkage and association studies. As demonstrated by Roberts et al. (1999), reducing genetic heterogeneity is an especially effective way of increasing the power and precision of genetic studies.

As the research on NPV began a number of decades ago, researchers have begun to update and expand the original findings by using modern assessment techniques to examine the correlates of high NPV. Curtis et al. (1999) showed deficits in neuropsychological tasks specific to frontal lobe function in high NPV schizophrenia subjects, as well as a relationship between NPV and ocular motor dysfunction - a well established physiological correlate of schizophrenia. Unexpectedly, they found less ventriculomegaly in high NPV patients than low NPV patients using computed tomography (CT) brain imaging. Recently, Sponheim et al. (2003) showed that among a group of biological indices altered in

schizophrenia (ocular motor function, low frequency & alpha electroencephalogram power, NPV, and nonspecific fluctuations in electrodermal activity) only NPV differentiated schizophrenia patients from both nonpsychiatric controls and affective psychosis patients.

The aim of the current study was to further investigate the correlates of nailfold plexus visibility in a sample of schizophrenia subjects and their family members. Following from the literature, we hypothesized that the rate of high levels of NPV in schizophrenia would be elevated, and that patients with high NPV would demonstrate more negative symptoms, greater levels of functional impairment, and more dysfunction on neuropsychological tasks tapping frontal lobe function. We also hypothesized that the prevalence of high NPV would be greater in first-degree relatives of high NPV patients than in relatives of low NPV patients. We further predicted that the family members of high NPV patients would exhibit mild versions of the neuropsychological deficits we expected to see in their ill relatives. Finally, we hypothesized that the relatives of high NPV schizophrenic patients would differ from the relatives of low NPV schizophrenic patients in terms of schizotypy symptoms. We were able to use several scales of schizotypy developed since the time of the Buchanan and Jones (1969) study that allow for separate evaluation of positive (e.g. odd beliefs or unusual perceptual experiences) and negative (e.g. restricted affect or lack of social interests) schizotypy symptoms. Given the predominance of negative symptoms in schizophrenia patients with high levels of NPV, we predicted that the relatives of these patients would be especially elevated in negative symptom schizotypy, while the relatives of low NPV patients would be more likely to be elevated in positive symptom schizotypy.

2. Method

2.1 Subjects

Subjects for the current study were participants in a family study of schizophrenia at the Veterans' Affairs Medical Center (VAMC) in Minneapolis, MN. Recruitment and sampling procedures have been described previously (Sponheim et al., 2004). Subjects meeting Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV, American Psychiatric Association, 1994) diagnostic criteria for schizophrenia and their family members were selected for study. All such subjects for whom NPV data was available were included in this sample. The final sample included 24 individuals diagnosed with schizophrenia and 28 of their adult first-degree relatives. Data from 17 of these schizophrenia subjects and 17 of their first-degree relatives were also included in Sponheim et al.'s (2004) report of verbal memory processes in schizophrenia.

2.2 Measures

NPV was rated using the Plexus Visibility Scale (PVS, Maricq, 1970). The nailbeds of each of the subject's fingers were coated with immersion oil, visualized using a low-power stereomicroscope, and given a PVS score between 0 and 4. Raters were trained on the PVS and checked to ensure high levels of inter-rater reliability before rating plexus independently. Text descriptions and photographs of different levels of plexus visibility were used as anchors in the rating process. Raters were blind to subject group membership, as subjects with other diagnoses (e.g. bipolar disorder), their family members, and normal

controls were also assessed as part of the larger family study. Following training, a reliability study was conducted using the two main raters on the PVS. As expected, the correlation between the raters on 20 observations was very high ($r(18)=0.94$, $P<0.0001$). When the individual ratings of plexus level were categorized as low, intermediate, and high (with high ratings corresponding to categorization as a high NPV subject) the level of agreement was much higher than that expected by chance ($k=0.73$, $P<0.0001$). There were no disagreements as to whether subjects in the reliability study had a high level of NPV.

The classical cutoff score of 10 on the PVS was used to divide the groups into high and low NPV patients in order to investigate naifold plexus visibility as a categorical variable. Each of the clinical, social-occupational & neuropsychological variables was examined across NPV level in the schizophrenia group. We also explored the use of NPV as a continuous measure. Since the distribution of PVS is highly positively skewed, the natural logarithm of (PVS+1) (lnPVS) was the measure of NPV used for linear correlation. All tests were two-tailed.

