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COGNITION AND COMMUNITY FUNCTIONING IN SCHIZOPHRENIA: THE NATURE OF THE RELATIONSHIP

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Abstract

Although cognition is one of the most important predictors of community functioning in schizophrenia, little is known about the causes of this correlation. To our knowledge, this study is the first to examine the extent to which this correlation is genetically mediated and whether the genetic correlation is specific to schizophrenia. Six hundred and thirty-six participants from 43 multigenerational families with at least two relatives with schizophrenia and 135 unrelated controls underwent diagnostic interview and cognition and functioning assessment. Quantitative genetic analyses were conducted using maximum-likelihood variance decomposition methods implemented in SOLAR (Almasy & Blangero, 1998). Among patients with schizophrenia, cognition and community functioning were positively correlated and genetic effects shared between them were significant contributors to this relationship whereas environmental effects shared between them were not. In contrast, genetic effects were not shared significantly between cognition in depressed or non-diagnosed relatives and community functioning in schizophrenia. In all analyses, the contributions of social cognition to community functioning were accounted for by general cognition. These findings support heritable factors that contribute to the correlation between cognition and community functioning that are relatively specific to schizophrenia and are not significantly shared with depression or a lack of psychopathology. This suggests the possibility of identifying specific genetic variants that contribute to this correlation and to these important individual differences among schizophrenia patients.

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Keywords

schizophrenia; heritability; genetic correlation; general cognition; social cognition; community functioning

Affecting approximately one in every hundred individuals over one's lifetime, schizophrenia is one of the leading causes of disability worldwide (Murray & Lopez, 1997). Much of this disability and its associated economic cost reflect the decreased occupational and social functioning (i.e., community functioning) that many schizophrenia patients exhibit, which often arises before the emergence of psychotic symptoms and typically persists for many years afterward (Agerbo, Byrne, Eaton, & Mortensen, 2004; Racenstein et al., 2002). Although these functioning deficits were key for Kraepelin (1971) in his conceptualization of Dementia Praecox and remain necessary for receiving the diagnosis (American Psychiatric Association, 2013), the degree of functional impairment varies substantially across individuals (Palmer et al., 2002). Given its personal and societal importance, much research has sought to predict, understand, and treat individual differences in functional impairment among schizophrenia patients.

Cognitive deficits are one of the best predictors of community functioning impairment in schizophrenia, yielding a correlation in a recent meta-analysis of approximately 0.25 (Fett et al., 2011). Also beginning with Kraepelin (1971), cognitive deficits have been consistently identified as an important feature of the diagnosis (Dickinson, Ragland, Gold, & Gur, 2008) but nevertheless they vary as much as community functioning among patients with schizophrenia (Joyce & Roiser, 2007). The substantial body of research on the correlation between cognition and community functioning in schizophrenia has however focused little on its underlying causes. Especially notable is the lack of studies examining the degree to which genetic factors might contribute to this correlation. Thus, the aim of this study is to examine the genetic and environmental causes and diagnostic specificity of the correlation between cognition and community functioning among schizophrenia patients.

Cognition and Community Functioning in Schizophrenia

In a literature currently spanning more than 200 studies, there is overall replicable evidence of a correlation of approximately 0.25 between cognition and community functioning in schizophrenia (Fett et al., 2011). As background for this study, we consider how cognition and functioning have been measured, how specific cognitive domains might relate to functioning, and the degree of specificity of these associations to schizophrenia compared to other diagnoses.

Previous research has generally assessed community functioning in three general ways: patient self-report questionnaires, patient role play, and interviewer ratings of real-world functioning (Figueira & Brissos, 2011). Because it can be considered a "gold standard" for real-world functioning compared to other measurement approaches (Priebe, 2007), this study assessed functioning using trained interviewers rating multiple objective outcomes.

Previous research has also addressed the question of whether some cognitive domains are more correlated with functioning than others. In the most recent meta-analysis, general (nonsocial) cognition was significantly correlated with community functioning (r=0.25) (Fett et al., 2011) and of specific general cognitive tasks, only verbal fluency was somewhat more highly correlated with functioning (r=0.32). Although specific nonsocial cognitive tasks appear to be largely similar to general cognition in their ability to predict functioning, social cognition has often been proposed to be a better predictor of functioning. In a recent review, all ten studies examining general cognition as a predictor of community functioning provided evidence for a potential role for social cognition, with predictive effects shared with general cognition (correlations) ranging from 0.14 to 0.28 (S. J. Schmidt, Mueller, & Roder, 2011), although its independent contribution is less clear. Overall then, general cognition is associated with functioning in schizophrenia and encompasses much of the variance in functioning predicted by specific cognitive domains. To examine whether social cognition may enhance prediction of functioning over and above that of general cognition, we also examined correlations with our measures of social cognition after controlling for general cognition.

Few studies have even compared the size of the correlation between cognition and functioning in schizophrenia to that within other diagnoses, and those few have suggested that cognition may be more highly associated with functioning in schizophrenia than in bipolar disorder (Jabben, Arts, van Os, & Krabbendam, 2010; Martínez-Arán et al., 2001). Here, to address etiological specificity more directly, we examined the correlation between cognition and community functioning *across* schizophrenia and depression and no psychopathology.

