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Assessment of cognition and personality as potential endophenotypes in the Western Australian Family Study of Schizophrenia

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Title: Assessment of cognition and personality as potential endophenotypes in the Western Australian Family Study of Schizophrenia

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ABSTRACT:

Phenotypic heterogeneity is a major barrier to understanding the genetic architecture underlying schizophrenia. Incorporating endophenotypes is one way to reduce heterogeneity and facilitate more powerful genetic analysis. Candidate endophenotypes require systematic assessment against endophenotype criteria, and a ranking of their potential utility for genetic analysis.

In this study we assess 20 cognitive and personality measures in a sample of 127 families with at least two cases of schizophrenia per family (n=535) plus a set of 30 control families (n=121) against four endophenotype criteria - a) be associated with the illness but not be a part of its diagnosis, (b) be heritable, (c) co-segregate with the illness in families, and (d) be found in unaffected relatives at a higher rate than in the general population.The endophenotype ranking score (ERV) was used to rank candidate endophenotypes based on their heritability and genetic correlation with schizophrenia. Finally, we used factor analysis to explore latent factors underlying the cognitive and personality measures.

Evidence for personality measures as endophenotypes was at least equivalent to that of the cognitive measures. Factor analysis indicated that personality and cognitive traits contribute to independent latent dimensions. The results suggest for this first time that a number of cognitive and personality measures are independent and informative endophenotypes. Use of these endophenotypes in genetic studies will likely improve power and facilitate novel aetiological insights.

INTRODUCTION:

Genome wide association studies (GWAS) have accounted for a modest fraction of the heritability estimates for schizophrenia (h^2 0.6-0.8,[1, 2]); with the polygenic risk score explaining ~7% of the variation on the liability scale[3]. A major barrier to elucidating schizophrenia's genetic architecture is its phenotypic heterogeneity. Gottesman and Gould[4] introduced the endophenotype concept to psychiatry as 'measurable components unseen by the unaided eye along the pathway between disease and distal genotype'.

Endophenotypes represent components of liability which are narrower than a dichotomized phenotype, such as a 'yes/no' clinical diagnosis. They promise improved power over affection status alone to detect risk genes by being both quantitative and closer to the level of gene action[5-7]. Assuming similar levels of imprecision, many studies have demonstrated that power for gene mapping is better with a quantitatively measured phenotype than with a direct dichotomization of that phenotype[8, 9]. In addition, as endophenotypes should be correlated with, but not part of, the clinical diagnosis, power can be further increased by joint analyses of the dichotomous diagnostic phenotype and the quantitative correlated endophenotype[10-12]. It is likely that multiple endophenotypes will be necessary to capture the complex pathophysiological processes involved in schizophrenia[13]. Objectively assessing candidate endophenotypes of schizophrenia and ranking them against each other will help to prioritise the most promising endophenotypes to target in future genetic studies. This study builds on previous work in this area[14, 15] by assessing for the first time both cognitive and personality measures as candidate endophenotypes for schizophrenia in a sample of families multiply affected by schizophrenia.

Gottesman and Gould[4] describe endophenotypes as 'neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological (including configured self-report data) in nature' and suggest that they should meet the following criteria: a) be associated with the illness but not be a part of its diagnosis, (b) be heritable, (c) co-segregate with the illness in families, (d) be found in unaffected relatives at a higher rate than in the general population, and (e) be state independent. As discussed by Glahn *et al.*[5], Gottesman and Gould's five endophenotype criteria are interrelated. Both 'co-segregation of endophenotypes and disease' and 'unaffected relatives (who are at high genetic risk) being intermediate between cases and unaffected controls' indicate joint genetic determination (genetic correlation) between the endophenotype and disease. Endophenotype and disease must be heritable and associated with each other for genetic

correlation (the proportion of trait covariance due to genetic factors) to be present. As genetic correlation indicates the endophenotype trait shares a biological basis with the disorder, a degree of state independence is inferred. Although the Gottesman and Gould criteria are not all independent of each other, a true endophenotype should nonetheless satisfy all the criteria assuming adequately powered samples. Therefore the candidate endophenotypes in this study were assessed against all the criteria possible from our data (a-d).

To complement this analysis, candidate endophenotypes which were associated with schizophrenia, significantly heritable and showed evidence for genetic correlation according to at least one of the two criteria (c and d), were ranked against each other using the endophenotype ranking variable (ERV[10]), developed by Glahn *et al.* to prioritise endophenotypes for genetic analysis. Finally we performed a factor analysis to ascertain to what extent the cognitive and personality measures contribute to independent latent variables.

Cognitive variables are among the most often-cited candidate endophenotypes in the psychiatric literature[5]. Cognitive deficits across multiple domains are a core feature of schizophrenia[16-18], present in up to 80% of cases[19], predate illness onset, and do not result from the positive or negative symptoms of the disorder, or antipsychotic treatment[20-23]. Studies of healthy individuals[24-27] and families with schizophrenia[15, 28, 29] have shown cognitive deficits to be significantly heritable (h^2~0.4-0.8 across different tests). The genetic correlation between cognitive traits and schizophrenia has been estimated by comparing unaffected relatives with healthy controls. A large meta-analysis[30] reported modest but reliable relative–control differences in attention/working memory, verbal memory, visual memory, executive function, spatial ability, motor function, language and general intelligence. There is evidence that a substantial proportion of the correlation observed among cognitive variables is due to a shared genetic basis[25-28, 31].

Abnormal premorbid personality traits have long been described in schizophrenia patients, as well as in their biological relatives[32, 33]. These personality differences are consistent and pervasive[34-40], predate psychotic illness and are stable over the course of psychotic illness[41]. Although they meet all the criteria for potential endophenotypes[42], personality measures have not been well studied as such, possibly be due to the fact that they have a history of being designed based on clinical observations and may have been considered too close to the clinical diagnosis of schizophrenia to be useful endophenotypes. However, accumulating evidence demonstrates that personality traits represent important potential endophenotypes which are independent of, but causally related to,

the disease process of schizophrenia itself[43], discussed in more detail below. In this study we assessed personality using two instruments - the Schizotypal Personality Questionnaire (SPQ[44]), which measures schizotypy, and the Temperament and Character Inventory (TCI), a self-report questionnaire designed to quantify individual differences on each of the temperament and character dimensions outlined in Cloninger's psychobiological model[45].

The term 'schizotype'[46] was introduced to describe a continuum of schizophrenic-like differences in perceptual, cognitive, and affective experiences. Schizotypy was originally interpreted under a quasi-dimensional model, whereby a small group of individuals, labelled 'schizotypes', are differentiated from the rest of the population in a categorical fashion[46, 47]. However recent neurobiological, neuropsychological, social and environmental evidence (reviewed in[48]) supports a fully dimensional model of schizotypy[49]. This model posits a continuum between schizotypy in healthy populations and disorders on the schizophrenia spectrum, consistent with the majority of current theories pertaining to schizophrenia, which describe continuity between clinical and non-clinical psychosis populations[50]. Under the fully dimensional model, high schizotypy is strongly associated with an increased risk of schizophrenia-spectrum psychopathology[51, 52], although it is not part of its diagnosis, and schizotypy may also relate to a range of psychotic disorders other than schizophrenia[51]. In addition, it has been repeatedly noted that many healthy individuals with high schizotypy not only function well but may benefit from their anomalous perceptual and other experiences and exhibit adaptive strengths such as creativity[48]. Schizotypy is a stable trait with high re-test reliability[53, 54] which does not solely manifest during acute phases of illness (i.e. is state-independent). Heritability estimates for total schizotypy in community samples are variable, likely reflecting the heterogeneity of schizotypal traits (h^2~0.15-0.70[55-59]). Few studies have looked for evidence of genetic correlation between schizotypy and schizophrenia; however, there is some evidence that unaffected relatives of probands with schizophrenia display higher schizotypy than healthy controls[60, 61]. Impaired cognition is not necessarily associated with high levels of schizotypy in general populations[62, 63] or in samples of schizophrenia patients[64], and schizotypy and cognitive measures are likely to represent distinct endophenotypes of schizophrenia.

