SUPPLEMENTAL MATERIAL

METHODS

Prior to linkage analysis, the variance component methodology implemented in SOLAR v.4.3.1 was used to obtain heritability (h^2) estimates for each of the endophenotypes to verify our previously published report of significant heritabilities for these endophenotypes and to evaluate potential covariates for linkage (1, 2). This maximum likelihood method assumes a multivariate normal distribution of phenotypes in a pedigree and can accommodate a defined set of covariates. The null hypothesis of no heritability ($h^2=0$) is tested by comparing a "full" model, which assumes that some fraction of the phenotypic variation is explained by genetic factors, to a "reduced" model, which assumes that no variation is explained by genes, using likelihood ratio tests. A correction was made for ascertainment bias, since the families were recruited through the identification of a proband with schizophrenia and are thus not representative of the general population. The type of correction scheme implemented in SOLAR conditions on the trait values of the probands, assuming that they are non-random (3). Because this method does not depend on the specification of a particular threshold value for ascertainment for which the correction will be based, it is more flexible than other methods and appropriate for our analyses. Although variance component methods are relatively robust to departures from normality within families,(3-5) the distribution of values for each endophenotype was analyzed prior to analysis to eliminate large departures. Outliers, defined as trait values greater than three standard deviations from the mean, were removed to improve the distribution of the endophenotypes. Two such subjects were removed for PPI, and five were removed for P50. Since ABF, S-M, and EMO deviated from normality following covariate adjustment with residual kurtosis values >0.8 and required normalization prior to analysis. The distributions of

all other endophenotypes approximated normality, and normalization of these endophenotypes produced consistent results.

Several factors that were likely to affect the endophenotypes (i.e., age, sex, and site of assessment) were explored as potential covariates. Covariates explaining a significant portion of the trait heritability ($P<0.05$) were included in the analysis of each endophenotype as follows: age at interview was included for all but P50; sex was included for PPI, CVLT-II, FMEM, SPA, and EMO; and site of assessment was included for the DS-CPT and CVLT-II. IQ and level of education were not included as covariates in these analyses because, despite the fact that they may be associated with many of the endophenotypes in question, they are also impacted by schizophrenia. Schizophrenia diagnosis was also not included as a covariate, since that would effectively remove the part of the gene-endophenotype linkage that is specifically related to schizophrenia.

Multidimensional scaling, as implemented in PLINK (6), was used to assess the degree of population stratification in this sample and to validate the self-reported subject ancestries. These results confirmed that subjects of European ancestry formed the largest and most genetically homogenous group, encompassing 89% of the sample. The remaining 11% of subjects showed varying degrees of Hispanic, Asian, and African ancestry. Since linkage analyses are family-based, we would not expect the presence of genetic admixture to result in an increased type I (false-positive) error rate, although there may be an artificial inflation of the type II (false negative) error rate, potentially leading to undetected true linkages. Nonetheless, we evaluated the possible effect of genetic admixture on the endophenotype heritabilities through inclusion of the first two principal components from the multidimensional scaling analysis as covariates. Further adjustment for genetic admixture had little effect on the magnitude of the genetic signal (data not shown); therefore, only the minimally adjusted models were interpreted further.

Bivariate environmental (ρ_E) and genetic (ρ_G) correlation estimates were also computed using SOLAR to verify our previous findings, as shown in Table S1 (1, 7). The genetic correlation between two endophenotypes is the component of the overall correlation that is due to pleiotropy (i.e., the influence of a gene or set of genes on both endophenotypes simultaneously), which is obtained from the kinship information in the pedigree. The environmental correlation between two endophenotypes is the component of the correlation due to environmental factors that influence both endophenotypes, which is obtained from the individual-specific error.

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Table S1 – Genetic and environmental correlation estimates observed between the 12 endophenotypes.

