Heritable cognitive and psychopathology factors in youth are predicted by brain fronto-temporal white matter pathway

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Abstract

A healthy transition from adolescence to adulthood relies on a continuous individual adaptation to a dynamic environment. Here, we employed data driven multivariate approaches to derive both general cognitive and psychopathology factors as well as brain phenotypes in children and adolescents in the publicly available PNC sample. We identified a distinct brain white matter pattern which proved central for prediction of heritable cognition and psychopathology scores, highlighting the importance of fronto-temporal connections for intellectual and mental development.

Introduction

Adolescence is a highly sensitive period and a major window for adaptation and opportunities. Modulated by the temporal evolution of a range of gene-environment interactions, it also coincides with the emergence of many mental disorders¹, which may reflect a costs of the potential for brain plasticity offered during this period. Several lines of evidence, including (1) substantial shared genetic contribution to mental disorders, (2) high rate of psychiatric comorbidity, (3) reports of a common underlying factor across diagnostic categories, on which high-scoring individuals are more likely to have cognitive impairments as well as compromised early-life brain function, all highlight the importance of identifying brain based intermediate phenotypes that may be shared across disorders and present before the onset of disease^{1,2,3}. Crucially, the myelinated axons of the brain white matter (WM) form the structural backbone that enables functional integration and adaptation of neural networks, together termed brain connectivity. There is a long-held notion of brain dysconnectivity as a transdiagnostic model for psychopathology, where aberrant brain biology and synchronization modulate the risk for mental health issues⁴. Recent demonstration of a link between a specific pattern of cross-talk between brain networks and a general positive-negative mode of population variability across a range of behavioral, demographic and lifestyle measures, supports that the level of individual adjustment can be conceptualized along a single dimension with a common brain basis⁵. Also, another recent study support the existence of a general and heritable psychopathology factor in children and youth⁶. Here we replicate and extend those findings in the Philadelphia Neurodevelopmental Cohort (PNC⁷), by

showing that a general cognitive and a general psychopathology factor are heritable with a shared genetic contribution, and are associated with a distinct pattern of white matter microstructure and connectivity in the developing human brain.

The microstructural and connectivity properties of the human brain WM undergo profound changes throughout childhood and adolescence, with a protracted maturation continuing well into the third decade^{8,9}, and thus play a paramount role in the development of a healthy mind. Whereas the boundaries of this maturational potential are likely regulated by genetic predispositions, experiences and environmental perturbations mediate the individual development of cognitive and mental characteristics¹⁰. The intricate biological processes shaping the brain connectome during neurodevelopment is highly coordinated across the brain, yet WM development in childhood and adolescence also display anatomically differentiated trajectories, suggesting regional variation in rates and timing of maturational changes⁸. Hence, when considered from a system-level perspective different brain circuits may compete for common resources, and the cognitive and clinical correlates may be modulated by the relative balance between different networks subserving distinct functions. Indeed, diffusion weighted imaging (DWI)-based indices of brain tissue organization may reflect the relative balance between differentially affected crossing fiber populations¹¹. Consequently, fusion of multimodal brain imaging indices, which allows for a joint consideration of different brain characteristics, may yield more biologically interpretable patterns of brain microstructure and connectivity sensitive to the development of cognitive and mental health.

Here, and in line with the aims of the NIMH Research Domain Criteria Project (RDoc) for mental disorders¹², we targeted a data driven multivariate delineation of both brain and behavioral phenotypes. Scores from a diverse battery of cognitive tests and clinical questionnaires for 6,487 individuals in the PNC were decomposed to form and isolate both general and specific phenotypic traits, including general cognitive (gF) and general psychopathology (mean-ICA) factors. In addition, we investigated seven independent clinical components each reflecting empirical clustering of specific psychopathology symptoms (Supplementary Fig. 1). We used Genome-wide Complex Trait Analysis (GCTA)¹³ to estimate the lower-bound heritability of the general cognitive and general psychopathology phenotypes based on variation in