In addition to schizotypy and schizophrenia being phenotypically independent, a recent overview[51] of genetic studies suggests that they are influenced by at least two different groups of genetic variants. The first group is postulated to explain mainly schizotypy variance and increased proneness for psychosis, regardless of clinical diagnosis. The second group conveys unspecific neuronal fragility and susceptibility to environmental insults, associated with the risk of transition between being well

(but possibly with healthy high schizotypy) and clinical schizophrenia, which is likely to be common to many disorders. The relationship between schizophrenia-associated genetic variants and schizotypy supports this hypothesis. Although several genes implicated in the aetiology of schizophrenia have also been associated with schizotypy, few of these genes have achieved genome-wide significance in large case-control GWAS of schizophrenia[51]. In these GWAS, both cases and controls are treated as homogeneous groups and therefore GWAS may predominantly pick up the second group, the more general 'disease resilience'-associated variants. This is supported by a cross-disorder GWAS which found substantial overlap between genetic risk variants for five psychiatric disorders[65] and by a study showing that genetic risk for schizophrenia from case-control GWAS (summarised using polygenic risk scores) is associated with negative symptoms but not with schizotypy in non-clinical populations[66, 67]. Individuals with high but healthy schizotypy would not be expected to have a high polygenic risk score for schizophrenia, as those with high polygenic risk scores and high schizotypic traits would be more likely to develop spectrum conditions than to be in a healthy sample. Unlike schizotypy**,** polygenic risk score for schizophrenia is associated with lower cognitive ability in non-clinical populations[68-71], indicating that poor cognition may be more correlated with the 'susceptibility to disease' variants picked up by GWAS than schizotypy is. Previous research from the WAFSS has shown that in this sample, patients with schizophrenia can be separated into distinct subtypes characterised by either cognitive deficit, or personality factors (heavily weighted on schizotypal symptoms), using grade of membership analysis[17]. The group has previously demonstrated genetic linkage between the cognitively deficit group and the MHC region later implicated in the large schizophrenia GWAS.

There is evidence for distinct and separable constructs within schizotypy[72], with the most consistent[48, 73] being a three-factor model comprising Cognitive-Perceptual Dysfunction (Ideas of Reference, Magical Thinking, Unusual Perceptual Experiences, Suspiciousness), Interpersonal-Affective Deficits (Social Anxiety, No Close Friends, Suspiciousness and Constricted Affect), and Disorganization(Odd Speech and Odd Behaviour) which broadly correspond to the positive, negative and disorganised dimensions of schizophrenia respectively[74]. High 'positive' schizotypy is associated with adaptive strengths like creativity[75, 76] and with better functioning in other psychiatric illness such as bipolar disorder[77]. High negative schizotypy has been shown to share considerable variance with neuroticism, a personality trait linked to other affective or anxiety disorders[55]. As recently argued by Grant[42], the ability of the dimensional model of schizotypy to represent the dimensionality of schizophrenia on a continuous scale makes it a valuable candidate endophenotype which is likely add power to genetic analyses and to aid investigation into the aetiology of schizophrenia and other

psychotic disorders. The SPQ can be interpreted within the three-factor model framework of schizotypy[74, 78-80] with each of the three factors being individually heritable[81].

The psychobiological model proposed by Cloninger and colleagues[45, 82, 83] is based on four temperament and three character dimensions and accounts for most of the variance in personality, both in the general population and in psychiatric patients[83]. The four temperament dimensions – Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD) and Persistence (P) are hypothesised to be closely connected with neurotransmitter systems[82] and are described as heritable biases in learning which lead to variation in responses to danger, novelty, and reward[84]. They have been shown to be relatively stable over lifetime and to be universal across different cultures and various political and ethnic groups[45].

The three character dimensions - self directedness (SD), cooperativeness (C) and self transcendence (ST) - are related to self-concepts about values and goals that impact the meaning of what is experienced[83]. Although character has been shown to be influenced be heritable/biological factors[85], environmental factors such as sociocultural pressures and random life events are thought to impact more on character than on temperament - character traits are dynamic and mature in response to learning and life experiences. Although the temperament traits are thought to be more heavily determined by biological factors, what little data are available suggest that both are moderately heritable (h^2~0.24-0.45, with HA, ST and C being significantly heritable[86, 87]). Schizophrenia has consistently been associated with abnormal temperament (especially increased HA and decreased RD[40, 88-90]) and character (especially low SD, low C, and high ST[40, 88-90]) dimensions, reviewed in[91]. Some studies have shown character differences between unaffected relatives of people with schizophrenia and controls. Unaffected relatives have shown lower C[37, 40, 86], SD[37, 40], and RD[37] and higher HA[40, 86] and ST[40, 86] compared to healthy controls. Other studies did not find significant differences between relatives and controls however[90], and some studies have shown group differences in the opposite direction, with individuals at high genetic risk for schizophrenia demonstrating lower ST[90, 92], and higher SD and C[35], indicating a more mature personality profile than healthy controls. These differences were more pronounced in individuals with less schizotypal features[35], indicating that temperament and character profile may depend on the schizotypy of the relatives. Very few studies have examined genetic correlation between the character domains and schizophrenia using co-segregation analysis, although one recent study of the TCI did not find significant genetic correlations[86]. Positive and negative schizotypy has been associated with different character and temperament features. In unaffected relatives of people with schizophrenia and in

healthy controls, negative schizotypy is associated with high HA, and positive and disorganised schizotypy has been associated with low SD and high ST[35]. This supports Cloninger's theory that schizotypy is characterized by the character traits; low SD and C, and high ST[83]. Similarly, looking at schizophrenia symptomatology, high HA is associated with negative symptoms and high ST with positive features[90]. Character dimensions may help to separate those who benefit from high schizotypy from those in whom it becomes pathological[40, 84]. For example, although high ST is correlated with schizotypal and paranoid symptoms, when coupled with high SD and C, high ST indicates maturity, spirituality, and creativity rather than psychopathology[84].

Given the promise of personality measures to be informative endophenotypes, the aim of this study was to evaluate them against endophenotype criteria and to compare them to the more well-established cognitive measures. Specifically, the study had three aims: (i) to comprehensively evaluate for the first time both cognitive and personality measures as candidate endophenotypes against four of Gottesman and Gould's five criteria(ii) to rank the strength of the evidence for cognitive and personality measures as candidate endophenotypes in relation to each other using the ERV and (iii) to examine the relationship between cognitive and personality measures by conducting a factor analysis to identify the composition of any latent variables.

METHODS:

The Western Australian Family Study of Schizophrenia (WAFSS):

The WAFSS study has been described in detail elsewhere[17, 93]. It was initiated in 1996 with the aim of comprehensively assessing families with ≥1 member affected with a disorder within the ICD-10 and DSM-IV schizophrenia spectrum (schizophrenia, schizoaffective disorder, schizotypal disorder and acute transient psychosis). The majority of probands were recruited from consecutive admissions to a psychiatric hospital. Full pedigree descriptions and family histories were collected using the National Institute for Mental Health Family Interview for Genetic Studies[94]. Clinical assessment included the Diagnostic Interview for Psychosis (DIP[95]) and a best-estimate diagnosis, established by consensus of two senior clinicians blinded to family relatedness. Control families were screened for psychopathology and excluded if they or a first-degree relative had been diagnosed with schizophrenia/schizophrenia spectrum disorder or bipolar affective disorder. Written informed consent was obtained from all participants. The study complied with the ethics guidelines of the institutions involved.

All WAFSS participants were administered a battery of tests by research psychologists that assessed performance across six domains of cognitive function and personality. The battery of tests was chosen on the basis of showing evidence of heritability[21] and reasonable effect sizes of test measures[18] at the time of the study design. For this study, all tests for which data were available for a reasonable number of study participants were included.