Given that schizophrenia is a highly heritable disorder, with approximately 65% to 80% of liability attributable to genetic variation (Lichtenstein et al., 2009), it is surprising that the heritability of cognitive and functional deficits has remained largely unexplored among relatives with schizophrenia. Although several studies have examined the familiality of cognition across non-schizophrenia relatives of schizophrenia patients (Calkins et al., 2010; Glahn et al., 2015), the only study to our knowledge of the familiality of cognition among schizophrenia patients reported that concordant first-degree relatives demonstrated correlated performance on some specific cognitive measures (Hoff et al., 2005). Similarly, five of six studies found composite and global measures of functioning in schizophrenia to be familial (Burke, Murphy, Bray, Walsh, & Kendler, 1996; Cardno et al., 1998; Deshpande et al., 2004; Kendler et al., 1997; McGrath et al., 2009; Vassos et al., 2008) whereas familial effects on specific functioning measures were mixed (Bhatia, Franzos, Wood, Nimgaonkar, & Deshpande, 2004; Deshpande et al., 2004; Wickham et al., 2002).

Although this small body of research suggests that variation in both cognition and community functioning among schizophrenia patients may each be affected by genetic variation, we sought to examine, utilizing an extended pedigree design that includes several degrees of kinship (i.e., first- through fourth-degree relatives), the extent to which the observed phenotypic correlation between cognitive performance and community functioning is mediated by genetic and environmental effects shared between them. Observed, or phenotypic, correlations between variation in one trait (such as cognition) and variation in

another trait (such as community functioning) can arise from several possible general causes. For example, genetic effects on cognition and genetic effects on functioning may be correlated; this genetic correlation (R_G) is reflected in (along with the heritability of each trait) the extent to which relatives' cognition correlates with other relatives' functioning (i.e., a cross-trait, cross-relative correlation). Genetic effects can be estimated by comparing these cross-correlations across relatives who differ in their genetic relatedness, such as first-degree relatives (sharing 50% of genetic variation) versus second-degree relatives (sharing 25%), versus third-degree relatives (sharing 12.5%), versus fourth-degree relatives (sharing 6.25%), assuming that relatives' resemblance for environmental effects also does not vary linearly with kinship. To the extent that environmental resemblance varies linearly with kinship, estimates of genetic effects will be overestimated. Environmental effects on cognition may also be correlated with environmental effects on functioning; this environmental correlation (R_E) is reflected in (along with the environmentality of each trait) the degree to which the phenotypic correlation between traits exceeds their genetic correlation and their respective heritabilities. That is, traits correlate within individuals because individuals share both genetic and environmental effects with themselves, whereas traits correlate across relatives linearly according to kinship due to correlated genetic effects across traits (Neale & Cardon, 1992), assuming that environmental effects shared among relatives do not also vary linearly with kinship.

To better understand the nature of genetic effects on the correlation between cognition and community functioning, we utilized a multiplex (multiple schizophrenia relatives per family), extended pedigree design (first through fourth degree relatives of schizophrenia probands) (R. E. Gur et al., 2007). Sampling large pedigrees allows us to estimate additive genetic effects (assuming resemblance for environmental effects does not vary similarly) by comparing observed resemblance across linearly varying degrees of kinship in contrast to typical studies of only first-degree relatives. In addition, the multiplex ascertainment strategy should enrich for genetic effects. The sample also includes relatives of schizophrenia probands who meet diagnostic criteria for other disorders, rendering them potentially useful for addressing the specificity of the correlation between cognition and community functioning to schizophrenia compared to other diagnoses.

Questions & Hypotheses

The primary aim of this study was to determine the relative influence and diagnostic specificity of correlated genetic and environmental effects on the correlation between cognition and community functioning in schizophrenia. First, we aimed to replicate prior research showing mean deficits in cognition and functioning in schizophrenia compared with controls and a significant phenotypic correlation between cognition and community functioning approximating 0.25 in schizophrenia. We also sought to estimate heritabilities for cognition and community functioning among schizophrenia relatives. The novel questions we then addressed are:

1. Among relatives concordant for schizophrenia, what are the genetic and environmental correlations between cognition and community functioning?

2. Are these genetic correlations specific to schizophrenia or are they shared between schizophrenia and other diagnoses (i.e., depression and no diagnoses)?

METHOD

PARTICIPANTS

The Multiplex, Multigenerational Genetics Investigation of Schizophrenia (MGI) Study (R. E. Gur et al., 2007) is a multi-site study based at the University of Pittsburgh, the University of Pennsylvania, and the Texas Biomedical Research Institute. All participants provided consent (or assent when applicable) according to protocols approved by their respective Institutional Review Boards (Pitt PRO 14120059, Penn 064200, TBRI HSC20010232H).

Probands were recruited at the University of Pittsburgh and the University of Pennsylvania through mental health and consumer organizations throughout Pennsylvania, New Jersey, Delaware, Ohio, West Virginia, Kentucky, Michigan and Indiana. Probands had a DSM-IV diagnosis of schizophrenia, were of European-American descent, proficient in English, at least 18 years old, and provided consent to contact at least one first-degree relative with a diagnosis of schizophrenia or schizoaffective disorder – depressed type and ten or more first- through fourth-degree relatives. Probands were not selected based on cognitive performance. Inclusion criteria for relatives were being at least 15 years old, European-American, proficient in English, and free of any brain injury or disorder that would interfere with interpretation of cognitive measures.

European-American individuals aged 18–84 were recruited for the control group. At Pittsburgh, potential control individuals residing in the regions from which most probands and their relatives had been recruited were contacted through random-digit dialing and efforts were made to group-match to the relatives based on average age and sex ratio. Controls at the University of Pennsylvania were recruited through advertisements. Controls were excluded if they or a first-degree relative had been diagnosed with a schizophrenia spectrum or psychotic disorder, were taking antipsychotic medications, experienced a recent exacerbation of non-psychotic psychiatric symptoms, underwent electroconvulsive therapy or treatment for substance abuse in the past six months, or reported a medical condition, head injury or sensory or physical impairments that could interfere with completion of study measures.