Clinical symptoms in the schizophrenia group were examined using measures of positive symptoms, negative symptoms and general level of functioning. Positive symptoms were measured using the Schedule for the Assessment of Positive Symptoms (SAPS; Andreason and Olsen, 1982), total score (SAPSSum). The primary measure of negative symptoms was the Schedule for the Assessment of Negative Symptoms (SANS; Andreason, 1982), total score (SANSSum). The 24-item Brief Psychiatric Rating Scale (BPRS; Ventura et al., 1993) total score was used as a measure of overall psychopathology, and its negative symptom factor score (BPRSnegative, Ventura et al., 2000) was the secondary measure of negative symptoms.

The schizophrenia group was also assessed with several measures of social and occupational functioning. The Global Adjustment and Global Work items were taken from the Social Adjustment Scale (SAS; Schooler et al., 1979). Employment status (Employed) and total non-family social contacts (NF Social) were derived from the Quality of Life Interview (QOLI; Lehman, 1988).

Both the schizophrenia patients and the relative groups were administered measures of frontal lobe functioning and compared on the following variables: Digit Span Backward (DSPB; Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III) subtest, Wechsler, 1997; total raw score), Controlled Oral Word Association Test (COWAT; Lezak, 1995; number of words generated) and the Delayed Response Test (DRT; Park and Holzman, 1992, Spatial Interference subtest). The version of the DRT used in this study had a 6 second delay interval and required the subject to press a stylus on a computer screen to indicate the location of a previously presented asterisk. The variable examined was the size of the error on the screen in millimeters, with subject visual distance of 24 centimeters. The Wisconsin Card Sort Test (WCST; Heaton et al., 1993; number of perseverative errors and number of categories achieved) was administered to a subset of the subjects with schizophrenia as well. In addition, subject intelligence quotient (IQ) was estimated from the Vocabulary and Block Design subtests of the WAIS-III using the method of Booker and Cyr (1986).

The rates of elevated NPV in relatives of high and low NPV schizophrenia subjects were compared. The scores of these two relative groups were also compared on the total score and the factor scores of the Schizotypal Personality Questionnaire (SPQ; Raine, 1991) a true-false inventory of schizotypal symptoms based on DSM-IV criteria. Both the cognitive-perceptual (assessing positive symptom schizotypy) and the social-interpersonal (assessing largely negative symptom schizotypy) factors of the SPQ have been demonstrated to differentiate clinically well first-degree relatives of schizophrenia patients from normal controls (Kremen et al., 1998; Yaralian et al., 2000; Calkins et al., 2004). Finally, the relative groups were compared on the Chapman scales of psychometric schizotypy (Social Anhedonia (Eckblad et al., 1982), Physical Anhedonia (Chapman, et al., 1976), Magical Ideation (Eckblad and Chapman, 1983) and Perceptual Aberration (Chapman et al., 1978). These true-false self-report inventories are designed to assess the symptoms of schizotypy enumerated by Meehl (1962). Subjects with high scores on the Chapman scales have been shown to exhibit elevated rates of high NPV (Gooding and Miller, 1998). The Social and Physical Anhedonia scales were combined to create an index of negative symptom schizotypy. The Chapman anhedonia scales have successfully distinguished relatives of first-episode psychotic patients from normal controls (Katsanis et al., 1990). The Perceptual Aberration and Magical Ideation (permag) scales were combined to measure positive symptom schizotypy.

3. Results

3.1 High vs. low NPV in schizophrenia

The incidence of high NPV in our sample was 21% (5/24), which is significantly higher than general population rates ($P < 0.04$ by binomial test, given a population prevalence estimate of 8%) and was consistent with previous studies using ambulatory subjects with schizophrenia. Furthermore, when all available subjects assessed for nailfold plexus visibility in the larger family study were included (total $n=140$), high NPV was found to be significantly associated with schizophrenia spectrum psychosis by Fisher's Exact Test (rate=21.4% ($n=28$) vs. 8.04% in controls ($n=112$), $P=0.05$). The high and low NPV schizophrenia groups did not differ in age (Means=38 and 45 years respectively, $t(22)=2.12$, ns) or in proportion that were female (0.40 and 0.32 respectively, $t(22)=0.12$, ns). The results of the analyses of differences between schizophrenia subjects with high and low NPV are presented in Table 1. Means and standard deviations of the main variables of interest for the high and low NPV groups are included in the table.