The cognitive and personality tests are summarised below:

(a) general cognitive ability:
Premorbid IQ (National Adult Reading Test, NART[96])
Current IQ (Shipley Institute of Living Scale, SILS[97])

(b) verbal learning and memory:
Rey Auditory Verbal Learning Test immediate (RAVLT-IW) and delayed (RAVLT-DW) word recall[98]

(c) sustained attention:
Continuous Performance Task degraded stimulus (CPT-DS[99])
Continuous Performance Task, identical pairs (CPT-IP[24])

(d) executive function:
Controlled Oral Word Association Test (COWAT[100]) of phonetic verbal fluency, FAS letters

(e) speed of information processing:
Visual Inspection Time (IT) Tasks[101], block A and B

(f) laterality:
Edinburgh Handedness Inventory (EHI[102]), laterality quotient

(g) schizotypal traits:
Schizotypal Personality Questionnaire (SPQ[44]) - three-factor model of Cognitive-Perceptual Deficits, Interpersonal Deficits, and Disorganization

(h) temperament and character :
Temperament and Character Inventory (TCI[45])

In the present study, we included all individuals for whom cognitive and personality measures were available, with at least one documented relative in the study for whom such measures were also available. Thus, the study cohort comprised 127 'affected' families with at least one member with schizophrenia (n=535 family members, including 160 schizophrenia cases) and a separate set of 30 control families (n=121, total n=656). The median family size was 4 (range 3-9, supplementary Figure 1). Affected families had a median of one case per family, although 26 families were multiplex (2-5

cases per family, supplementary Figure 2). Data were available in both the multiply affected families and the control families for all measures apart from the IT tasks, for which insufficient data were available in the control families.

Aim (i) to comprehensively evaluate for the first time both cognitive and personality measures as candidate endophenotypes against four of Gottesman and Gould's five criteria.

Data analysis:

All analyses were performed in R version 3.3.1[103]. Pedigree analyses were performed using the 'gap' package version 1.1-16[104]. The kinship matrix was directly estimated from recorded pedigrees. All cognitive and personality measures were adjusted for age, sex and years of formal education; linear regression of each of the candidate endophenotypes on all three covariates was performed and the resulting residual statistics were each transformed to an (approximately) normal distribution using the 'boxcox' function in the R package MASS version 7.3-45[105] prior to analysis. Additional correction for NART and medication use in cases (chlorpromazine equivalence) was performed as a sensitivity analysis.

Multiple testing corrections:

Benjamini and Hochberg's False Discovery Rate (FDR) correction[106] was applied to account for multiple testing within each of Gottesman and Gould's criteria (a-d), with q values <0.05 considered statistically significant.

Posthoc power calculations:

As this sample was used in different ways to test each of the criteria (a-d), some tests were more powerful than others. To aid in the interpretation of the results of each test, we report posthoc power calculated for each test (at α=0.05). The probability of estimating h^2 (criterion b) and the genetic correlation (ρ_g, criterion c) greater than zero in this sample was estimated using the GCTA-GREML power calculator[107]. The variance of the genetic relationships was set as the empirical variance of the off-diagonals of the GRM (in this case, 0.000356).

Power for detecting a difference between schizophrenia cases and their unaffected relatives (criterion a) and for difference between unaffected relatives and healthy controls (criterion d) was estimated using the R package 'simr', which conducts simulation-based power analysis for mixed

models. Power was estimated using the existing family structures and sample sizes, for a range of effect size estimates.

Test of criterion (a) – 'significantly associated with schizophrenia'.

We examined association with schizophrenia by testing for differences between schizophrenia cases and their unaffected family members for each cognitive and personality measure. Groups were compared using a maximum likelihood estimation model including the kinship matrix (the null model, describing only the relationship between the measure and genetic relatedness) to the same model including variable differentiating cases from controls using log likelihood ratio tests. We had approximately 5% power to detect a between-group difference in the candidate endophenotypes of 0.01 sd, 27% power to detect a change of 0.05 sd, and 100% power to detect a change of 0.3 sd and above. Although the primary analysis for this criterion was a comparison of cases and their unaffected family members, a comparison of cases and control families is also reported for completeness.

Test of criterion (b) – 'significantly heritable'.

Total additive genetic (narrow sense) heritability is an estimate of the proportion of variability of a trait attributable to the additive effect of genes. The underlying variance-component model asserts that variation in the trait can be partitioned into genetic, known covariates, and environmental components. Each component can then be estimated. In this study, heritability estimation was performed for schizophrenia (h^2_{SZ}) and all cognitive and personality measures (h^2_{CP}) using maximum likelihood variance-component estimation[108]. The null hypothesis of no heritability was tested by comparing two maximum likelihood models: the sporadic model, which assumes no genetic effects ($h^2=0$) and the polygenic model, which assumes that some fraction of the phenotypic variation is explained by genetic factors (in this case, the kinship matrix), using likelihood ratio tests. The heritability of schizophrenia was estimated on the continuous liability scale under the assumption of a normal threshold model from all affected families and corrected for ascertainment bias[109], as the families were recruited through a proband and are not representative of the general population (the proportion of schizophrenia cases among WAFSS family members was 24% compared to a lifetime morbid risk in the general population of 1%). For the candidate endophenotypes, this sample provided 68% power to detect $h^2_{CP}\neq0$ assuming a true h^2_{CP} of 0.3, 90% power assuming a true h^2_{CP} of 0.4, and 90% power assuming a true h^2_{CP} of 0.5.

Test of criterion (c) - 'significantly genetically correlated with schizophrenia'.

The proportion of the phenotypic correlation between schizophrenia and each of the cognitive or personality measures which was attributable to shared genetic effects (ρ_g) can be estimated by decomposing Pearson's *r* into ρ_g and ρ_e, where ρ_g is the proportion of variability due to shared genetic effects, and ρ_e is the proportion of variability due to shared environmental effects. Genetic correlation with schizophrenia was calculated for all measures which were significantly heritable using maximum likelihood variance-component estimation, comparing the sporadic model (assuming no genetic effects, $\rho_g=0$) and the polygenic model (maximised without constraint of ρ_g) using likelihood ratio tests.

Power to detect $\rho_g \neq 0$ between schizophrenia (binary) and the quantitative trait candidate endophenotypes, assuming $h^2_{CP}=0.5$ and $h^2_{SZ}=0.8$ (on the liability scale; the actual estimate in this sample) was as follows: 41% power to detect genetic correlation of 0.2, 78% power to detect genetic correlation of 0.3 and 98% power to detect genetic correlation of 0.4.

Test of criterion (d) – 'significantly different between unaffected relatives and control families'.

Group differences between unaffected relatives and control families were examined using the same methods as criterion (a) above. As the comparison group (control families) was slightly smaller than for criterion (a) (schizophrenia cases), power was lower for this analysis, with approximately 1% power to detect a between-group difference in the candidate endophenotypes of 0.01 sd, 5% power to detect a change of 0.05 sd, 81% power to detect a change of 0.5 sd and 100% power to detect a change of 0.6 sd and above.

Aim (ii) to rank the strength of the evidence for cognitive and personality measures as candidate endophenotypes in relation to each other using the ERV.

The ERV was developed by Glahn *et al.*[10] to rank candidate endophenotypes using both heritability and genetic correlation, therefore incorporating both the strength of the genetic signal for the endophenotype and its relationship to the disorder of interest into a quantitative measure of the strength of the evidence for the candidate endophenotype. The ERV describes the standardised genetic covariance with values between 0 and 1, where higher values indicate that the candidate endophenotype and the illness are more strongly influenced by shared genetic factors. It is calculated as the absolute value of the square-root of the heritability of schizophrenia (h^2_{SZ}), multiplied by the square-root of the heritability of the candidate endophenotype (h^2_{CP}) multiplied by the genetic correlation between them: $ERV=|\sqrt{h^2_{SZ}}\sqrt{h^2_{CP}}\rho_g|$.

Aim (iii) to examine the relationship between cognitive and personality measures; correlations and factor analysis.

The phenotypic and genetic correlations between candidate endophenotypes with significant heritability and genetic correlation were calculated from the entire cohort. Phenotypic correlations were adjusted for relatedness using maximum likelihood estimation to incorporate the kinship matrix. Genetic correlations between candidate endophenotypes were calculated using maximum likelihood variance-component estimation, as described above.

Very Simple Structure and Parallel analysis were used to determine the optimal number of factors to extract using the 'vss' and 'factpar' commands in the R package 'psych'[110]. Factor analysis was performed using Maximum Likelihood Factor Analysis entering raw data and extracting the user-specified number of factors, with varimax rotation using the 'factanal' command in the R package 'stats'[103].

RESULTS:

Aim (i) to comprehensively evaluate for the first time both cognitive and personality measures as candidate endophenotypes against four of Gottesman and Gould's five criteria.

Test of criterion (a) – 'significantly associated with schizophrenia'

Cases were significantly younger, more likely to be male and had significantly lower educational attainment compared to their unaffected family members and healthy control families, and all of the above were included as covariates in all analyses. Cases showed significant impairment compared to their unaffected family members across all measures ($q<0.05$, Table 1) apart from P, which did not differ significantly between groups.