The final sample included 771 participants with diagnostic information who had at least two of the four functioning measures or at least six of the 11 cognition measures, for a total of 636 relatives from 43 multiplex, multigenerational families and 135 unrelated controls. Only two unrelated pedigree members, both diagnosed with schizophrenia, were excluded from this final sample because they had fewer than half of both Cognition and Functioning variables (having data for five Cognition variables and one Functioning variables). More than 60% of participants had complete data for all Cognition and Functioning variables. Eight pedigree members who had Functioning data had invalid computerized cognitive data (these included four individuals in the Schizophrenia group, two individuals in the No Diagnoses group, and two individuals with other psychopathology). Since their cognitive testing differed from the rest of the sample, their data on the pencil-and-paper tasks (Trails

A, Trails B and CVLT) were also excluded. Sample sizes for each measure are presented in Supplemental Table 1.

Relatives were classified into five hierarchical, mutually exclusive diagnostic groups: schizophrenia (*N*=103, including 10 individuals with schizoaffective disorder – depressed type and 4 individuals with schizoaffective disorder – manic type), depression (*N*=109), other diagnosis (*N*=169), and no diagnoses (*N*=255). Due to their diagnostic heterogeneity, relatives in the Other diagnoses group were not included in further analyses. Within the control group (*N*=135), 21 individuals were diagnosed with depression, nine with substance abuse, three with concomitant depression and substance abuse, five with adjustment disorder, two with depressive disorder (not otherwise specified), and 95 with no diagnoses. The schizophrenia group had a significantly higher proportion of males, fewer years of education, and lower Wide Range Achievement Test Reading scores (WRAT; Jastak & Jastak, 1978) than other groups; controls were significantly older, more educated, and had higher WRAT scores than the pedigree groups. There were no significant differences among groups in parental education (Table 1). The average age of psychosis onset for schizophrenia relatives was 20.6 (SD=8.5), duration of illness was 25.1 years (SD=12.9), and 83.5% reported currently taking antipsychotic medication, with an average chlorpromazine equivalent daily dosage of 938.5mg (SD=1322.4) (Woods, 2003). For depressed relatives, onset of depression averaged 25.2 years (SD=11.9) and duration of illness averaged 17.5 years (SD=13.1).

Within families, the number of pairings between schizophrenia relatives was 105; between schizophrenia and depressed relatives was 300; and between schizophrenia and non-diagnosed relatives was 651.

MEASURES

Diagnostic Assessment—Participants underwent clinical evaluation using the Diagnostic Interview for Genetic Studies, version 2.0 (DIGS) (Nurnberger et al., 1994), the Family Interview for Genetic Studies (FIGS) (Maxwell, 1992), and a review of medical records if available. Assessment was conducted in person, usually in the person's home, by trained interviewers who were not blind to the participant's status (i.e., proband/relative/control). At least two investigators (licensed psychologists and psychiatrists) reviewed each case and resolved differences by consensus to provide DSM-IV lifetime diagnoses. In addition, current schizophrenia symptomatology was rated with the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989), with scores ranging from 0 to 5. Summary scores for the SANS and SAPS were derived from the mean of global ratings for each symptom subscale. As expected for a community-based sample, schizophrenia relatives showed relatively low levels of symptoms on average based on ratings for the SAPS (*M*=0.94, *SD*=0.76) and SANS (*M*=1.52, *SD*=1.02).

Community Functioning—To reflect the domains included in other standard measures of community functioning used in schizophrenia research (e.g., Strauss-Carpenter Level of Functioning Scale (Strauss & Carpenter, 1977) and the Major Role Adjustment Inventory

(Hogarty, Goldberg, & Schooler, 1974), the following four objective measures of current community functioning from the DIGS were selected and coded so that high scores reflected better functioning.

Current marital status. (DIGS A7): As a measure of social functioning, participants were ranked as: 1) never married; 2) separated or divorced; 3) married or widowed.

Current living situation. (DIGS A8): As a measure of independent living, participants were ranked as living: 1) in a residential treatment facility; 2) in home of relatives; 3) alone or with roommates (i.e. non-lineal relatives or friends); 4) with unmarried partner for at least one year; 5) in own home with spouse and/or children.

Current occupational status. (DIGS A10): As a measure of work functioning employment was ranked (Hollingshead, 1975) as: 1) unemployed (under the age of 65); 2) disabled; 3) homemaker; 4) operators, fabricators, and laborers; 5) farming, forestry fishing, production, craft and repair; 6) service; 7) full time student; 8) technical, sales, and administrative support; 9) professional; 10) managerial positions. For individuals who were retired (unemployed and over the age of 65), the most responsible job they had ever held was coded as their occupational status according to the ordered ranking.

Current global functioning. (DIGS T3): The Global Assessment of Functioning Scale (GAF) (Endicott, Spitzer, Fleiss, & Cohen, 1976) gauges lowest level of functioning during the past month on a scale of 1 to 100, with 1 representing the most impairment and 100 representing the most adaptive.

Cognition—Participants were administered the 60-minute Penn Computerized Neurocognitive Battery (CNB) (R. C. Gur, Ragland, Moberg, Bilker, et al., 2001; R. C. Gur, Ragland, Moberg, Turner, et al., 2001) in a fixed order using laptop computers. Accuracy and median reaction times for correct items were recorded for each test. Efficiency scores were then calculated for each domain by averaging accuracy and speed (both standardized based on the control group performance); higher efficiency scores thus reflect equal contributions of accuracy and speed of performance.