common single-nucleotide polymorphisms (SNP-heritability) in a subsample of 2963 individuals of European descent. We also estimated the genetic correlation between the traits and its precision by means of resampling. In a subset with available diffusion-weighted MRI data (n=813), we used linked ICA (LICA)¹⁴ to decompose eight WM maps per individual reflecting different microstructural and connectivity properties (fractional anisotropy [FA], axial diffusivity [L1], radial diffusivity [RD], mean diffusivity [MD], mode of anisotropy [MO], dominant fiber direction [f1], non-dominant fiber direction [f2] and probabilistic tractography density [CD] maps) into 20 independent components. Each component is characterized by group level spatial maps (one per WM index), and corresponding subject weights (one per participant) reflecting individual participant's contribution to the observed brain patterns. These weights were used in multivariate cross-validated prediction analysis as well as to test for univariate associations with age, cognition and psychopathology.

Methods

Sample and exclusion criteria: The analysis was based on the publicly available Philadelphia Neurodevelopmental Cohort^{7, 15} (PNC, access obtained with permission #8642, project title: Neurodevelopmental brain networks: Integrating multimodal imaging, cognition and genetics). The institutional review boards of the University of Pennsylvania and the Children's Hospital of Philadelphia approved all study procedures, and written informed consent was obtained from all participants. We accessed diffusion weighted imaging (DWI) data from 883 individuals. After removal of all participants with severe or major medical health conditions (n=44, rating of medical condition was performed by trained personnel in the PNC study team), and datasets that did not pass quality assessment (n=91), the final MR-sample comprised 748 individuals (343 males) aged 8.7 to 22.6 years (mean: 15.1 years, SD: 3.3 years). We accessed cognitive and clinical data for 6,487 participants for decomposition of neuropsychological and clinical scores using PCA and ICA. Of the 748 participants included in the MR-sample, 729 had available clinical data. We accessed genetic data for 4,450 participants of European descent.

MRI acquisition: DWI scans were acquired at University of Pennsylvania¹⁵ on a 3T Siemens TIM Trio scanner, acquired using a twice-refocused spin-echo (TRSE) single-shot EPI sequence (FOV: 240 x 240 mm; matrix: 128 x 128 x 70; 64 diffusion-weighted directions; $b = 1000 \text{ s/mm}^2$; voxel resolution 1.875 x 1.875 x 2 mm).

MRI Quality Assessment: We computed temporal-signal-to-noise ratio (tSNR) for all DWI datasets using scripts and cut-off values previously described for the PNC sample¹⁶. Out of the 839 datasets remaining after exclusion based on medical conditions, 91 individuals (10.8%) were excluded based on a tSNR cut-off of 5.7.

Image processing: DWI data were processed using FMRIB's Diffusion Toolbox (FDT), part of FSL 5.0¹⁷, and included correction for motion and eddy current distortions using eddy¹⁸. FA, eigenvector and λ -value maps were computed by fitting a tensor model to the raw diffusion data and used to derive mean diffusivity (MD), radial diffusivity (RD) and mode of anisotropy (MO)-maps.

Cross fiber modeling: Estimation of the probability distribution of the diffusion directions was performed with the GPU-accelerated version of bedpostx¹⁹, with up to three fibers estimated per voxel.

Probabilistic fiber tracking: Whole brain probabilistic fiber tracking was performed using probtrackx2²⁰. In line with a recent application in aging and dementia²¹, for each participant and from each voxel inside the native space whole brain seed mask, 100 pathways were sampled, resulting in a 3D-volume tractography-map per participant which were normalized by dividing with the total number of streamlines processed. Thus, the value in each voxel represents the likelihood that any streamline will pass through that voxel (connection density). We also performed a second probabilistic tracking analysis, sampling 5000 streamlines pr. voxel inside four ROIs in the insular region bilaterally, based on the results from the LICA.