To control for the possibility that the between-group differences in the cognitive tests were simply reflective of higher IQ in the controls, the tests for group differences were repeated adjusting for NART (supplementary Table 1). All of the significant differences shown in Table 1 were recapitulated in this sensitivity analysis.

Test of criterion(b) - significantly heritable.

The additive heritability of schizophrenia after correction for ascertainment was estimated at h^2_{SZ} =0.80). Eleven of the candidate endophenotypes showed significant heritability in this sample, and some measures of both cognition (IT tests and RAVLT-IW) and personality (SPQ disorganisation, SPQ cognitive-perceptual and C) had particularly high estimates (h^2_{CP}>0.5, Table 2). Only measures which were significantly heritable and associated with schizophrenia were assessed for genetic correlation in the following two sections.

Test of criterion (c) - 'significantly genetically correlated with schizophrenia'.

Ten of the eleven significantly associated and heritable traits also showed significant genetic correlation with schizophrenia liability in the co-segregation analysis (q<0.05, Figure 1) and the magnitude of genetic correlation largely mirrored that of heritability.

Test of criterion (d) – 'significantly different between unaffected relatives and control families'.

Unaffected family members were intermediate between cases and controls for all of the cognitive traits, and showed significant impairment compared to the control families in the CPT-IP, NART and SILS IQ, (q<0.05, Table 1). For the personality measures, unaffected family members and controls were only significantly different for C, where unaffected family members had higher mean scores than both their affected family members and control families.

Summary of Endophenotype Criteria met:

Two of the candidate endophenotypes, CPT-IP and NART, met all four criteria for being an endophenotype (Table 2). Eight measures, many of the traits with the highest ERV scores, met three of the four criteria but did not differ significantly between unaffected family members and healthy controls in the expected direction.

Aim (ii) to rank the strength of the evidence for cognitive and personality measures as candidate endophenotypes in relation to each other using the ERV

When traits were ranked according to their ERV, RAVLT-IW, both IT tasks, NART premorbid IQ, SPQ cognitive-perceptual and C had the highest scores (ERV>0.20, Figure 2).

Aim (iii) to examine the relationship between cognitive and personality measures; correlations and factor analysis

The phenotypic and genetic correlations between all traits with significant heritability and genetic correlation with schizophrenia are shown in supplementary Figure 3. There were moderate-strong positive phenotypic correlations among most of the cognitive measures (although less consistent for IT and EHI), and within the SPQ factors. Phenotypic correlations between the cognitive and the personality measures were low, and high genetic correlations indicate that what phenotypic correlations exist are largely driven by a shared genetic component. Genetic correlations between most of the cognitive traits were substantial, especially for premorbid IQ.

Factor analysis was performed for all individuals in the affected families (unaffected families were not included due to lack of IT measures) with complete data across the 11 traits which had significant association with schizophrenia, heritability and genetic correlation (n=253, including 82 schizophrenia cases). Very Simple Structure and Parallel analysis suggested that the optimal number of factors to extract from this dataset was three. Maximum Likelihood Factor Analysis was then performed specifying the number of factors as 3 (Table 3). The cumulative variability explained by the 3-factor model is modest, at 0.50. Factor 1, which explains the most variance, is heavily loaded on the three SPQ domains, whereas Factors 2 and 3 are driven by cognitive measures - primarily the RAVLT scores (Factor 2), and the IT scores (Factor 3). All three factors were strongly and significantly heritable (h^2 0.6-0.90, P<0.01, Table 2). Phenotypic correlations among factors indicated that the three factors were independent of each other and what little correlation was found between them was largely due to shared genetic factors (supplementary Table 2).

DISCUSSION

This study reports for the first time a thorough assessment of cognitive and personality measures as candidate endophenotypes against four of the criteria suggested by Gottesman and Gould; a systematic prioritising of the strongest endophenotypes using the ERV and an examination of the underlying structure of this group of candidate endophenotypes using factor analysis.

One of the strengths of this study was in the use of a large sample of families multiply affected by schizophrenia, which allows us to directly examine the co-segregation (genetic correlation) of schizophrenia and candidate endophenotypes (criteria c), in addition to implying genetic correlation by comparing unaffected relatives with healthy controls (criteria d). Previous studies have largely relied on group comparisons (criteria d) only to infer genetic correlation. In addition, our family sample meant that we could infer the degree of genetic similarity between individuals in its entirety

from the pedigree structure, meaning that our estimates of heritability of the candidate endophenotypes and their genetic correlation with schizophrenia will be more complete than studies which use SNP-based genetic relationships, representing only part of the genetic similarity between individuals.

Most of the cognitive and personality measures in this study have previously been shown to be associated with schizophrenia; therefore it was unsurprising that group differences between cases and unaffected relatives were significant for all but P in this study. The direction of associations were all in line with previous studies – cognition was impaired in cases, cases scored higher in all three SPQ domains and the group differences in TCI domains were in concordance with those previously reported[40, 88-91], with particularly significant increased HA and ST and decreased SD in cases. Adjustment of group differences in specific cognitive tests for a generalized cognitive deficit was not performed in the main analysis because this generalized cognitive deficit is a core feature of schizophrenia. As noted by Miller and Chapman[111], adjustment for a covariate which is closely related to the independent variable of interest is inappropriate, as the removal of variance due to the covariate would remove considerable variance in the independent variable of interest. We did perform a sensitivity analyses which showed that the between-group differences were robust to correction for NART and medication use in cases. A limitation of these analyses is that we had insufficient data to adjust for some potential confounders, such as drug and alcohol misuse, although in the limited data available these potential confounders were not correlated with the candidate endophenotypes measured.

Heritability estimations for the cognitive traits in the WAFSS were in keeping with previous reports (h^2 ~0.4-0.8). We show for the first time substantial heritability estimates for all three SPQ factors in a clinical cohort, in keeping with a previous report in healthy adolescents[81]. Our heritability estimates for the TCI were in a similar range to those reported previously (h^2 0.3-0.45[86, 87]). Heritability estimates of C, HA and ST were significant in Korean families[86], whereas only C was significantly heritable in the WAFSS.

The proportion of phenotypic correlation between schizophrenia and the candidate endophenotypes which was due to shared genetic effects (the genetic correlation with schizophrenia) calculated using variance components analysis was particularly high for NART IQ, RAVLT-IW and IT, in keeping with a previous variance components analysis showing high genetic correlation with schizophrenia for measures of memory and IQ[29]. All three SPQ factors showed

significant genetic correlation with schizophrenia using variance components analysis. To our knowledge, this represents the first finding of genetic correlation between SPQ measures and schizophrenia using co-segregation analysis. Within the TCI domains, only the negative phenotypic correlation between C and schizophrenia exhibited a significant genetic component, although this is difficult to interpret in the context of the mean C for unaffected relatives not being intermediate between patients and controls (discussed below).

Group differences in the candidate endophenotypes between unaffected relatives of people with schizophrenia and controls, indicative of the measure being genetically correlated with schizophrenia, were significant for NART, SILS, CPT-IP and C. Previous studies have shown differences in most of the cognitive measures examined in this study[30]. Similarly, previous reports of differences in schizotypy[62] between unaffected relatives and controls were not replicated, although the interpersonal and cognitive-perceptual factors showed trends in the expected direction, consistent with previous findings of elevation of these factors among unaffected relatives, with less consistent results for disorganised symptoms[62]. Differences between unaffected relatives and healthy controls in HA, ST and C[40, 86] were not replicated in this study. There was a significant difference in C between unaffected relatives and healthy controls; unaffected relatives had higher scores than both patients and healthy controls which has been shown previously[35, 40]. It is likely to be an environmental rather than a genetic effect, as the unaffected relatives are not, in this case, intermediate between their affected relatives and healthy controls.