When PVS score was analyzed as a continuous variable, schizophrenia patients with greater plexus visibility had higher ratings of negative symptomatology on the SANS, $t(22)=0.40$, $P=0.05$, and showed a trend toward higher negative symptom ratings on the BPRS negative symptom factor, $t(22)=0.35$, $P=0.09$. Using the categorical ratings, high NPV schizophrenia patients had more negative symptoms on the BPRS than low NPV schizophrenia patients, $t(22)=4.94$, $P=0.04$. However, the groups failed to differ on negative symptoms on the SANS, $t(22)=2.28$, ns . NPV was unrelated to overall level of psychopathology (BPRS total score) or to level of positive symptoms (SAPSsum) in schizophrenia.

Deficits in social and occupational functioning were more pronounced in high NPV schizophrenia subjects. Specifically, high NPV schizophrenia subjects had significantly

fewer non-family social contacts, as measured by the Quality of Life Inventory, $t(22)=4.43$, $P<0.05$, $r(22)=-0.43$, $P<0.03$, and showed a trend toward more impairment in overall social adjustment, $t(22)=3.41$, $P<0.08$. Higher scores indicate more dysfunction on the SAS.

The only group differences on the neuropsychological tests indicated marginally better performance by high NPV subjects on the digit span backwards and delayed response tests. WCST data in these analyses were available for only 15 of the 24 schizophrenia patients (5 high NPV and 10 low NPV subjects). Both WCST variables were significantly correlated with age, but correction for this association did not affect the results. The high and low NPV schizophrenia subject groups did not differ in estimated IQ (Means = 100.8 and 95.1 respectively, $t(22)=0.54$, *ns*) and adjustment for estimated IQ had no significant effects on the results of these analyses.

3.2 NPV in schizophrenia relatives

Comparisons between relatives of high and low NPV patients are summarized in Table 2. 55% (5/9) of relatives of high NPV schizophrenia subjects had high NPV while only 5% (1/19) of relatives of low NPV schizophrenia subjects had high NPV (Fisher Exact Test, $P<0.007$). These two relative groups did not differ on the neuropsychological variables. Relatives of high NPV schizophrenia subjects did not show increases in total SPQ scores or in the social-interpersonal or disorganization factors of the SPQ compared to the relatives of low NPV schizophrenia subjects. However, the relatives of low NPV patients scored higher on the cognitive-perceptual factor, a measure of positive schizotypy (rank-sum test, $P=0.05$). Similarly, the relative groups did not differ on the combined anhedonia Chapman scale (negative schizotypy) but the relatives of low NPV schizophrenia subjects scored higher on the permag (positive schizotypy) scale (rank-sum test, $P=0.004$). Table 2 presents the group means and standard deviations as well as the group difference test results for these analyses. Nonparametric rank-sum tests were performed when group variances were significantly different.

4. Discussion

In this study of nailfold plexus visibility in schizophrenia patients and their biological relatives we confirmed that high NPV is prevalent in individuals with schizophrenia. The schizophrenia patients with increased plexus visibility exhibit more negative symptoms and social dysfunction than patients with normative nailfold plexus visibility. We also found that the relatives of high NPV schizophrenia patients tend to have high NPV and a different pattern of schizotypal symptoms than relatives of low NPV patients. This suggests familial aggregation of the NPV abnormality, which appears to identify risk for a type of schizophrenia with specific clinical characteristics.

Kirkpatrick and colleagues (1989, 2001) have proposed a deficit syndrome in schizophrenia consisting of a specifically defined set of primary enduring negative symptoms. This syndrome shows promise as a discrete subtype of schizophrenia with distinct pathophysiology (Kirkpatrick et al., 2001) but has not yet been investigated with regard to NPV.