Spatial normalization: All maps were nonlinearly transformed to the FMRIB58_FA template and skeletonized using the FDT TBSS pipeline²². For visualization of skeleton-based results we used tbss_fill which thickens the skeleton

for easier visual interpretation. Fiber orientation maps were warped and skeletonized using `tbss_x`²³.

Linked independent component analysis (LICA): We performed data-driven decomposition of imaging features into independent components using FMRIB's LICA (FLICA, <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FLICA>), which models the inter-subject variability across modalities^{14, 24}. The model order was heuristically chosen at 20 components based on inspection of the spatial maps.

Neurocognitive test battery and gF-score: All PNC participants completed a computerized neurocognitive battery²⁵. We included performance scores from 12 neurocognitive tests (Supplementary Table 2) spanning executive control and WM, episodic memory, verbal and non-verbal reasoning, and social cognition in a PCA. All scores were adjusted for age before entering the PCA, and the first factor was extracted as a general measure of neurocognitive performance (gF).

Clinical measures and mean-ICA score: A computerized protocol was used to assess symptoms of anxiety, mood, behavioral, eating and psychosis spectrum disorders with collateral informants for individuals below 18 years of age²⁵. We included 129 clinical symptom score items covering 18 psychological clinical domains (Supplementary Table 3) for all the available participants in the PNC sample (n=6,487), excluding all follow-up and conditional items, and computed summary scores for each domain. 1,627 participants had missing values on one or several clinical items. For all but two participants which had missing values on all 129 clinical items, the missing values was replaced with the nearest-neighbor value based on Euclidean distance. The percentage of missing values for the 129 items ranged from 0-7%.

All available clinical item scores were submitted to independent component analysis (ICA) using ICASSO²⁶, decomposing them into seven independent components. The model order of the ICA was chosen after testing several different model orders ranging from 3-15, each of which 100 permutations was run, and based

on the observed independence and reliability of the resulting components. The mean subject weight across components were computed (mean-ICA) and used as a general measure of psychopathology. For comparison, we submitted the clinical variables to a PCA and extracted the first principal component (pF). The correlation between mean-ICA and pF was $r=.97$.

Statistical analysis: Prediction of Age, gF and mean-ICA using LICA subject-weights was performed using shrinkage linear regression, with automatic estimation of the correlation shrinkage intensity²⁷. We performed 1000 iterations each with a separate 10-fold cross-validation, before calculating the mean correlation across all iterations. Feature importance was assessed by correlation-adjusted marginal correlation (CAR)-scores²⁸. To assess significance, for each trait we performed 10,000 permutations of the 10-fold cross validated prediction while randomly permuting the trait-scores. Univariate associations between LICA subject weights and cognitive and clinical variables were performed using linear models, and included age, gender and tSNR as covariates, and corrected for multiple comparisons using false discovery rate (FDR). All reported p-values are two-tailed unless otherwise specified. For visualization of age-curves of LICA subject weights for high and low scoring individuals (gF and clinical ICA-score) we used a cut-off of ± 1 s.d. to form the following groups: gF high ($n=114$), gF low ($n=75$), mean-ICA high ($n=76$), mean-ICA low ($n=115$), IC2 high ($n=126$), IC3 high ($n=80$) and IC4-high ($n=108$). We then repeatedly fitted a smooth function with automatic estimation of the smoothness parameter²⁹ and computed the mean and s.d. across 10,000 bootstraps for each of the groups.

Genomwide complex trait analysis: Genotyping of the PNC sample²⁵ was performed by the Center for Applied Genomics, at the Children's Hospital of Philadelphia. We included data from the following platforms: Illumina OmniExpress ($n = 1,241$), Illumina Human-610 Quad ($n = 1,895$), Illumina HumanHap-550-v1 ($n = 317$), Illumina HumanHap-550-v3 ($n = 997$). The chip-genotyped SNPs overlapping across the platforms were extracted and used to form a data set to apply the following filters on: individuals with relatedness $> .05$ ($n=296$); removal of SNPs in the major histocompatibility complex (25:35 Mb region on chr6) and the inversion region of chr8 (7:13 Mb); SNPs with genotyping rate $< 99\%$, minor allele frequency $< 5\%$ and Hardy-Weinberg Equilibrium test p-value $< .0000001$; pairwise pruning of SNPs in