Only CPT-IP, a measure of sustained attention, and NART, a measure of general cognitive ability, met all four criteria proposed by Gottesman and Gould assessed in this study. However, all three SPQ domains, both RAVLT measures and both IT measures showed evidence for genetic correlation with schizophrenia in the co-segregation analysis. Group comparisons between unaffected relatives and controls were not available for the IT measures however, as the IT tests were not performed in the control families. Furthermore, a limitation of this study was the modest size of the sample of control families, which meant that the different methods employed in this study to assess the endophenotype criteria did not have equal power, as outlined in the methods section. For the effect sizes observed in this study, the power for detection of genetic correlation using co-segregation analysis in all the affected families was higher than the power to detect group differences between unaffected family members and healthy controls, which is slightly underpowered compared to the other tests due to the relatively small number of healthy control families available for inclusion in this study. The differences in power may account for the fact that the genetic correlation assessed

by variance components analysis was more pronounced in this study than the genetic correlation suggested by group differences, although most of the traits show a non-significant trend towards unaffected family members being intermediate between patients with schizophrenia and healthy controls. Despite the small differences in power between the different tests of the endophenotype criteria, we had good power to assess all four of the different criteria for being an endophenotype in this study for all but very small effects, meaning that we can presume candidate endophenotypes which did not show evidence for genetic correlation with schizophrenia in the group comparison do not have particularly high genetic correlation with schizophrenia in this sample.

Both NART and the CPT-IP have been consistently shown to share a genetic basis with schizophrenia [25-27, 29, 30, 112] and in a recent meta-analysis, both NART and CPT-IP measures had substantial effect sizes when comparing unaffected relatives with controls. A recent paper from the Consortium on the Genetics of Schizophrenia (COGS) study[113] reported that CPT-IP deficits in schizophrenia could be reliably detected across five sites in the Consortium on the Genetics of Schizophrenia (COGS) study despite significant site differences in participant age, sex, education, and racial distribution; deficits were relatively independent of current symptom severity but rather, related to functional capacity. Although cognitive measures are by no means the only promising endophenotypes for schizophrenia, within the neurocognitive literature there is increasing evidence that the CPT-IP is one of the strongest candidate endophenotypes. A recent study of 16 endophenotypes (15 neurocognitive, 1 neurophysiological) in the COGS study reported a model including four important endophenotypes: CPT-IP, the California Verbal Learning Test, emotion identification and the antisaccade task, had the same power to discriminate between schizophrenia cases and healthy controls as the model including all 16 endophenotypes (84% vs. 85% accuracy[14]).

A novel aspect of this study was the examination of personality measures as endophenotypes and in ranking them compared to cognitive measures using the ERV. We show for the first time that ERVs for the top ranked personality traits and cognitive traits are similar in magnitude. The top ranked cognitive measures in this study were verbal learning and memory, sustained attention and premorbid IQ. This is in keeping with ERV scores reported by Glahn *et al.*[15] for a different cognitive battery which showed that measures of verbal learning and memory, sustained attention, speed of information processing, and general IQ had high ERV scores. The fact that SPQ cognitive-perceptual had an ERV score equivalent to these top cognitive measures suggests that it should be considered an equivalently promising endophenotype for schizophrenia.

In addition, our dataset enabled us to examine the relationship between cognition and personality traits for the first time. There were no significant phenotypic correlations between personality and cognitive measures, reaffirming previous reports[63, 64, 66] including previous work in the WAFSS[17] showing that these measures are largely independent of each other. Genetic correlations between personality and cognitive traits however were high; indicating that what little phenotypic correlation exists between them is largely due to a shared genetic contribution. The substantial genetic correlation we observed among most of the cognitive measures, especially with IQ, has been shown previously[25, 27, 28, 31]. Previous data suggest that the positive and negative facets of schizotypy are influenced genetically by two distinct latent genetic factors[58], which is supported by the moderate genetic correlations between the three domains in this study (r_g<0.37 - 0.45, supplementary Figure 3).

The results of the factor analysis extended previous work showing that cognitive deficits are separable into distinct factors by incorporating personality measures. Factor analysis in the COGS cognitive battery[23] showed distinct factors with moderate phenotypic and high genetic correlation with each other. By comparison, we demonstrate much lower phenotypic correlation between factors, likely due to the fact that we included both cognitive and personality factors. This study also confirmed the finding that verbal memory and processing speed are largely uncorrelated and contribute to two distinct factors among cognitive batteries[114]. Data from the Dunedin cohort study have shown varying longitudinal trajectories in those who go on to develop schizophrenia, with functions which reflect processing speed deteriorating over time, but little evidence of a decline in functions reflecting verbal memory[115].

In summary, the richly phenotyped, familial WAFSS cohort is one of the few suitable for a comprehensive analysis of cognitive and personality traits as candidate endophenotypes for schizophrenia. We demonstrate that the strength of genetic support for personality traits as endophenotypes is broadly equivalent to that of cognitive traits, and factor analysis showed that both personality and cognitive traits contribute to independent latent factors. The recent development of the ERV facilitated a systematic ranking of these traits for the first time. Future genetic studies incorporating highly ranked cognitive and personality endophenotypes will hopefully aid in identifying latent genetic variants previously missed due to the heterogeneity of the neurobiological disorders subsumed under the clinical diagnosis of schizophrenia. However, sufficiently powered studies including large samples with these measures will be necessary to perform these analyses.

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Table 1. Cognitive and personality traits distribution and heritability in WAFSS participants.

characteristics	cases (n=160, 25%)	relatives (n=375, 57%)	controls (n=121, 18%)	p (cases vs rels)	p (cases vs controls)			p (rels vs control)
Male sex [n, %]	121 (75%)	176 (47%)	61 (50%)	**1.0E-08**	**7.3E-04**			0.57
Age at assessment (yrs) [mean, sd]	34.0 (10.8)	42.5 (22.2)	39.8 (15.6)	**4.7E-15**	**2.6E-05**			0.16
Education (yrs formal) [mean, sd]	11.2 (2.2)	11.8 (3.0)	12.8 (2.7)	**0.03**	**7.20E-09**			**2.2E-03**
cognitive and personality traits	**cases (n=160, 25%)**	**relatives (n=375, 57%)**	**controls (n=121, 18%)**	**q (cases vs rels)**	**q (cases vs controls)**	**h^2**	**q**	**q (rels vs control)**
NART IQ	99.5 (11.1)	104.7 (10.8)	106.6 (8.7)	**3.1E-02**	**1.9E-03**	0.48	**3.4E-03**	**0.043**
SILS IQ	93.4 (14.8)	104.5 (11.8)	108.9 (8.3)	**5.3E-07**	**1.0E-10**	0.44	**0.012**	**5.4E-03**
RAVLT-IW	21.5 (6.6)	25.9 (6.0)	27.2 (5.2)	**7.7E-09**	**4.7E-09**	0.60	**1.3E-03**	0.105
RAVLT-DW	6.2 (3.1)	8.3 (3.2)	9.06 (2.8)	**4.7E-08**	**1.2E-08**	0.41	**5.4E-03**	0.094
IT block A	69.6 (107.9)	47.9 (28.0)	-	**1.2E-05**	-	0.55	**6.3E-03**	-
IT block B	62.4 (96.7)	42.5 (34.1)	-	**1.0E-05**	-	0.60	**3.1E-03**	-
CPT-IP	3.13 (1.7)	3.99 (1.5)	4.88 (1.6)	**2.7E-08**	**9.0E-11**	0.43	**0.011**	**0.022**
CPT-DS	4.50 (1.5)	5.31 (1.2)	5.62 (1.19)	**1.8E-10**	**2.2E-04**	0.14	0.574	-
COWAT (FAS version)	30.7 (10.4)	37.0 (11.9)	38.0 (9.9)	**2.3E-04**	**4.8E-05**	0.16	0.307	-
EHI (lq)	51.7 (53.0)	62.7 (53.9)	72.0 (37.8)	**4.9E-03**	**8.6E-05**	0.24	0.211	-
SPQ cognitive-perceptual	12.4 (9.2)	2.8 (4.4)	2.5 (4.3)	**6.1E-18**	**7.4E-11**	0.59	**5.9E-04**	0.094
SPQ interpersonal	9.9 (7.1)	3.9 (4.9)	3.6 (4.7)	**2.3E-13**	**5.2E-09**	0.47	**6.9E-03**	0.102
SPQ disorganisation	5.8 (4.8)	1.8 (2.8)	2.0 (3.2)	**9.4E-12**	**3.4E-07**	0.52	**5.2E-03**	0.119
TCI cooperativeness	30.5 (7.1)	36.0 (4.5)	34.0 (5.4)	**1.1E-06**	**0.023**	0.73	**0.012**	**0.023**
TCI self-directedness	26.5 (7.6)	35.9 (6.7)	33.9 (6.0)	**3.7E-13**	**7.9E-05**	0.28	0.168	-
TCI persistance	4.4 (1.6)	4.4 (1.9)	4.0 (2.0)	0.276	0.089	-	-	-
TCI self-transendence	18.4 (7.7)	11.2 (6.3)	10.4 (6.9)	**4.1E-11**	**6.9E-06**	0.31	0.149	-
TCI reward dependence	14.0 (3.9)	16.1 (3.7)	16.1 (3.5)	**7.0E-04**	**4.3E-03**	0.21	0.223	-
TCI novelty seeking	18.9 (5.3)	17.9 (5.9)	18.1 (6.2)	**0.015**	**0.024**	0.16	0.322	-
TCI harm avoidance	18.4 (7.5)	13.3 (6.5)	14.1 (5.8)	**4.6E-09**	**6.0E-05**	0.07	0.689	-