In a post-hoc analysis, we explored the relationship between NPV and deficit syndrome symptoms in schizophrenia. We modified the BPRS negative symptom factor and the SANS scale to include only items consistent with deficit syndrome symptoms. Specifically, we excluded an item on emotional withdrawal (which can have multiple causes) from the BPRS negative symptoms factor and excluded items on inappropriate affect and attention (which are not part of the deficit syndrome) from the SANS negative symptom score. The results, presented in Table 3, suggest a stronger relationship between high NPV and these more restrictive scales (designated as SANS-ds and BPRS-ds in Table 3) than between high NPV and broadly defined measures of negative symptoms. Therefore, the high NPV phenotype may be associated with the deficit syndrome in schizophrenia rather than negative symptoms in general. Future research on this question should include prospective assessment of deficit syndrome status using the Schedule for the Deficit Syndrome (Kirkpatrick et al., 1989) in patients also rated on NPV.

We did not have sufficient numbers of high NPV families available in this sample to assess whether schizotypy correlated with plexus visibility level within families, as demonstrated by Buchanan and Jones (1969). When examined across families, the relatives of high NPV patients did not differ from the relatives of low NPV patients on total schizotypy as measured by the SPQ, or on measures of negative symptom schizotypy. However, the relatives of low NPV patients scored significantly higher on positive schizotypy measures derived from both the SPQ and the Chapman scales, partially supporting our hypothesis. Thus, the clinically well relatives of high NPV patients may be better characterized as having a distinct pattern of symptoms on scales of schizotypy compared to relatives of low NPV patients, rather than as demonstrating more generalized deviance.

High NPV patients performed more poorly on the COWAT and the WCST in this study, but not significantly so. Therefore, this work did not confirm a differential deficit in these frontal lobe tasks among patients with high NPV, as originally demonstrated by Curtis et al. (1999). In part, this may have resulted from low power to detect such differences in this sample, especially with regard to WCST data. Given their large sample size, Curtis et al. (1999) were also able to exclude subjects with intermediate levels of NPV from their analyses, thereby likely strengthening their group differences. On the other hand, the high NPV schizophrenia patients tended to perform better on the digit span backwards and delayed response tasks in this study. Analogous to the findings on schizotypy in relatives noted above, it is possible that high NPV patients are better described as exhibiting a different pattern of frontal lobe task performance than other patients with schizophrenia rather than greater deficits across the board. This question bears further examination. There were no significant differences between first-degree relatives of high and low NPV schizophrenia patients on neuropsychological variables in this study.

It is of interest to characterize the central nervous system bases for the differences between schizophrenia subjects with high versus low NPV levels. We had access to Magnetic Resonance Imaging (MRI) scans of the brains of 7 of the schizophrenia subjects in this study, which allowed us to take a preliminary look at this question. Structural MRI images and Diffusion Tensor Imaging (DTI) were obtained in a 1.5 Tesla GE Signa LX Scanner. A measure of cerebral spinal fluid volume as a percentage of total brain volume (CSF %) was

obtained from segmentation of the structural MRI scans, and frontal lobe fractional anisotropy (frontal FA) was calculated from the DTI scans as a measure of frontal white matter tract structural integrity (details of these methods available upon request). Decreased fractional anisotropy has been demonstrated in the white matter of patients with schizophrenia (Lim et al., 1999). In this group of seven subjects CSF% was highly positively correlated with NPV ($r=0.71$, $P=.08$) while the correlation of frontal FA with NPV was negligible ($r=0.10$, ns). Thus, this preliminary data suggests that ventriculomegaly may increase at higher levels of NPV, in contrast to Curtis et al.'s (1999) surprising finding of less ventriculomegaly in high NPV subjects. Our center has since transitioned to a 3 Tesla scanner, and it will be important to follow up this preliminary data with brain imaging in a larger sample of schizophrenia subjects characterized with respect to NPV.

Acknowledgments

This work was supported by grants from the Department of Veterans Affairs Medical Research Service (Dr. Sponheim) and by the Mental Health Patient Service Line at the Veterans Affairs Medical Center, Minneapolis, Minnesota. Presented in part at the International Congress on Schizophrenia Research (2005), Savannah, Georgia.