linkage disequilibrium ($r^2 > 0.2$, window of 5,000, step of 500). We used GCTA¹³ to create a genetic relationship matrix based on the remaining SNPs ($n=49,774$), before running univariate and bivariate REML-analysis to estimate SNP-heritability for gF and mean-ICA, as well as the genetic correlation between these traits, in participants with overlapping phenotypic and genetic data ($n=2,946$). Age, gender and platform were included as covariates. The genetic correlation (r_G) between gF and mean-ICA-scores was estimated through sub-sampling by drawing 6000 random sub-samples ($n=2,746$) from the full sample ($n=2,945$) without replacement, before estimating the mean and standard deviation of r_G across the sub-samples.

Results

Common SNPs explained 18% ($p < .05$) of the individual differences in general cognition and 16% ($p < .05$) of the differences in general psychopathology (Supplementary Table 1). These two traits also showed a negative genetic correlation (resampling mean $r = -.74$; s.e. = .15, 99% CI [-1, -.36]; Supplementary Fig. 2). The LICA components captured distinct patterns of neurodevelopment (Fig. 1A). All components combined predicted age with high accuracy (correlation between observed and predicted age: $r = .77$, $p < .0001$; p-value obtained from non-parametric permutation testing, Supplementary Fig. 3). This confirms the high sensitivity of brain features for age-prediction in the PNC sample³⁰, and was primarily driven by the first component, capturing spatially global variance in FA, RD and MD (LICA-01, Supplementary Fig. 4). Strikingly, the components also allowed for significant prediction of general cognition ($r = .39$, $p < .0001$) and general psychopathology ($r = .24$, $p = .0001$). These were both strongly driven by the same component (LICA-09) of which anatomical distribution and multimodal contribution is consistent with degree of crossing fibers in fronto-temporal connections (Fig. 1B).

Specifically, the spatial foci of LICA-09 encompassed the intersection between the uncinate fasciculus (UF) and the inferior occipito-frontal fasciculus (IFOF)^{31, 32}, with negative spatial weights for FA, f1, MO and CD and positive weights for f2 and RD. While an increase in FA is often interpreted in terms of increased WM integrity, FA may also increase in crossing fiber regions if one of the fiber population is degraded, and may be inferred based on the conjunction of MO changes in the same region¹¹. Further, f1 and f2 models the evidence for two underlying fiber populations

and the joint multivariate pattern revealed by LICA-09 thus seems sensitive to the underlying anatomy at the intersection of two major WM pathways in this region. The robust clinical and cognitive relevance of this component was supported by significant univariate associations with a wide range of cognitive and clinical domain scores (Fig. 2). Strikingly, associations indicated that the brain pattern in LICA-09 was less expressed in individuals with more severe general psychopathology, and more expressed in individuals with higher neuropsychological performance level. The reduction in subject weights for LICA-09 with increasing psychopathology implies a reduction of crossing fibers in the same area for individuals with increased symptom burden (Supplementary Fig. 5). Although LICA-09 showed a significant negative association with age, its associations with cognitive and clinical features were relatively stable across the sampled age-range. Importantly, Supplementary Fig. 6 illustrates that the general cognitive score and psychopathology exhibited independent associations with LICA-09. This WM microstructural pattern is of particular interest with respect to mental health for several reasons: UF is among the tracts with the highest heritability³³, it displays a protracted maturation pattern as compared to other fiber tracts⁸, and is hypothesized to subserve a limbic temporo-amygdala-orbitofrontal network, critically involved in integration of emotional states with cognition and behavior^{32, 34}. When investigating individual clinical ICA components, each of which express more symptom specificity compared to the general psychopathology score, similar relationships with LICA-09 subject weights (Supplementary Fig. 7) was observed for anxiety and harm avoidance (IC2), antisocial and norm violating behavior (IC3) as well as for psychosis prodrome and psychotic symptoms (IC4). This confirms that the reported brain pattern is broadly associated with a range of psychopathology symptoms rather than showing specificity with a certain clinical domain. These three symptom-categories have been shown to belong to separate empirical symptom-factors, often termed internalizing, externalizing and thought-disorder symptoms, however they also load on a general psychopathology factor implying shared common risk³. The present results point to altered limbic temporo-amygdala-orbitofrontal pathways as a candidate for such a transdiagnostic brain phenotype in psychiatric disease.