Trait distribution in schizophrenia cases, their unaffected relatives and control families free of psychopathology. Residuals of cognitive and personality measures after regression of age, sex and years of formal education were used and transformed to an (approximately) normal distribution prior to analysis. *q* values are analogous to *p*-values that incorporate FDR-based multiple testing correction. *q* values which are significant after FDR-correction at α=0.05 are shown in bold. Only significantly heritable traits were assessed for genetic correlation (comparison between relatives and healthy controls). NART: National Adult Reading Test IQ; SILS: Shipley Institute of Living Scale (SILS)

IQ; RAVLT-IW*:* Rey Auditory Verbal Learning Test immediate word recall; RAVLT-DW*:* Rey Auditory Verbal Learning Test delayed word recall; IT: inspection time; CPT-IP: Continuous Performance Task identical pairs; CPT-DS Continuous Performance Task degraded stimulus; COWAT: controlled oral word association test; EHI: Edinburgh Handedness Index; SPQ: Schizotypal Personality Questionnaire; TCI: Temperament and Character Inventory.

Table 2: Endophenotype criteria met.

	associated with schizophrenia	heritable	co-segregates with schizophrenia	relatives intermediate
NART IQ [mean, sd], n=524	✓	✓	✓	✓
SILS IQ [mean, sd], n=517	✓	✓	×	✓
RAVLT-IW [mean, sd], n=532	✓	✓	✓	×
RAVLT-DW [mean, sd], n=529	✓	✓	✓	×
IT block A [mean, sd], n=336	✓	✓	✓	-
IT block B [mean, sd], n=335	✓	✓	✓	-
CPT-IP [mean, sd], n=474	✓	✓	✓	✓
CPT-DS [mean, sd], n=397	✓	×	-	-
COWAT (FAS version) [mean, sd], n=528	✓	×	-	-
EHI (lq)	✓	×	-	-
SPQ cognitive-perceptual	✓	✓	✓	×
SPQ interpersonal	✓	✓	✓	×
SPQ disorganisation	✓	✓	✓	×
TCI cooperativeness [mean, sd], n=375	✓	✓	✓	×
TCI self-directedness [mean, sd], n=375	✓	×	-	-
TCI persistence [mean, sd], n=375	×	-	-	-
TCI self-transendence [mean, sd], n=375	✓	×	-	-
TCI reward dependence [mean, sd], n=375	✓	×	-	-
TCI novelty seeking [mean, sd], n=375	✓	×	-	-
TCI harm avoidance [mean, sd], n=375	✓	×	-	-

Check marks indicate that FDR-corrected significance was achieved and the direction of effect was as hypothesised. Measures which were not significantly both associated with schizophrenia and heritable were not assessed against the two measures of genetic correlation (indicated by '-').As no data were available for the inspection time task in the control families, the assessment of whether relatives were intermediate between cases and controls was not available for the IT tasks. Abbreviations as shown in Table 1.

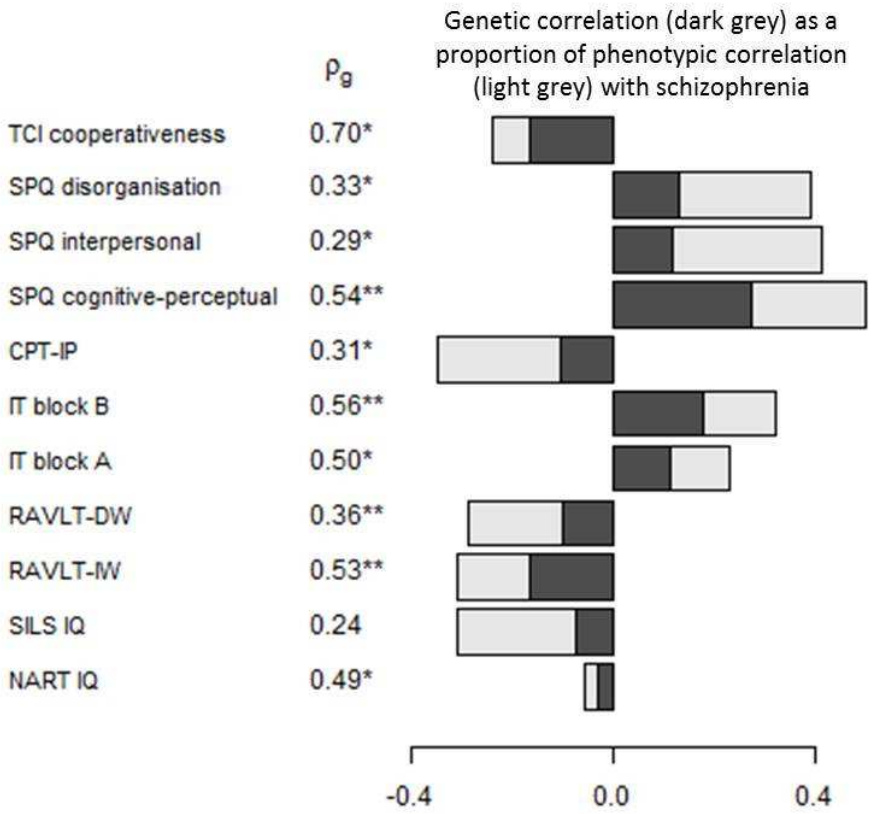

Figure 1. Genetic correlation (ρ_g) between candidate endophenotypes and schizophrenia. Only significantly heritable traits were assessed for genetic correlation. The genetic correlation (dark grey) as a proportion of the phenotypic correlation (Pearson's *r*) with schizophrenia (light grey) is shown. *q<0.05, **q<0.01. SZ: schizophrenia/ schizophrenia spectrum disorder. Other abbreviations as shown in Table 1.