The following tests assessed General Cognition:

Abstraction and Mental Flexibility: The Penn Conditional Exclusion Test (Kurtz, Ragland, Moberg, & Gur, 2004) simultaneously presents four objects for each trial; the participant then selects the object that does not belong with the other three based on one of three sorting heuristics. Feedback guides the identification of three changes in sorting heuristics. Index of accuracy: (number of categories completed +1)*(number correct responses/total number of responses) (time: 12 minutes).

Attention: The Penn Continuous Performance Test (Kurtz, Ragland, Bilker, Gur, & Gur, 2001) uses a continuous performance test paradigm in which the participant responds to seven-segment displays whenever they form a digit. There is no working memory load since

the stimulus is presented for the full duration of a trial. Number of correct responses (time: 8 minutes).

Verbal Memory: The Penn Word Memory Test (R. C. Gur et al., 1993) presents 20 target words followed by an immediate recognition trial with the targets and 20 distractor words randomly interspersed, and a delayed recognition trial 20 minutes later. The distractor words are chosen to match target words on frequency, length, concreteness, and low imageability using Paivio's norms. Average of correct responses and of reaction times at immediate and after delay yielded overall scores. (time: 4 minutes).

Spatial Memory: The Visual Object Learning Test (Glahn, Gur, Ragland, Censits, & Gur, 1997) presents 20 Euclidean shapes followed by an immediate recognition trial with random foils and a delayed recognition trial 20 minutes later. Number correct responses and reaction times at immediate and after delay were averaged to produce overall scores. (time: 4 minutes).

Spatial Processing: Judgment of Line Orientation (Benton, Varney, & Hamsher, 2012) is a computer adaptation of Benton's test, in which participants are presented two lines at an angle and select the corresponding lines on a simultaneously presented array. Correct responses (time: 6 minutes).

Sensorimotor Dexterity: The participant uses a mouse to click on squares appearing at different locations on the computer screen; the squares become progressively smaller in later trials (time: 2 minutes).

Participants also completed two pencil-and-paper tasks of general cognition:

Trail Making Task: Attention and processing speed were assessed using both versions (A & B) of the Trail Making Task (Reitan, 1958). In Part A, participants are instructed to connect a set of 25 dots each containing a number in sequential order as quickly as possible. In Part B, participants connect dots that alternate between numbers and letters. For both parts, the time to completion (in seconds) was multiplied by −1. Thus, higher scores reflect faster, better performance.

California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, & Ober, 1987): Participants are read aloud a list of sixteen common words belonging in four categories, then are asked to recall (without regard for order) as many of these items as possible after each of five trials. The number of words correctly recalled on the fifth trial was used as a measure of verbal learning and memory.

In addition, participants completed the Reading subtest of the Wide Range Achievement Test (Jastak & Jastak, 1978) to provide an estimate of verbal intelligence.

The CNB also assesses two domains relevant to face processing, a putative aspect of social cognition, Face Memory and Emotion Processing. The face processing index derived from these two tasks was examined in secondary analyses and was found to add little independent

prediction to that provided by general cognition. Further information regarding tasks, analyses and results for face processing can be found in the supplement.

ANALYSES

All measures were first inspected for outliers, skewness, and kurtosis. Using the total pedigree and control sample, because of some significant correlations, all cognition and community functioning measures were residualized for recruitment site, sex, and age and then subjected to separate exploratory factor analyses in Mplus (version 6.11) (Muthén & Muthén, 2007) with orthogonal varimax rotation using WLSMV (weighted least squares, mean- and variance-adjusted), a robust procedure for estimating factor models with ordinal data (Schmitt, 2011). Significance of factors was determined by Horn's parallel analysis, which compares observed eigenvalues with those estimated based on randomized data. Those factors with observed eigenvalues above the 95th percentile of those calculated based on random data are considered significant.

Quantitative genetic analyses were performed in SOLAR (version 4.0.7 (Almasy & Blangero, 1998) using maximum-likelihood variance decomposition to estimate model parameters and likelihood-ratio tests to evaluate their statistical significance. SOLAR maximum-likelihood estimates utilize all the data that are relevant to a particular parameter. Parameters were conservatively estimated using the t-distribution in SOLAR which is robust to non-normal trait distributions (Blangero, Williams, Almasy, 2001). All SOLAR analyses included age and sex as covariates. Although using age as a covariate removes main effects of age, these analyses conservatively assume that genetic and environmental effects are consistent across age and thus generally estimate the average heritability and genetic correlations across ages (if there is any variation in effects across age). To provide a better estimate of general population means and variances, the control group was included in all analyses except where noted.

Heritability was estimated for cognition and community functioning and refers to the proportion of total phenotypic variance (σ^2_P) due to additive genetic effects: $h^2=\sigma^2_G/\sigma^2_P$. It is estimated by comparing the observed phenotypic covariance matrix with the covariance matrix predicted by kinship, such that closer kinship linearly predicts increased resemblance. The significance of the heritability estimate is tested by comparing the likelihood of a model in which σ^2_G is estimated to that of a model in which σ^2_G is constrained to zero. This estimation procedure assumes that resemblance for environmental effects does not vary linearly with degree of kinship. To the extent that environmental effects violate this assumption, heritabilities will be over-estimated. The environmentality of a trait denotes phenotypic variance that is not accounted for by additive genetic effects and is defined as $1.0-h^2$. In the extended pedigree design, environmentality includes environmental effects that are not shared between relatives in a linear fashion according to kinship as well as measurement error.