Figure 1 LICA brain components robustly predicted age, cognition and psychopathology **(A)** The circular plot shows the feature importance for each of the 20 components in cross-validated prediction of age, cognition (gF) and psychopathology (mean-ICA). While LICA-01 is the most important feature for prediction of age, LICA-09 is most important for prediction of cognition and mental health. **(B)** The scatter plots show the correlations between the true and predicted scores, all significant at $p < .001$ (FWE, 10,000 permutations). **(C)** The LICA-09 subject weights plotted as a function of age, and stratified by gF- and clinical ICA-scores. High- and low-scoring groups were defined as those scoring at least ± 1 s.d. from the group average. Clinical IC2 represents high anxiety, while clinical IC3 and IC4 represent norm violating behavior and psychosis prodrome, respectively. Curves and shaded area represent the mean and s.d. of smooth function fitting across 10,000 bootstraps. **(D)** Brain maps represent the spatial weights for the diffusion MRI modalities of LICA-09, with percentages representing the relative modality contributions. Warm and cool colors represent positive and negative LICA-weights, respectively (z -threshold of ± 3), overlaid on the UF (pink) and IFOF (purple) from the JHU WM-tractography atlas.

Figure 2: Univariate results for the subject weights of the 20 LICA components supports the cognitive and clinical relevance of LICA-09. All clinical and cognitive associations are adjusted for age, gender and tSNR, and corrected for multiple comparisons using a false discovery rate (FDR) of $q=0.05$. The brain pattern captured by LICA-09 shows robust and inverse associations with cognitive and clinical scores, both for the gF/mean-ICA and ICA component scores, as well as for individual cognitive and clinical domain scores.

Fronto-temporal connectivity has been implicated in a range of mental illnesses including schizophrenia and its prodrome³⁵, conduct disorder and psychopathy³¹ as well as anxiety and harm avoidance^{36, 37}. The current findings show that such abnormalities are present also in non-diagnosed, but putatively at-risk youth. The distinct brain pattern predicting cognitive and clinical traits captures the developmental coordination of two major white matter tracts during late childhood and early adolescence, accompanying global age-related maturation of brain WM.

The current work comes with some limitations. The size of the available sample for the heritability analysis in the PNC sample is on the lower end, and so point estimates should be interpreted with caution as the confidence intervals are wide. However, the estimated negative genetic correlation between cognition and psychopathology is unlikely to occur in a population with zero or positive values for r_G , and the sign of the correlation is also in agreement with large-scale studies on cognition and psychopathology in adult populations³⁸. Future studies with larger samples are needed to determine whether there is also a genetic correlation between the observed brain phenotype and psychopathology. However, its robust associations with heritable general psychopathology and general cognitive factors warrant further investigation of fronto-temporal connectivity as an intermediate brain based phenotype in mental illness, and serve as a proof-of-principle for the emerging concept that a healthy transition from childhood to adolescence is dependent on an integrated yet partly independent development of distinct WM pathways in the brain.