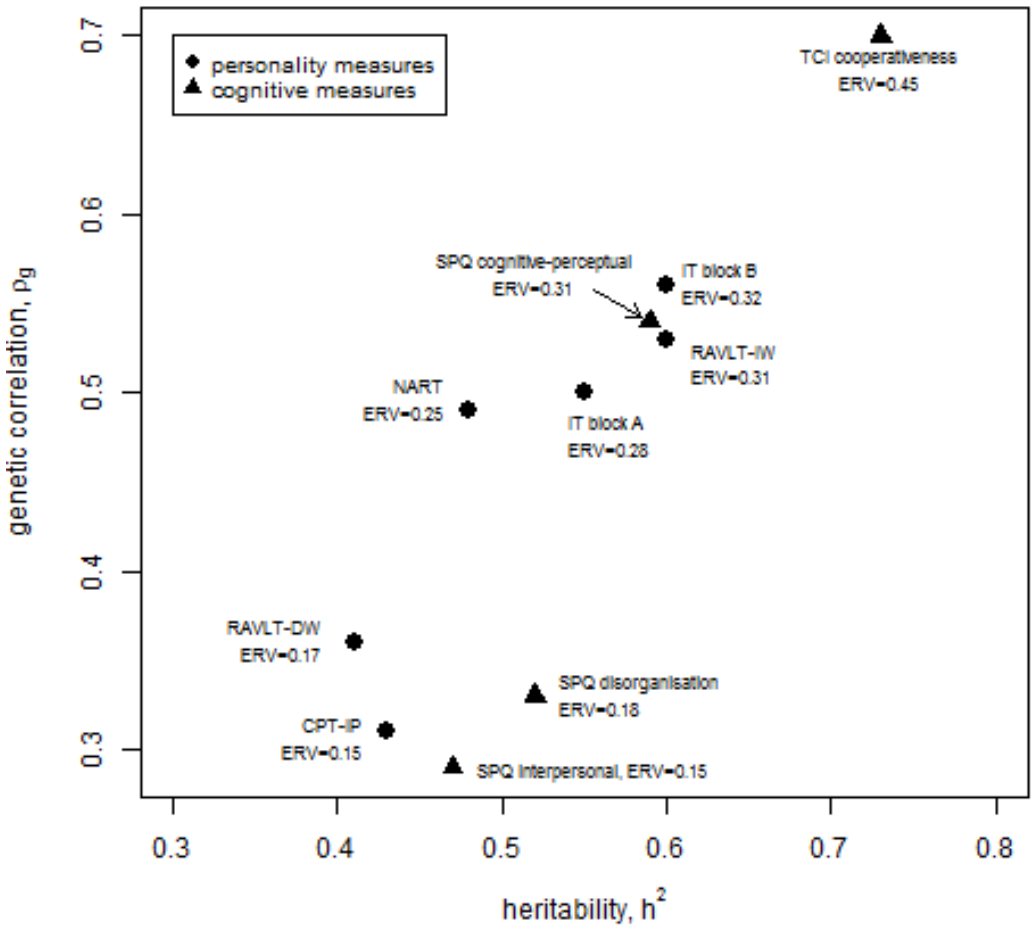

Figure 2. Genetic correlation, heritability and endophenotype ranking variables (ERV). Only traits with significant heritability and genetic correlation with schizophrenia are shown. Personality traits are shown as triangles, cognitive traits as circles. TCI: Temperament and Character Inventory; SPQ: Schizotypal Personality Questionnaire; CPT-IP: Continuous Performance Task identical pairs; IT: inspection time; RAVLT-DW*:* Rey Auditory Verbal Learning Test delayed word recall; RAVLT-IW*:* Rey Auditory Verbal Learning Test immediate word recall; NART: National Adult Reading Test IQ.

Table 3. Factor analysis of cognitive and personality traits.

	Factor1	Factor2	Factor3
NART IQ	0.013	**0.441**	0.004
CPT-IP	**0.219**	**0.272**	**0.148**
RAVLT-IW	**0.110**	**0.854**	**0.211**
RAVLT-DW	**0.149**	**0.857**	**0.204**
IT block A	**0.144**	**0.206**	**0.581**
IT block B	**0.141**	-0.054	**0.986**
EHI (lq)	-0.009	**0.229**	-0.033
SPQ cognitive-perceptual	**0.838**	0.073	**0.112**
SPQ interpersonal	**0.749**	0.038	**0.140**
SPQ disorganisation	**0.832**	-0.072	0.072
TCI cooperativeness	**0.347**	**0.196**	0.058
SS loadings	2.197	1.881	1.460
Proportion Var	0.200	0.171	0.133
Cumulative Var	0.200	0.371	0.504
heritability	0.826	0.687	0.675

Loadings >0.1 are shown in bold. All heritabilities were significant at P<0.01**.** Chi square test of the hypothesis that 3 factors are sufficient: 49.59 on 25 degrees of freedom, p=0.00239. TCI: Temperament and Character Inventory; SPQ: Schizotypal Personality Questionnaire; CPT-IP: Continuous Performance Task identical pairs; IT: inspection time; RAVLT-DW*:* Rey Auditory Verbal Learning Test delayed word recall; RAVLT-IW*:* Rey Auditory Verbal Learning Test immediate word recall; NART: National Adult Reading Test IQ.

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SUPPLEMENTARY

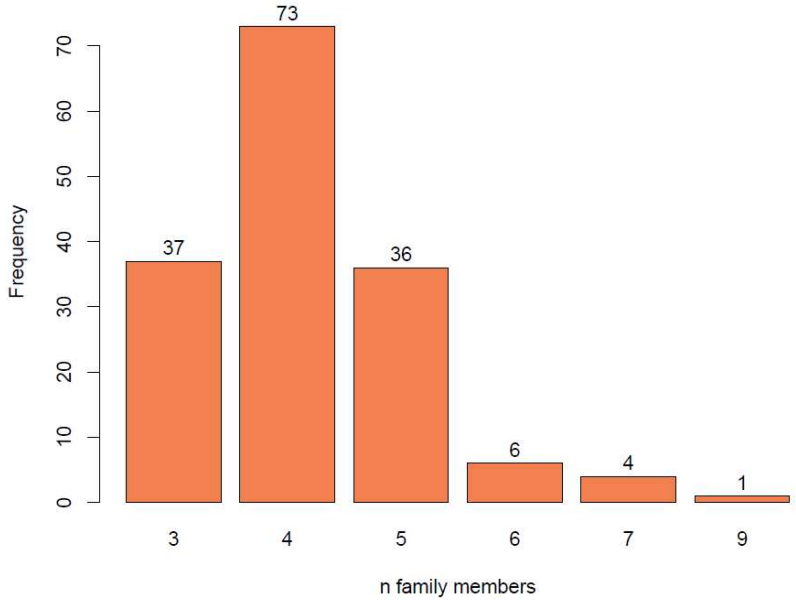

Figure 1. Distribution of family size for the families included in the analysis (157 families, n=656).

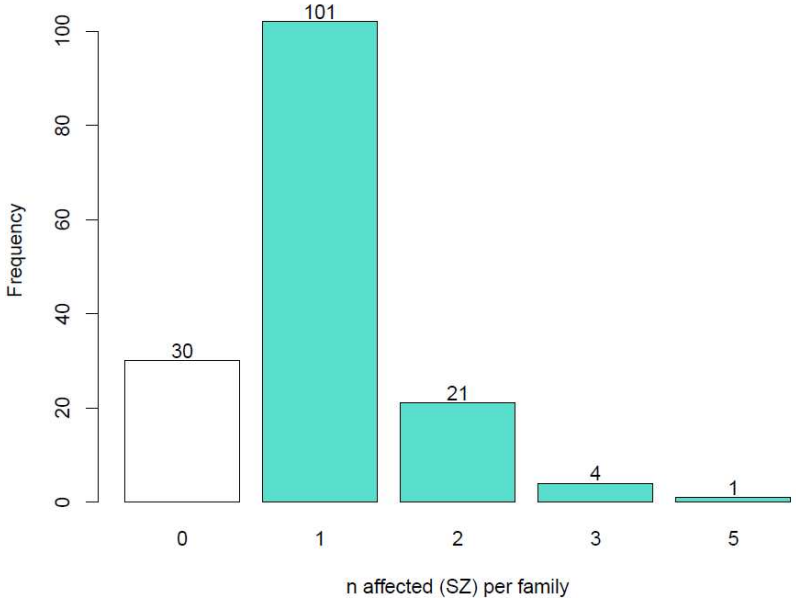

Figure 2. Number of cases per family for all 157 families included in the analysis. Affected families (127 families, n=535) contained 160 cases, with a median of one case per family. The sample also included including 30 control families (n=121)

Table 1. Between-group differences adjusted for NART IQ and medication use in cases.