References

- Andreasen NC. 1982; Negative symptoms in schizophrenia. Definition and validation. Archives of General Psychiatry. 39:784–788. [PubMed: 7165477]
- Andreasen NC, Olsen S. 1982; Negative v positive schizophrenia. Definition and validation. Archives of General Psychiatry. 39:789–794. [PubMed: 7165478]
- Booker BH, Cyr JJ. 1986; Tables for clinicians to use to convert WAIS-R short forms. Journal of Clinical Psychology. 42:983.
- Buchanan CE, Jones MB. 1969; A within-family study of schizophrenia and a visible subpapillary plexus in the nailfold. Schizophrenia. 1:61–75.
- Calkins ME, Curtis CE, Grove WM, Iacono WG. 2004; Multiple dimensions of schizotypy in first degree biological relatives of schizophrenia patients. Schizophrenia Bulletin. 30(2):317–325. [PubMed: 15279049]
- Chapman LJ, Chapman JP, Raulin ML. 1976; Scales for physical and social anhedonia. Journal of Abnormal Psychology. 85(4):374–382. [PubMed: 956504]
- Chapman LJ, Chapman JP, Raulin ML. 1978; Body image aberration in schizophrenia. Journal of Abnormal Psychology. 87:399–407. [PubMed: 681612]
- Cirillo, MA. Plexus visibility and cultured fibroblast functioning in schizophrenia [Dissertation]. University of Texas; Austin: 1997. Unpublished Ph.D. Doctoral Dissertation
- Clementz BA, Iacono WG, Ficken J, Beiser M. 1992; A family study of nailfold plexus visibility in psychotic disorders. Biological Psychiatry. 31(4):378–390. [PubMed: 1558900]
- Curtis CE, Iacono WG, Beiser M. 1999; Relationship between nailfold plexus visibility and clinical, neuropsychological, and brain structural measures in schizophrenia. Biological Psychiatry. 46(1): 102–109. [PubMed: 10394479]
- Eckblad, M, Chapman, LJ, Chapman, JP, Mishlove, M. The Revised Social Anhedonia Scale. University of Wisconsin; Madison: 1982. Unpublished manuscript
- Eckblad ML, Chapman LJ. 1983; Magical ideation as an indicator of schizotypy. Journal of Consulting and Clinical Psychology. 51:215–225. [PubMed: 6841765]
- Gooding DC, Miller MD. 1998; Nailfold capillary plexus visibility in relation to schizotypy. Schizophrenia Research. 32:207–221. [PubMed: 9720126]
- Gottesman II, Gould TD. 2003; The endophenotype concept in psychiatry: Etymology and strategic intentions. American Journal of Psychiatry. 160:1–10.