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Supplementary figures and tables

Supplementary Figure 1

The weights for each of the 129 clinical questionnaire items on the seven estimated independent components. Clinical IC1 captures variance related to the attention deficit disorder (ADD) items, but also the attention item from the prodromal symptom severity scale (SIPS). IC2 encompasses items across several anxiety questionnaires, with highest weighting for social anxiety, but also agoraphobia, specific phobias and separation anxiety. IC3 is related to norm violating behaviours. Highest weights are assigned to conduct disorder items and oppositional defiance disorder, but also PTSD items related to experiences of violent behaviour. IC4 includes items from the SIPS questionnaires related to positive symptoms and delusions, as well as items on the psychosis questionnaire related to hallucinations. IC5 captures variance related to items across several clinical domains, including depression, generalized anxiety disorder, panic disorder, the negative symptoms of the SIPS questionnaire, as well as suicidal ideation. Component six (IC6) is related to mania and items capturing episodes of increased energy, reduced need for sleep, and increased speed of thought and speech. Component seven (IC7) is related to obsessive-compulsive disorder, and has the highest weights for items related to repetitive behaviours of counting, arranging and cleaning, but also to intrusive thoughts such worrying about germs/contamination. Color scale represents item loading on the independent components.

Supplementary Figure 2: To get an estimate of the precision for the point estimate of the genetic correlation (r_G) between gF and mean-ICA-scores, we employed resampling by drawing 6000 random subsamples ($n=2,746$) from the full sample ($n=2,945$), without replacement. The density plot shows the distribution of r_G -estimates across sub-samples. The mean genetic correlation (r_G) was $r=-.74$, $s.e.=.15$ and the 99% CI was $[-1, -.36]$, indicated by the red diamond and line, respectively.

Supplementary Figure 3: For each of the predicted traits (Age, gF and mean-ICA) we performed 10,000 permutations to assess whether the correlation between true and predicted scores were above chance level.

Density plots represent the null-distributions, diamonds indicate the observed correlations. For Age and gF none of the permuted values exceeded the observed correlations, while the permuted p-value for mean-ICA prediction was .0001 (two-tailed).

Supplementary Figure 4: LICA-01 captures spatially global changes across the age-span. **(A)** Subject weights decrease as a function of age. **(B)** This indicates an increase predominantly in FA, f1, RD and MD (percentages represent the modalities contribution to the LICA-component) during neurodevelopment. Spatial map thresholded $z=3$. **(C)** A negative association between gF and LICA-01 subject weights indicate higher FA, f1, RD and MD in high performing individuals.

Supplementary Figure 5: Seed based probabilistic tractography confirm involvement of UF. **(A)** To confirm that the crossing fiber area in the insular region is indeed related to intersection of IFOF (purple) and UF (pink) fibers (left panel, MNI x-coordinate=35 mm), we performed a seed-based probabilistic whole-brain tractography from ROIs based on LICA-09 weights in this region. **(B)** The seeds were based on voxels showing a conjunction of changes in both FA and MO (thresholded at $z=3$), an approach previously reported as sensitive to crossing fiber regions. The cluster with negative LICA spatial weights (blue) represent the insular UF-region with increased FA and MO with higher symptom burden while the more inferior cluster with positive values (red) represent a more inferior part of the UF showing the opposite pattern clinical pattern. **(C)** When contrasting their whole-brain connectivity probabilities the former cluster shows higher connectivity probability with the IFOF while the latter shows higher connectivity probability with the UF.

Supplementary Figure 6: The full and partial correlations (including adjustment for age, gender and tSNR) between LICA-09 subject weights, gF, and clinical IC2 (anxiety and harm avoidance), IC3 (norm violating behaviour) and IC4 (psychosis prodrome) scores. Matrix threshold at $q < .05$ (FDR).