Bivariate genetic analyses decompose the observed phenotypic correlation between cognition and community functioning among schizophrenia relatives into genetic and environmental correlations, based on degree of kinship. Specifically, cross-correlations between different traits in different relatives arise as a function of the genetic effects on each

trait and the degree of correlation of genetic effects across traits. More formally, $R_{PCSZ1\text{-}FSZ2} = \sqrt{h^2}_{CSZ} * K * R_{GCSZ\text{-}FSZ} * \sqrt{h^2}_{FSZ}$, where $R_{PCSZ1\text{-}FSZ2}$ is an observed cross-trait (i.e., between cognition and functioning) cross-relative correlation, K is the degree of kinship (e.g., 0.50 for first-degree relatives, 0.25 for second-degree), h^2_{CSZ} and h^2_{FSZ} are the heritabilities of cognition and functioning, respectively among schizophrenia relatives. The genetic correlation ($R_{GSZ\text{-}FSZ}$) represents the genetic effects that are correlated between cognition and community functioning among schizophrenia relatives. As above, this estimation procedure assumes that resemblance for correlated environmental effects across traits does not vary linearly with degree of kinship. To the extent that correlated environmental effects violate this assumption, genetic correlations will be over-estimated. The significance of the genetic correlation was tested by comparing the likelihood of a model in which genetic effects on cognition and functioning are estimated compared to a model in which genetic effects on cognition are constrained to be uncorrelated with genetic effects on functioning. Genetic correlations that differ significantly from zero suggest pleiotropy, or correlated genetic effects across cognition and community functioning. The statistical significance of the genetic correlation depends importantly and appropriately on the heritabilities of the two traits (Verhulst, 2017). The total genetic contribution to the phenotypic correlation (i.e., the bivariate heritability) is the square root of the heritability of trait 1 * genetic correlation * the square root of the heritability of trait 2 (e.g., $\sqrt{h^2}_{CSZ} * RG_{CSZ\text{-}FSZ} * \sqrt{h^2}_{FSZ}$). Thus, the genetic correlation can be high but if one or both traits has low heritability, then the overall contribution of genetic effects to the phenotypic correlation between traits will be very small and thus appropriately not significant. For this reason, we interpret only significant genetic correlations. The environmental correlation (R_E) is estimated as the residual portion of the phenotypic covariation between cognition and functioning after accounting for genetic effects. Similar considerations apply to the environmental correlation concerning statistical significance if the one or both environmentalities are low. It is important to note that the initial analyses presented below concern decomposing the correlations between cognition and community functioning among only schizophrenia relatives.

In contrast, to investigate the diagnostic specificity of any significant genetic correlations, correlations between cognition in relatives with other diagnoses (i.e., depression and no diagnosis) and community functioning in schizophrenia relatives were also analyzed. Here, analyses rely not upon correlations between two traits across schizophrenia relatives but upon correlations between two traits across relatives with different diagnoses (i.e., cognition in depressed relatives with community functioning in schizophrenia relatives). As above, such a cross-trait, cross-relative (and now cross-diagnosis) correlation arises as a function of the genetic effects on each trait in each diagnosis and the degree of sharing of these genetic effects. Thus, $R_{PMDC1\text{-}SZF2} = \sqrt{h^2}_{CMD} * K * R_{GCMD\text{-}FSZ} * \sqrt{h^2}_{FSZ}$, where $R_{PMDC1\text{-}SZF2}$ is the observed correlation between cognition in depressed relatives and functioning in their schizophrenia relatives, h^2_{CMD} is the heritability of cognition among depressed relatives, K is the degree of kinship, $R_{GCMD\text{-}FSZ}$ is the genetic correlation between depression cognition and schizophrenia functioning, and h^2_{FSZ} is the heritability of community functioning in schizophrenia. To illustrate, consider trios of siblings in which a schizophrenia proband has a brother with schizophrenia and another brother with depression. If the genetic correlation

between cognition and functioning is not diagnostically specific across these diagnoses (i.e. is transdiagnostic), the schizophrenia brothers' cognition and the depressed brothers' cognition should both be correlated with the schizophrenia probands' community functioning to similar extents. However, if the genetic correlation between cognition and functioning is specific to schizophrenia, the schizophrenia brothers' cognition will be correlated with the schizophrenia probands' functioning, whereas the depressed brothers' cognition will not be correlated with the schizophrenia probands' functioning.

RESULTS

Data Preparation and Reduction

After inspection of distributions, five cases with Cognition or Functioning scores deviating more than three standard deviations from the next ranked case were winsorized (assigned the next score closest to the mean). Examination of the skewness and kurtosis of each measure in the four diagnostic groups found none with absolute skewness of greater than 2.0 (value often used as suggestive of moderate non-normality) and none with excess kurtosis greater than 7.0 (value often used as suggestive of moderate non-normality) (West, Finch, & Curran, 1995), suggesting that factor analysis was appropriate for data reduction of these measures. A single factor emerged for the Functioning measures according to Horn's parallel analysis with an observed Eigenvalue greater than the 95th percentile of Eigenvalues of factors derived from randomized data only for the first factor (Table 2a). All items loaded significantly on this factor, which on average accounted for 44% of the variance in the items, with Marital Status and Living Situation having the highest loadings (Table 2b). A separate factor analysis also yielded a single factor for the General Cognition measures based on Horn's parallel analysis (Table 2a). The General Cognition factor accounted on average for 50% of the variance in the items, with all items having high loadings with Trails A having the lowest (Table 2b). Neither the community functioning nor the general cognition factors had absolute skewness greater than 2.0 or excess kurtosis greater than 7.0 in any of the groups.