- Gottesman, II, Shields, J. Schizophrenia and Genetics: A Twin Study Vantage Point. New York: Academic Press; 1972.
- Granier F, Vayssairait M, Priollet P, Housset E. 1986; Nailfold capillary microscopy in mixed connective tissue disease: Comparison with systemic sclerosis and systemic lupus erythematosus. *Arthritis and Rheumatism*. 29(2):189–195. [PubMed: 3954804]
- Hamilton, D. Psychometric and neuropsychological correlates of nailfold plexus visibility and neurologic liability in a college sample [Dissertation]. University of Texas; Austin: 1994. Unpublished Ph.D. Doctoral Dissertation
- Hauptman A, Myerson A. 1948; Studies of finger capillaries in schizophrenia and manic-depressive psychoses. *Journal of Nervous and Mental Disease*. 108(2):91–108. [PubMed: 18876437]
- Heaton, RK, Chelune, GJ, Talley, JL, Kay, GG, Curtis, G. The Wisconsin Card Sorting Test Manual - Revised and Expanded. Psychological Assessment Resources, Inc.; Odessa, FL: 1993.
- Iacono WG. 1985; Psychophysiological markers of psychopathology: A review. *Canadian Psychology*. 26:96–112.
- Jones MB, Whitson DW. 1971; Visibility of the nailfold capillaries in retarded adolescents. *Biological Psychiatry*. 3:331–337. [PubMed: 4273867]
- Katsanis J, Iacono WG, Beiser M. 1990; Anhedonia and perceptual aberration in first-episode psychotic patients and their relatives. *Journal of Abnormal Psychology*. 99:202–206. [PubMed: 2348016]
- Kirkpatrick B, Buchanan RW, McKenney PD, Alphs LD, Carpenter WT. 1989; The schedule for the Deficit Syndrome: An instrument for research in schizophrenia. *Psychiatry Research*. 30:119–124. [PubMed: 2616682]
- Kirkpatrick B, Buchanan RW, Ross DE, Carpenter WT. 2001; A separate disease within the syndrome of schizophrenia. *Archives of General Psychiatry*. 58:165–171. [PubMed: 11177118]
- Kremen WS, Faraone SV, Toomey R, Seidman LJ, Tsuang MT. 1998; Sex differences in self-reported schizotypal traits in relatives of schizophrenic probands. *Schizophrenia Research*. 34:27–37. [PubMed: 9824874]
- Lehman AF. 1988; A quality of life interview for the chronically mentally ill. *Evaluation and Program Planning*. 11:51–62.
- Lezak, M. Neuropsychological Assessment. 3. Oxford University Press; New York: 1995.
- Lim KO, Hedehus M, Moseley M, deCrespigny A, Sullivan EV, Pfefferbaum A. 1999; Compromised white matter tract integrity in schizophrenia inferred from diffusion tensor imaging. *Archives of General Psychiatry*. 56:367–374. [PubMed: 10197834]
- Maricq HR. 1963; Capillary pattern in familial schizophrenics: A study of nailfold capillaries. *Circulation*. 272:406–413.
- Maricq HR. 1964; A study of subpapillary plexus in the nailfold in mental defectives. *Journal of Nervous and Mental Disease*. 139:287–293. [PubMed: 14212181]
- Maricq HR. 1970; Wide field” photography of nailfold capillary bed and a scale of plexus visibility scores (PVS). *Microvascular Research*. 2:335–340. [PubMed: 5523933]
- Maricq, HR; Blume, RS; LeRoy, EC. Wide-field study of nailfold capillary bed in disorders of connective tissue. Sixth European Conference of Microcirculation; 1970. 116–122.
- Maricq HR, Jarvik LF, Ranier JD. 1968; Chronic schizophrenia, lymphocyte growth, and nailfold plexus visualization score. *Diseases of the Nervous System*. 29:659–667. [PubMed: 5717281]
- Maricq HR, Jones MB. 1976; Visibility of the nailfold plexus and schizophrenia. *Biological Psychiatry*. 11(2):205–215. [PubMed: 971446]
- Meehl PE. 1962; Schizotaxia, schizotypy, schizophrenia. *The American Psychologist*. 17:827–838.
- Norris AS, Chowning JR. 1964; Capillary morphology and the nailfold in the mentally ill. *Journal of Neuropsychiatry*. 5:225–234. [PubMed: 14147034]
- Park S, Holzman PS. 1992; Schizophrenics show spatial working memory deficits. *Archives of General Psychiatry*. 49(12):975–982. [PubMed: 1449384]
- Pokorny AD, Mefferd RB, Stevens GM. 1970; Nailfold capillary plexus and schizophrenia. *Journal of Nervous and Mental Disease*. 150:146–154. [PubMed: 5417540]