TOP 20 Items loading on clinical IC2

[SOC] Felt afraid or uncomfortable acting/performing/sport, giving talk/speech
 [SOC] Afraid/uncomfortable doing something in front of a group like speaking in class
 [SOC] Afraid/uncomfortable when center of attention, concerned something embarrassing might happen
 [SOC] Afraid/uncomfortable/shy meeting new people/parties, or eating/drinking/working in front of others
 [SOC] Afraid/uncomfortable talking on phone or with people your age you don't know very well
 [AGR] Been very nervous or afraid of going over bridges or through tunnels
 [PHB] Been very nervous or afraid of flying or airplanes
 [PHB] Been very nervous or afraid of storms, thunder, or lightning
 [PHB] Been very nervous or afraid of being in really high places, e.g. roof/tall building
 [AGR] Been very nervous or afraid of traveling away from home
 [PHB] Been very nervous or afraid of animals or bugs, like dogs, snakes, or spiders
 [AGR] Been very nervous or afraid of traveling by yourself
 [SEP] Been very upset and worried about going to be away from home/parents
 [AGR] Been very nervous or afraid of being in crowds, e.g. classroom/cafe/restaurant/theater
 [AGR] Been very nervous or afraid of using public transportation
 [SEP] Wanted to stay home from school or not go to other places e.g. sleep-overs without parents
 [PHB] Been very nervous or afraid of closed spaces, like elevators/closets
 [PHB] Been very nervous or afraid of doctors, needles, or blood
 [AGR] Been very nervous or afraid of going to public places, e.g. store/mail
 [SEP] Scared to be alone in your room or need a parent to stay with you while you fell asleep

TOP 20 Items loading on clinical IC3

[CDD] Did you ever attack someone to steal from them
 [CDD] Did you ever threaten someone
 [CDD] Set fires, break into cars, or destroy someone's property on purpose
 [CDD] Hurt someone with a weapon e.g. bat/brick/knife/bottle/gun.
 [CDD] Did you ever hold someone up
 [CDD] Skip school, stay out later than allowed, run away from home overnight.
 [CDD] Hit/threaten/scared someone younger, start physical fights
 [CDD] Been physically cruel to an animal or person
 [PTD] Have you ever been threatened with a weapon
 [PTD] Have you ever been attacked by somebody or badly beaten
 [CDD] Done things that got you into trouble with adults, e.g. lying/stealing
 [CDD] Do you have a probation officer / been on probation
 [ODD] Gotten in trouble for getting even by hurting or telling lies about someone or messing up their things
 [PTD] Have you ever seen or heard somebody get killed or get hurt very badly or die?
 [ODD] Gotten in trouble with adults for refusing to do what they told or for breaking rules
 [ODD] Annoy other people on purpose or blame other people for your mistakes
 [PTD] Been in a situation where you thought you or someone close to you was going to be killed/badly hurt
 [ODD] Gotten into trouble with adults eg. by losing temper, arguing, talking back, being grouchy or irritable
 [PTD] Have you ever been in a bad accident?
 [ODD] Often irritable or grouchy, or often angry because you thought that things were unfair

TOP 20 Items loading on clinical IC4

[SIP] I believe that I have special natural or supernatural gifts beyond my talents and natural strengths.
 [SIP] Hearing faint or clear sounds of people or a person mumbling or talking when there is no one near me.
 [SIP] Felt there could possibly be something interrupting/controlling my thoughts, feelings, or actions.
 [SIP] I think I might feel like my mind is "playing tricks" on me.
 [SIP] May get confused at times whether something I experience/perceive is real or part of my imagination
 [SIP] I think that I might be able to predict the future.
 [SIP] Thought that it might be possible that others can read my mind, or that I can read others' minds
 [SIP] I have had the experience of doing something differently because of my superstitions.
 [SIP] I think that I may hear my own thoughts being said out loud.
 [SIP] I think that I have felt that there are odd or unusual things going on that I can't explain.
 [SIP] I wonder if people may be planning to hurt me or even may be about to hurt me.
 [SIP] I have been concerned that I might be "going crazy."
 [PSY] Have you ever heard voices when no one was there
 [PSY] Have you ever seen visions or seen things which other people could not see
 [PSY] Strange feelings in your body like things were crawling on you or someone touching you
 [SIP] CHANGES IN SPEECH, DISORGANIZED COMMUNICATION, TANGENTIAL SPEECH: Severity Scale
 [SIP] EXPRESSION OF EMOTION: Severity Scale
 [PSY] Has there ever been anything unusual about the way things smelled or felt or looked
 [PSY] Have you ever smelled strange odors other people could not smell?
 [SIP] AVOLITION: Severity Scale