Mean Diagnostic Group Differences

Given that schizophrenia patients had a larger standard deviation than the controls for both indexes (as is usually observed), we followed Glass' recommendation and standardized using the control group standard deviation rather than pooling the heterogeneous standard deviations (Smith & Glass, 1977). As expected, the schizophrenia group had significantly poorer (1.41 control group standard deviations below the control group mean) community functioning than the other groups, which did not differ significantly (Table 3). Nevertheless, there was substantial variation, with 84% of functioning scores in schizophrenia below the mean of controls and 16% above the mean of controls. The schizophrenia group also performed significantly more poorly on general cognition (on average 2.53 control standard deviations below the control mean) than the other groups, which did not differ significantly.

Correlations in Schizophrenia

As presented in Table 4, both functioning (h^2=0.481) and general cognition (h^2=1.00) were estimated to be significantly heritable among schizophrenia relatives. Although the

heritability of cognition is presumably not exactly 1.0 due to the undoubted presence of measurement error, apparently individual differences in cognition among schizophrenia patients are extremely heritable.

Phenotypic, genetic and environmental correlations between the two indexes in schizophrenia relatives are also presented in Table 4. As predicted, the phenotypic correlation between general cognition and functioning in schizophrenia was significant (R_P=0.335). Importantly, the genetic correlation between general cognition and functioning was also significant (R_G=0.956), suggesting that correlated genetic effects contribute importantly to the phenotypic correlation observed between cognition and community functioning in schizophrenia. In contrast, the environmental correlation between general cognition and functioning was not in the predicted direction and was not significant in the schizophrenia group. While the environmental correlation was estimated as −1.0, this accounts for basically none of the phenotypic correlation between cognition and functioning due to the very low (0.0) environmentality of cognition in schizophrenia and was thus not statistically significant.

Although not the focus here, in contrast, within depression and no diagnosis groups, genetic correlations between general cognition and functioning were not significant (Supplemental Table 5 presents complete results for non-schizophrenia relatives), which as explained above was not surprising given the low heritabilities of community functioning in depression and no diagnosis groups.

Overall, these findings suggest that among schizophrenia patients, the significant phenotypic correlation between cognition and community functioning arises importantly due to genetic effects but not environmental effects that are correlated across the two traits.

Diagnostically Specific or Transdiagnostic? Cognition in Relatives with Depression or No Diagnoses Predicting Functioning in Schizophrenia Relatives

As presented in Table 5, the genetic correlation between general cognition in relatives with depression and community functioning in schizophrenia relatives was not significant, suggesting that cognition among depressed relatives (which was itself significantly heritable, h^2=0.541, p=0.032, Supplemental Table 5) has no significant genetic relationship with functioning in their schizophrenia relatives. Likewise, no significant genetic correlation was observed between no-diagnoses relatives' general cognition (which was not significantly heritable, h^2=0.143, p=0.101, Supplemental Table 5) and schizophrenia relatives' functioning, indicating specificity to schizophrenia also compared to no psychopathology.

Although the focus of this study is on understanding the causes of individual differences in community functioning among schizophrenia patients, we also explored if cognition in schizophrenia might be genetically correlated with community functioning in non-schizophrenia relatives. However, on examination, the genetic correlations between schizophrenia cognition and community functioning in depression and no diagnosis groups were not significant (Supplemental Table 6). This is consistent with the main finding that cognition in non-schizophrenia groups is not significantly genetically correlated with functioning in schizophrenia and also argues for diagnostic specificity.

DISCUSSION

Although they were able to live in the community at the time of this study, consistent with previous studies (Bartels, Mueser, & Miles, 1997; Bowie et al., 2010), individuals with schizophrenia still demonstrated significant deficits on average in community functioning even compared to their relatives with depression. Despite this overall functioning deficit, variability in functioning was substantial, with approximately one in six individuals with schizophrenia demonstrating *better* functioning than the control mean. Similarly, the schizophrenia mean for the general cognition index was −1.53 standard deviations below the control mean (based on the pooled schizophrenia and control standard deviations), which is very similar to effect sizes reported in meta-analyses using pooled standard deviations of schizophrenia and control groups (Szöke et al., 2008) (Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009; Rajji, Ismail, & Mulsant, 2009). This variability in functioning among schizophrenia patients was predicted by their cognitive performance (R_P=0.335) at a level somewhat above that found in the most recent meta-analysis (Fett et al., 2011).

These individual differences in general cognition and community functioning were both heritable among schizophrenia relatives. Specifically, we found that much of this variation in functioning was heritable among individuals with schizophrenia (h^2=0.481), which is consistent with most of the few other studies of functioning among relatives concordant for schizophrenia (Burke et al., 1996; Cardno et al., 1998; Kendler et al., 1997; McGrath et al., 2009; Vassos et al., 2008; Wickham et al., 2002). We similarly found general cognition to be highly heritable among schizophrenia relatives (h^2=1.00), substantially extending the one previous finding in a small sample of 17 concordant sib-pairs (Hoff et al., 2005). Although certainly not precisely 100% heritable due to undoubted measurement error, this nevertheless suggests that differences among schizophrenia patients are very affected by genetic variation, perhaps more than in the general population.

Our primary study question concerned the degree to which these genetic effects on cognition and community functioning are correlated. The large and significant genetic correlation (R_G=0.956) observed between cognition and functioning among schizophrenia relatives suggests that these genetic effects on cognition overlap almost entirely with the genetic effects on functioning in schizophrenia. In contrast, the environmental correlation between cognition and functioning among schizophrenia relatives was not significant, suggesting little overlap in environmental effects. In addition, as detailed in the Supplement, our measure of face processing contributed little over and above the effects of general cognition.