	PPI	P50	AS	DS-CPT	CVLT	LNS	ABF	FMEM	SMEM	SPA	S-M	EMO
PPI		0.22 ±0.11	ns	0.22 ±0.08	ns	0.22 ±0.08	ns	ns	ns	ns	ns	ns
P50	ns		ns	0.19 ±0.09	ns	0.22 ±0.08	ns	ns	ns	ns	ns	ns
AS	ns	ns		**0.30 ±0.06**	0.22 ±0.07	0.16 ±0.07	ns	**0.25 ±0.07**	0.18 ±0.07	0.19 ±0.08	**0.28 ±0.07**	**0.27 ±0.06**
DS-CPT	ns	ns	0.44 ±0.12		0.18 ±0.06	**0.28 ±0.06**	0.15 ±0.07	**0.23 ±0.06**	ns	ns	**0.27 ±0.07**	**0.22 ±0.06**
CVLT	ns	ns	ns	ns		ns	0.20 ±0.06	**0.26 ±0.06**	0.15 ±0.07	0.21 ±0.07	0.18 ±0.07	**0.31 ±0.06**
LNS	ns	ns	0.31 ±0.14	ns	**0.31 ±0.06**		ns	ns	ns	**0.26 ±0.07**	0.16 ±0.07	**0.23 ±0.06**
ABF	ns	ns	0.43 ±0.19	0.55 ±0.18	0.50 ±0.20	0.54 ±0.18		**0.21 ±0.06**	ns	0.22 ±0.07	**0.22 ±0.06**	0.19 ±0.06
FMEM	ns	ns	ns	ns	ns	ns	ns		**0.24 ±0.06**	0.22 ±0.07	**0.33 ±0.06**	**0.31 ±0.05**
SMEM	ns	ns	0.40 ±0.13	0.35 ±0.14	**0.63 ±0.17**	0.30 ±0.15	**0.68 ±0.18**	0.42 ±0.14		0.21 ±0.07	ns	0.14 ±0.06
SPA	ns	ns	**0.54 ±0.10**	**0.51 ±0.12**	0.33 ±0.14	0.29 ±0.12	**0.65 ±0.16**	ns	0.33 ±0.12		0.16 ±0.08	0.21 ±0.07
S-M	ns	ns	ns	ns	ns	ns	ns	ns	0.30 ±0.15	0.27 ±0.12		**0.28 ±0.06**
EMO	ns	ns	ns	ns	ns	ns	ns	0.64 ±0.15	0.43 ±0.18	**0.61 ±0.15**	ns	

Bivariate genetic correlations (ρ_G) and their standard errors are indicated below the diagonal with environmental correlations (ρ_E) indicated above the diagonal. Correlations with $p<0.0008$ remain significant after correction for multiple testing and are indicated in bold. All nonsignificant correlations ($p>0.05$) are indicted as "ns".

Table S2 – Summary of all linkage peaks with LOD>1.0 identified by SOLAR and MERLIN.

		SOLAR			MERLIN	
Chrom	**Endophenotype**	**Position (cM)**	**LOD**	**Empirical P**	**Position (cM)**	**LOD**
1p36	LNS	25	1.6	0.004	27	1.4
1p36	EMO	38	3.5*	<0.0001	37	2.5*
1p32	SMEM	77	1.3	0.009		
1p31	EMO	102	1.6	0.006		
1q31	FMEM				191	1.1
1q32	DS-CPT				204	1.3
1q41	AS	224	1.7	0.007	223	1.6
1q43	AS	246	1.8	0.006		
2p25	SPA				18	2.5*
2q24	S-M	164	1.4	0.008	168	2.8*
2q32	S-M	188	1.5	0.006	190	2.7*
2q35	ABF	221	1.2	0.007	216	1.3
3p26	DS-CPT	15	1.7	0.006	14	1.7
3p24	S-M				43	1.4
3p24	FMEM				44	1.2
3p22	CVLT-II				63	1.3
3p14	AS	87	4.0**	<0.0001	88	2.4*
3q26	PPI	175	1.4	0.013	177	1.9
4p16	SMEM				9	2.1
4p15	DS-CPT				26	1.1
4p15	FMEM	32	1.0	0.007	26	1.8
4p15	PPI				45	1.2
4p14	FMEM				57	1.3
4q21	PPI	91	1.2	0.013		
4q32-33	ABF	159	1.5	0.003	166	1.3
5p15	PPI	0.6	2.5*	0.0001	0.6	2.4*
5p15	CVLT-II				34	1.5
5p13	AS	64	1.1	0.025	52	1.2
5q15	ABF	106	1.4	0.003	108	1.3
6p25	ABF				4	1.5
6q21	CVLT-II				114	1.8
6q21	DS-CPT	113	1.8	0.005	115	2.2
6q23	EMO	136	1.1	0.016		
6q24	SMEM				149	1.4
7p22	S-M				3	1.4