- Poole, JH. Plexus visibility in schizophrenic, schizoaffective, and other psychiatric disorders [Dissertation]. University of Texas; Austin: 1993. Unpublished Ph.D. Doctoral Dissertation
- Poole JH, Maricq HR, Alson E, Willerman L. 1991; Negative symptoms in schizophrenia and nailfold plexus visibility. *Biological Psychiatry*. 29(8):757–773. [PubMed: 2054450]
- Poole JH, Maricq HR, Willerman L. 1993; Negative symptoms of schizophrenia and plexus visibility: A replication with medicated and unmedicated patients. *Biological Psychiatry*. 34(6):414–416. [PubMed: 8105980]
- Raine A. 1991; The SPQ: A scale for the assessment of schizotypal personality based on DSM -III-R criteria. *Schizophrenia Bulletin*. 14(4):555–564.
- Roberts SB, MacLean CJ, Neale MC, Eaves LJ, Kendler KS. 1999; Replication of linkage studies of complex traits: An examination of variation in location estimates. *American Journal of Human Genetics*. 65(3):876–884. [PubMed: 10441592]
- Schooler, NR, Hogarty, GE, Weissman, MM. Social Adjustment Scale II (SAS II). In: Hargreaves, WA, Attkisson, CC, Sorenson, JE, editors *Resource Materials for Community Mental Health Program Evaluators*. U.S. Department of Health, Education and Welfare; Washington, D.C.: 1979. 290–330.
- Sponheim SR, Iacono WG, Thuras PD, Nugent SM, Beiser M. 2003; Sensitivity and specificity of select biological indices in characterizing psychotic patients and their relatives. *Schizophrenia Research*. 63(1–2):27–38. [PubMed: 12892855]
- Sponheim SR, Steele VR, McGuire KA. 2004; Verbal memory processes in schizophrenia patients and biological relatives of schizophrenia patients: Intact implicit memory, impaired explicit recollection. *Schizophrenia Research*. 71:339–348. [PubMed: 15474904]
- Ventura J, Lukoff D, Nuechterlein KH, Liberman RP, Green MF, Shaner A. 1993; Manual for the expanded Brief Psychiatric Rating Scale. *International Journal of Methods in Psychiatric Research*. 3:227–243.
- Ventura J, Nuechterlein KH, Subotnik KL, Gutkind D, Gilbert EA. 2000; Symptom dimensions in recent-onset schizophrenia and mania: A principal components analysis of the 24-item Brief Psychiatric Rating Scale. *Psychiatry Research*. 97(2–3):129–135. [PubMed: 11166085]
- Wechsler, D. Manual for the Wechsler Adult Intelligence Scale. 3. Psychological Corporation; San Antonio, TX: 1997.
- Wertheimer N, Wertheimer M. 1955; Capillary structure: Its relationship to psychiatric diagnosis and morphology. *Journal of Nervous and Mental Disease*. 122:14–27. [PubMed: 13278739]
- Yaralian PS, Raine A, Lencz T, Hooley JM, Bihle SE, Milles S, Ventura J. 2000; Elevated levels of cognitive-perceptual deficits in individuals with a family history of schizophrenia spectrum disorders. *Schizophrenia Research*. 46:57–63. [PubMed: 11099886]

Table 1

Functional differences between High and Low NPV schizophrenia subjects on symptoms, social functioning and cognition

Variables	High NPV subjects (n=5)		Low NPV subjects (n=19)		Categorical Analysis		Continuous Analysis	
	Mean (S.D.)		Mean (S.D.)		Test Value(df)	P value	Test Value (df)	P value
<u>Clinical Symptoms</u>								
SANSSum	27.20(9.04)		20.05(9.49)		$\chi^2(2) = 2.28$	0.14	$\chi^2(2) = 0.40$	0.05
BPRSnegative	7.80(2.95)		5.68(1.57)		$\chi^2(2) = 4.94$	0.04	$\chi^2(2) = 0.35$	0.09
SAPSSum	20.20(17.3)		18.89(15.5)		$\chi^2(2) = 0.03$	0.87	$\chi^2(2) = 0.10$	0.65
BPRS total	44.20(13.1)		41.94(9.67)		$\chi^2(2) = 0.18$	0.67	$\chi^2(2) = 0.16$	0.48
<u>Social/Occupational</u>								
Nonfamily Social	9.40(5.18)		13.15(3.08)		$\chi^2(2) = 4.43$	0.05	$\chi^2(2) = -0.43$	0.03
Employed	20%		53%		Fisher Exact Test	0.22	NA	NA
Global Work	4.80(1.30)		3.74(1.37)		$\chi^2(2) = 2.43$	0.13	$\chi^2(2) = 0.21$	0.32
Global Adjustment	3.60(0.55)		3.00(0.67)		$\chi^2(2) = 3.41$	0.08	$\chi^2(2) = 0.29$	0.16
<u>Neuropsychological</u>								
Digit Span Backward	8.20(1.92)		6.05(1.95)		$\chi^2(2) = 4.74$	0.04	$\chi^2(2) = 0.37$	0.08
COWAT	31.40(9.48)		39.79(13.3)		$\chi^2(2) = 1.72$	0.20	$\chi^2(2) = 0.20$	0.35
Delayed Response Test	12.95(3.50)		20.84(8.51)		$\chi^2(2) = 4.01$	0.06	$\chi^2(2) = -0.35$	0.09
WCST-perseverations	34.40(24.6) n=5		27.00(16.1) n=10		$\chi^2(2) = 0.50$	0.49	$\chi^2(2) = 0.11$	0.70
WCST-categories	3.00(2.55) n=5		3.70(2.11) n=10		$\chi^2(2) = 0.32$	0.83	$\chi^2(2) = -0.31$	0.26