An important question concerns the degree to which these effects are specific to schizophrenia and do not just reflect effects that also occur in the general population or are trans-diagnostic across psychopathologies. For example, functioning measures such as income and occupational status yield heritabilities approximating 0.40 in the general population (Rowe, Vesterdal, & Rodgers, 1998; Weinert & Hany, 2000), meta-analyses have found the heritability of IQ to be 0.50 or higher during adulthood in the general population (Chipuer, Rovine, & Plomin, 1990; Devlin, Daniels, & Roeder, 1997; Haworth et al., 2010), and studies typically report phenotypic correlations between cognitive ability and occupational status or income in the general population of 0.34 (Rowe et al., 1998; F. L.

Schmidt & Hunter, 2004; Tambs, Sundet, Magnus, & Berg, 1989; Weinert & Hany, 2000), with genetic effects contributing a large proportion of this correlation (Rowe et al., 1998). We addressed this important issue in a novel manner by examining whether the genetic correlation between cognition and functioning operated *across* diagnostic categories of schizophrenia and depression as well as no diagnoses. Importantly, the functioning of schizophrenia relatives was not significantly genetically predicted by cognition in relatives with depression or with no diagnoses. Thus, the genetic effects on functioning in schizophrenia appear to overlap primarily with genetic effects on cognition in schizophrenia but not with genetic effects on cognition in depression or no diagnosis, suggesting diagnostically specific not transdiagnostic effects. Furthermore, this diagnostic specificity also suggests that general factors such as socioeconomic status are unlikely to drive the relationship between cognition and functioning in schizophrenia. If the phenotypic and genetic correlations between cognition and functioning among schizophrenia patients were largely the result of a general cognition-functioning correlation in the general population, then such correlations should hold across schizophrenia, depressed and non-diagnosed relatives in the same family. However, this was not the case, suggesting that the correlations in schizophrenia arise from more diagnostic specific causes. Although not supportive in this case, these results and methods bear importantly on current interests in investigating transdiagnostic processes as exemplified by the NIMH Research Domain Criteria (RDoC) initiative (Morris & Cuthbert, 2012).

Overall, the results of this community-based, multiplex, extended pedigree study suggest that the correlation between cognitive performance and community functioning that is so widely observed in schizophrenia arises largely from correlated genetic effects that are relatively specific to schizophrenia compared to depression and no diagnoses.

Strengths and Limitations

To our knowledge, this is the first study to examine the heritable basis of the correlation between cognition and community functioning in schizophrenia despite hundreds of studies of their observed phenotypic relationship (Fett et al., 2011). This large, extended-pedigree, multiplex family sample has several advantages, including the estimation of genetic effects by comparing relatives with first through fourth degrees of genetic relatedness, likely increased genetic effects due to multiplex ascertainment, considerable variation in cognition and functioning due to the community-based sample, and a variety of diagnoses among relatives.

Despite these strengths, this study also has limitations. The multiplex and ethnically homogenous sample may limit the generalizability of our findings. As noted above, the extended pedigree design estimates genetic effects (heritability and genetic correlations) by assuming that resemblance for environmental effects does not also vary linearly with degree of kinship. If this is the case, genetic effects will be over-estimated. Although, the extended pedigree design has the advantage of basing genetic estimates on linear predictions across a wide range of kinship relationships (here first to fourth degree), other designs, such as adoption or twin studies are likely to be more robust to confounding by shared environmental effects (although of course these designs also rely on their own assumptions).

In addition, although the use of relatives with depression and no diagnoses allowed the examination of the diagnostic specificity of effects, these diagnoses may not be representative of cases who do not have schizophrenia relatives. Notably however, this should bias results against finding the degree of diagnostic specificity that was observed. Finally, the cross-sectional nature of this study cannot resolve the directionality of the cognition-functioning genetic correlation. That is, the genetic correlation may arise due to: genetic effects on cognition, which then has a direct causal effect on functioning, genetic effects on functioning, which then has a direct causal effect on cognition, and/or genetic effects that affect both cognition and functioning.

Implications

As this is the first study to investigate this question as far as we are aware, its results should be considered in the context of "discovery" and are thus in need of replication, ideally using other complementary designs, such as twin or adoption studies. Furthermore, these findings that genetic effects are almost completely correlated between cognition and community functioning in schizophrenia should be considered in context. Although significant (R_P=0.335), cognition did not predict most of the variation in community functioning in schizophrenia and despite important genetic effects on community functioning (h^2=0.481), about half of its variation in schizophrenia was due to environmental causes and measurement error. Thus, these findings do not constitute evidence against the existence of environmental effects or the potential of environmental treatments for improving community functioning in schizophrenia. They do however suggest that treatments targeting cognition to improve functioning should provide novel environmental manipulations, as current environmental variation apparently has little effect on the cognition-functioning correlation within schizophrenia (Eack, Pogue-Geile, Greenwald, Hogarty, & Keshavan, 2011).

The largely genetic basis of the correlation between cognition and functioning in schizophrenia suggests the possibility of identifying specific genetic variants that contribute to this association. The specificity of this genetic correlation to schizophrenia suggests that such genetic variants may themselves contribute to risk for schizophrenia or perhaps may interact with schizophrenia risk variants. Thus, schizophrenia risk variants identified in genome-wide association studies of schizophrenia (Ripke et al., 2014) may provide useful initial candidates for better understanding this important correlation between cognition and community functioning in schizophrenia. The apparent diagnostic specificity to schizophrenia and the novel methods employed here also have important implications for exploring transdiagnostic processes, such as those proposed in the NIMH RDoC initiative (Morris & Cuthbert, 2012).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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General Scientific Summary

Cognition is one of the most important predictors of community functioning in schizophrenia, yet little is known about the causes of this correlation. The study indicates that this relationship is driven by genetic effects shared between cognition and functioning in schizophrenia, but not in another psychiatric diagnosis, major depression, or in healthy individuals.