cognitive and personality traits	cases (n=160, 25%)	relatives (n=375, 57%)	controls (n=121, 18%)	q (cases vs rels)	q (cases vs controls)	q (rels vs control)
SILS IQ	93.4 (14.8)	104.5 (11.8)	108.9 (8.3)	**4.35E-07**	**3.53E-08**	**4.17E-04**
RAVLT-IW	21.5 (6.6)	25.9 (6.0)	27.2 (5.2)	**3.85E-07**	**5.64E-06**	0.087
RAVLT-DW	6.2 (3.1)	8.3 (3.2)	9.06 (2.8)	**1.44E-05**	**1.98E-05**	0.151
IT block A	69.6 (107.9)	47.9 (28.0)	-	**2.36E-06**	-	
IT block B	62.4 (96.7)	42.5 (34.1)	-	**1.42E-06**	-	
CPT-IP	3.13 (1.7)	3.99 (1.5)	4.88 (1.6)	**3.15E-07**	**2.28E-08**	**0.014**
CPT-DS	4.50 (1.5)	5.31 (1.2)	5.62 (1.19)	**1.49E-09**	**9.03E-04**	
COWAT (FAS version)	30.7 (10.4)	37.0 (11.9)	38.0 (9.9)	**2.15E-03**	**2.11E-03**	
EHI (lq)	51.7 (53.0)	62.7 (53.9)	72.0 (37.8)	**2.10E-03**	**6.56E-05**	
SPQ cognitive-perceptual	12.4 (9.2)	2.8 (4.4)	2.5 (4.3)	**7.82E-18**	**1.01E-10**	**0.049**
SPQ interpersonal	9.9 (7.1)	3.9 (4.9)	3.6 (4.7)	**4.90E-14**	**6.86E-09**	0.060
SPQ disorganisation	5.8 (4.8)	1.8 (2.8)	2.0 (3.2)	**5.92E-11**	**3.18E-07**	0.143
TCI cooperativeness	30.5 (7.1)	36.0 (4.5)	34.0 (5.4)	**1.34E-05**	**0.034**	**2.78E-03**
TCI self-directedness	26.5 (7.6)	35.9 (6.7)	33.9 (6.0)	**5.22E-13**	**3.44E-04**	
TCI persistance	4.4 (1.6)	4.4 (1.9)	4.0 (2.0)	0.266	0.080	
TCI self-transendence	18.4 (7.7)	11.2 (6.3)	10.4 (6.9)	**2.24E-09**	**5.15E-05**	
TCI reward dependence	14.0 (3.9)	16.1 (3.7)	16.1 (3.5)	**1.01E-03**	**6.82E-03**	
TCI novelty seeking	18.9 (5.3)	17.9 (5.9)	18.1 (6.2)	**0.022**	**0.032**	
TCI harm avoidance	18.4 (7.5)	13.3 (6.5)	14.1 (5.8)	**2.65E-09**	**3.84E-05**	

FDR-adjusted q values, comparing cases and controls or cases and relatives adjusting for family structure, sex, age, education, NART IQ and medication use (chlorpromazine equivalence, cases only).

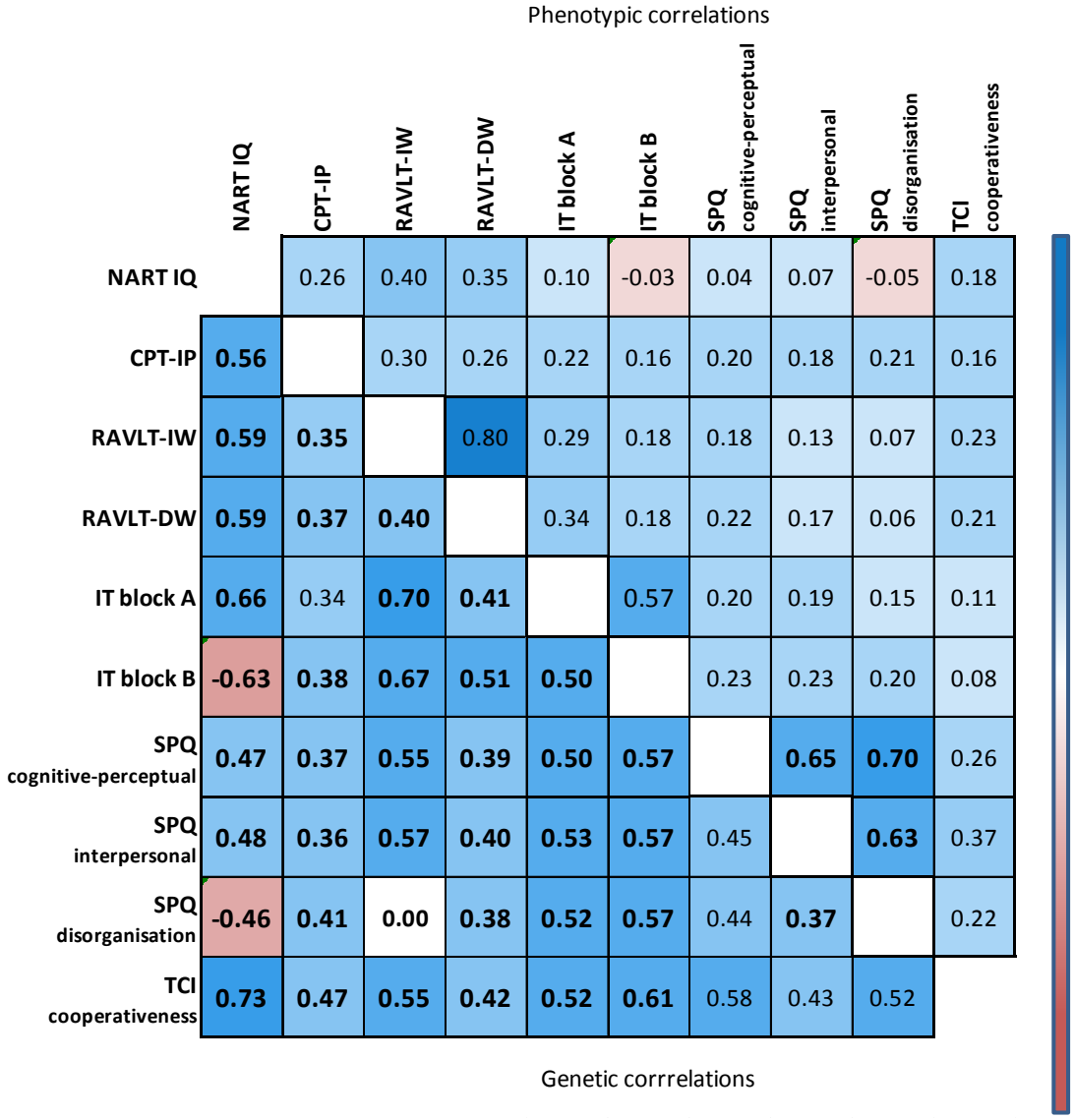

Figure 3. Phenotypic and genetic correlations between candidate endophenotypes. Correlations were calculated from the entire cohort. Phenotypic correlations were adjusted for relatedness. Only traits with significant heritability and genetic correlation with schizophrenia were included.

Table 2. Phenotypic and genetic correlations between factors (Pearson's r).

phenotypic *r*	Factor 1	Factor 2	Factor 3	Factor 4
Factor 1	1	0.019	0.024	-0.009
Factor 2	0.019	1	-0.008	0.010
Factor 3	0.024	-0.008	1	0.002
Factor 4	-0.009	0.010	0.002	1

genetic *r*	Factor 1	Factor 2	Factor 3	Factor 4
Factor 1	1	0.860	0.849	0.850
Factor 2	0.860	1	0.647	0.652
Factor 3	0.849	0.647	1	0.649
Factor 4	0.850	0.652	0.649	1

Table 3. Factor analysis in traits with significant heritability and genetic correlation with schizophrenia in cases and unaffected family members separately.

schizophrenia cases	Factor1	Factor2	Factor3
NART IQ	**0.458**	-0.110	-0.092
CPT-IP	**0.362**	-0.036	0.098
RAVLT-IW	**0.900**	0.018	**0.252**
RAVLT-DW	**0.818**	0.051	**0.348**
IT block A	**0.120**	**0.131**	**0.917**
IT block B	0.084	-0.015	**0.678**
SPQ cognitive-perceptual	0.004	**0.790**	**0.109**
SPQ interpersonal	0.003	**0.791**	-0.075
SPQ disorganisation	-0.271	**0.724**	0.066
TCI cooperativeness	**0.192**	**0.399**	0.031
SS loadings	2.034	1.985	1.528
Proportion Var	0.185	0.180	0.139
Cumulative Var	0.185	0.365	0.504

unaffected family members	Factor1	Factor2	Factor3
NART IQ	0.087	**0.447**	**0.101**
CPT-IP	**0.210**	**0.182**	**0.185**
RAVLT-IW	0.083	**0.854**	0.024
RAVLT-DW	**0.112**	**0.869**	0.055
IT block A	-0.029	**0.205**	**0.976**
IT block B	**0.242**	0.002	**0.546**
SPQ cognitive-perceptual	**0.825**	0.081	0.048
SPQ interpersonal	**0.648**	0.057	**0.230**
SPQ disorganisation	**0.835**	0.023	0.070
TCI cooperativeness	**0.216**	**0.193**	0.067
SS loadings	1.996	1.838	1.363
Proportion Var	0.181	0.167	0.124
Cumulative Var	0.181	0.349	0.472