NPV=naïfold plexus visibility, S.D.=standard deviation. SANSSum=Schedule for the Assessment of Negative Symptoms total score. BPRSnegative=negative factor score on Brief Psychiatric Rating Scale 24-item version. SAPSSum=Schedule for the Assessment of Positive Symptoms total score. NA=not applicable. BPRS total=BPRS total score. Nonfamily Social=Social contacts outside the family from the Quality of Life Interview. Global Work and Global Adjustment are taken from the Social Adjustment Scale. Digit Span Backward=cumulative score from Digit Span Backward. COWAT=Controlled Oral Word Association Test. WCST-perseverations and WCST-categories = number of perseveration errors and number of categories achieved in the Wisconsin Card Sort Test.

Table 2
Functional differences between first-degree relatives of High and Low NPV schizophrenia subjects

Variables	Relatives of High NPV patients (n=9)	Relatives of Low NPV patients (n=19)	Test Value (df)	P value
	Mean (S.D.)	Mean (S.D.)		
<u>Neuropsychological</u>				
Digit Span Backward	7.22(1.56)	6.22(2.37)	$\chi^2(26)=1.31$	0.26
COWAT	45.88(11.4)	41.94(8.21)	$\chi^2(26)=1.07$	0.31
Delayed Response Test	12.67(5.07)	10.46(12.0)	rank-sum	0.50
<u>Schizotypal Symptom Inventories</u>				
SPQ Total	11.11(5.06)	16.82(13.8)	$\chi^2(26)=1.42$	0.25
SPQ Cognitive/Perceptual	2.67(2.40)	6.59(5.73)	rank-sum	0.05
SPQ Social/Interpersonal	6.67(5.55)	8.18(6.44)	$\chi^2(26)=0.35$	0.56
SPQ Disorganization	2.33(1.87)	3.65(3.95)	$\chi^2(26)=0.88$	0.36
Permag	2.11(1.62)	7.38(5.91)	rank-sum	0.005
Social/Physical Anhedonia	20.11(9.75)	20.88(9.87)	rank-sum	0.85

NPV=naïfold plexus visibility. S.D.=standard deviation. Digit Span Backward=cumulative score from Digit Span Backward. COWAT=Controlled Oral Word Association Test. SPQ Total=Schizotypal Personality Questionnaire (SPQ) total score. Cognitive/Perceptual, Social/Interpersonal, and Disorganization refer to factor scores on the SPQ. PerMag=score on combination of Perceptual Aberration and Magical Ideation Chapman scales. Social/Physical Anhedonia=score on combination of Social Anhedonia and Physical Anhedonia Chapman scales.

Table 3

Negative symptoms vs. deficit symptoms across NPV levels in schizophrenia

Variables	High NPV subjects (<i>n</i> =5)		Low NPV subjects (<i>n</i> =19)		Categorical Analysis		Continuous Analysis	
	Mean (S.D.)		Mean (S.D.)		Test Value(<i>df</i>)	<i>p</i> value	Test Value (<i>df</i>)	<i>P</i> value
<u>Negative Symptoms</u>								
SANSsum	27.20(9.04)		20.05(9.49)		$\chi^2(2)=2.28$	0.14	$t(22)=0.40$	0.05
BPRSnegative	7.80(2.94)		5.68(1.56)		$\chi^2(2)=4.94$	0.04	$t(22)=0.35$	0.09
<u>Deficit Symptoms</u>								
SANS-ds	26.40(9.07)		17.42(8.74)		$\chi^2(2)=4.12$	0.05	$t(22)=0.45$	0.03
BPRS-ds	5.20(1.64)		3.57(1.26)		$\chi^2(2)=5.80$	0.02	$t(22)=0.48$	0.02

NPV=naifold plexus visibility. S.D.=standard deviation. SANSsum=Schedule for the Assessment of Negative Symptoms (SANS) total score. BPRSnegative=negative factor score on Brief Psychiatric Rating Scale (BPRS) 24-item version. SANS-ds=score on modification of the SANSsum to eliminate items inconsistent with the deficit syndrome. BPRS-ds=score on modification of BPRSnegative to eliminate items inconsistent with the deficit syndrome.