7p12	PPI	73	1.6	0.006		
7q21	S-M				94	1.2
7q21	SPA	99	1.2	0.016	98	1.3
7q31	SMEM	128	1.8	0.002	127	2.2
7q32	FMEM				135	2.1
7q36	S-M				159	1.3
7q36	FMEM	164	1.6	0.001		
7q36	EMO	193	1.3	0.011		
8p23	CVLT				9	1.4
8q11	EMO	63	1.1	0.016		
8q22	LNS				106	1.2
8q24	CVLT-II	153	1.1	0.008	136	2.4*
9p24	LNS	14	1.7	0.004	0	1.5
9p23	PPI	27	1.1	0.016		
9q31	S-M				106	1.2
9q31	SPA	110	1.1	0.019		
9q31	AS	113	1.2	0.019	112	1.3
9q33	FMEM	128	1.2	0.005		
9q33	S-M				133	1.4
9q34	FMEM				148	1.7
10q23-24	P50	115	1.6	0.003	119	1.5
10q26	DS-CPT	153	1.9	0.004	155	2.4*
10q26	AS	160	1.2	0.019	168	1.0
10q26	SMEM	167	1.5	0.005	168	1.3
10q26	FMEM	168	2.2*	0.0001	171	2.4*
11p15	ABF				22	1.2
11p15	LNS				27	1.2
11p11-12	EMO	65	1.8	0.003	61	1.9
11q14	AS	85	1.6	0.009		
11q21	CVLT-II				96	1.1
11q22	SPA				109	1.2
12p13	ABF	2	1.2	0.006		
12p13	S-M	14	1.6	0.005		
12p12	CVLT-II	34	1.3	0.004	32	1.5
12p12	FMEM				34	2.8*
12q15	P50				85	1.3
12q21	AS	97	1.3	0.018	99	1.2
12q24	EMO	139	1.2	0.015	129	1.6
13q12	CVLT-II				8	1.5
13q13	DS-CPT	32	1.6	0.006	29	1.3

13q22	SPA				71	1.4
14q23	LNS	65	2.0	0.003	61	2.5
15q13	SMEM				16	1.1
15q14	ABF	28	1.1	0.010	29	1.4
15q14	DS-CPT	37	1.3	0.012		
15q21	PPI	44	1.2	0.014		
15q26	DS-CPT				125	1.0
16p13	PPI	2	1.8	0.004		
16p13	P50	15	1.2	0.011	13	1.5
16p13	FMEM				29	1.1
16q22	ABF	86	1.3	0.004	86	1.7
16q23	SPA	102	2.6*	0.0005	105	2.5*
17p13	DS-CPT	6	1.4	0.011		
17p13	SMEM	8	1.3	0.009	4	1.6
17p13	FMEM	10	1.8	0.0007		
17p13	S-M	10	1.2	0.016	16	1.7
17p13	FMEM	28	1.6	0.001	28	2.0
17q11	FMEM	51	1.6	0.001		
17q11	EMO				56	1.6
17q12	ABF				58	1.4
17q24	EMO	98	1.2	0.013		
18q21-22	P50	76	1.1	0.016	93	1.7
18q22	DS-CPT				102	1.6
19q13	CVLT-II	103	1.8	0.001	105	1.8
20p12	DS-CPT	27	1.1	0.019	24	1.4
20q13	PPI	109	1.0	0.020	87	1.2
21q22	ABF	58	1.2	0.008		
22q11	FMEM				2	1.1
22q11	SPA				8	1.5
22q12	DS-CPT	24	1.5	0.008		
22q12	S-M				43	2.0
Xp11	DS-CPT				76	2.2*

Empirical P values from 10,000 simulations are indicated for each SOLAR LOD score >1.0. *Indicates LOD scores >2.2 meeting criteria for suggestive linkage. **Indicates LOD scores >3.6 meeting criteria for significant linkage