Table 1

Demographic comparisons among diagnostic groups.

Diagnostic Group	N	Sex	Age	Parental Education	Education	WRAT Score
		% Male (N)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Relatives	636	48.3% (307)	45.17 (17.36)	11.77 (3.27)	13.15 (2.93)	98.95 (14.53)
Schizophrenia	103	58.3% [a] (60)	46.63 [a] (12.54)	12.34 [a] (2.90)	12.44 [a] (2.72)	92.42 [a] (15.82)
Depression	109	27.5% [b] (30)	43.31 [a] (14.47)	12.10 [a] (3.56)	13.65 [b] (2.89)	101.07 [b] (12.05)
No Diagnoses	255	41.2% [b] (105)	46.54 [a] (20.08)	11.61 [a] (3.42)	13.51 [b] (2.93)	102.84 [b] (13.01)
Controls	135	37.0% [b] (50)	54.71 [b] (16.75)	12.61 [a] (3.02)	14.92 [c] (2.43)	108.34 [c] (8.43)
Test		Chi-square	ANOVA	ANOVA	ANOVA	ANOVA
Statistic		21.78	11.69[ø]	2.914	15.95	26.21[ø]
df		3	3, 290	3, 545	3, 596	3, 213
p-value		0.0001	0.0001	0.034	0.0001	0.0001

Other Diagnoses group (N=169) not included.

Statistics sharing superscripts did not differ significantly ($p \leq 0.05$) from each other according to Tukey's HSD (i.e., were included in a homogeneous subset).

Parental education was calculated from the mean of maternal and paternal education; if either was unavailable, the education level of one parent was used.

WRAT, Wide Range Achievement Test, Reading subtest, age standardized score.

[ø] significant group differences in homogeneity of variance; Welch's statistic reported instead of F-statistic.

Table 2a

Eigenvalues for separate parallel analyses of factors derived from Community Functioning items and General Cognition tests.

Community Functioning				
Factor Rank	**1**	**2**	**3**	**4**
Observed Eigenvalues	2.232	0.982	0.527	0.259
95th Percentile of Eigenvalues from Uncorrelated Normal Variables	1.130	1.052	0.999	0.954
General Cognition				
Factor Rank	**1**	**2**	**3**	**4**
Observed Eigenvalues	4.615	0.893	0.751	0.584
95th Percentile of Eigenvalues from Uncorrelated Normal Variables	1.247	1.158	1.107	1.065

Factors with observed eigenvalues greater than the 95th percentile of Eigenvalues based on random data are considered significant ($p<0.05$).

Table 2b

Factor loadings from separate exploratory factor analyses of functioning and cognition in the total pedigree and control sample.

	Factor Loadings
Community Functioning	
Marital Status	0.795
Living Situation	0.918
Current Occupation	0.328
Global Functioning	0.438
General Cognition	
Abstraction and Mental Flexibility	0.707
Attention	0.682
Verbal Memory	0.715
Spatial Memory	0.578
Spatial Processing	0.925
Sensorimotor Dexterity	0.756
Trails A	0.414
Trails B	0.712
California Verbal Learning Test	0.764

Factors based on site-, age- and sex-adjusted items.

Table 3

Mean group comparisons for Community Functioning and Cognition.

Index	Schizophrenia	Depression	No Diagnoses	Controls	F	df	p
Functioning	−1.405 [a] (1.155) N=103	0.243 [b] (1.092) N=109	0.169 [b] (1.100) N=252	0.000 [b] (1.000) N=88	58.23	3, 548	0.0001
General Cognition	−2.527 [a] (2.342) N=82	−0.213 [b] (0.919) N=104	−0.422 [b] (1.249) N=242	0.000 [b] (1.000) N=135	29.69[ʻ]	3, 231	0.0001

All indexes were standardized based on the total control group means and standard deviations. Means are presented with standard deviations in parentheses. Results of one-way ANOVAs and post-hoc Tukey's pairwise tests are presented; statistics sharing the same superscripts did not differ significantly ($p \leq 0.05$) from each other (i.e., were included in a homogeneous subset).

[ʻ] indicates significant difference across groups in homogeneity of variance; Welch's statistic reported instead of F-statistic.

Table 4

Heritabilities and phenotypic, genetic and environmental correlations between indexes within schizophrenia.

Estimate	Trait	Schizophrenia
Heritability (h^2)	**Functioning**	0.481 * (0.029)
	General Cognition	1.000 * (0.0001)
Phenotypic Correlation (R_P)	**General Cognition/Functioning**	0.335 * (0.005)
Genetic Correlation (R_G)	**General Cognition/Functioning**	0.956 * (0.0001)
Environmental Correlation (R_E)	**General Cognition/Functioning**	−1.000 (0.072)

All analyses were conducted in SOLAR on factor scores residualized in SPSS for recruitment site, age and sex. Phenotypic correlations were calculated without controls whereas univariate heritabilities, genetic correlations and environmental correlations included controls. *p*-values are indicated in parentheses. Covariates included age and sex. The t-distribution option was employed.

* $p<0.05$

Table 5

Genetic correlations between Cognition in other diagnostic groups and Community Functioning in schizophrenia.

	Genetic Correlation (R_G)
Depression General Cognition/Schizophrenia Functioning	0.138 (0.792)
No Diagnosis General Cognition/Schizophrenia Functioning	−0.256 (0.642)

Genetic correlations and environmental correlations were calculated including controls in SOLAR. Covariates included age and sex. The t-distribution option was employed. *p*-values are indicated in parentheses.