Supplementary Figure 7: LICA-09 is associated with a wide range of clinical symptoms. Three of the clinical ICA-components showed an association with LICA-09 subject weights. Left panels shows the 20 highest loading clinical questionnaire items for clinical IC2 (anxiety and harm avoidance), IC3 (antisocial and norm violating behavior) and IC4 (psychosis prodrome). Warm colors represent higher weights. Right panel displays the LICA-09 subject weights regressed against the clinical ICA scores, adjusted for age, gender and tSNR.

SNP heritability				
Trait	N	V(G)/Vp	s.e.	p
gF (cognitive)	2946	0.183	0.09	0.013
mean-ICA (clinical)	2946	0.156	0.095	0.049
Genetic correlation				
Traits	N	r(g)	se	p (one-tailed)
gF/mean-ICA	5893	-0.81	0.51	0.032

Supplementary Table 1: General cognitive ability and general symptom burden are linked to common SNPs. SNPs explained 18% of the variability in gF scores and 16% of the variability in mean-ICA scores. V(G)/Vp is the estimated phenotypic variability attributable to additive effects of SNPs. r(g) is the estimated genetic correlation between phenotypes.

dbGaP Study Accession	Variable name	Description	Name of test
phv00194764.v1.p1	padt_pc	Percent Correct Responses for All Test Trials, by genus	The Penn Age Differentiation Test
phv00194776.v1.p1	pfmt_ifac_tot	Total Correct Responses for All Test Trials	The Penn Face Memory Test
phv00194780.v1.p1	peit_cr	Total Correct Responses for All Test Trials, by genus	Penn Emotion Identification Test
phv00194802.v1.p1	pwmt_kiwrdr_tot	Total Correct Responses for All Test Trials	Penn Word Memory Test
phv00194806.v1.p1	pvrt_cr	Total Correct Responses for All Test Trials, by genus	Penn Verbal Reasoning Test
phv00194823.v1.p1	pedt_pc	Percent of Correct Responses for All Test Trials, by genus	Penn Emotion Differentiation Test
phv00194831.v1.p1	mp_mp2rtcr	Median Response Time for Correct Mouse Click Responses	Penn Motor Praxis task
phv00194837.v1.p1	pmtat_pc	Percent of Correct Responses for All Test Trials, by genus	Penn Matrix Reasoning Test
phv00194845.v1.p1	tap_tot	Sum of Mean of Tap Responses for Dominant Hand Trials and Mean of Tap Responses of Non-Dominant Hand Trials	Finger Tapping Test
phv00194848.v1.p1	volt_svt	Total Correct Responses for All Test Trial	Visual Object Learning Test
phv00194864.v1.p1	lnb_mcr	Number of Correct Responses to for 1-Back and 2-Back Trials	Letter N-Back Test
phv00194879.v1.p1	pcet_cat	Number of Categories Achieved	Penn Conditional Exclusion Test
phv00194880.v1.p1	pcet_acc2	Calculated Accuracy Measure	Penn Conditional Exclusion Test
phv00194892.v1.p1	pcpt_t_tp	Total of Correct Responses to Number Trials (TP) and Letter Trials (TP)	Penn Continuous Performance Test
phv00194893.v1.p1	pcpt_t_tprt	Median Response Time for Correct Responses to Number Trials (TP) and Letter Trials (TP)	Penn Continuous Performance Test
phv00194900.v1.p1	plot_pc	Percent Correct Responses for All Test Trials, by genus	Penn Line Orientation Test
phv00194903.v1.p1	wrat_cr_raw	WRAT: Wide Range Assessment Test 4 Total Raw Score	Wide Range Assessment Test (Reading/IQ)

Supplementary Table 2: List of variables included in the PCA to compute the general cognition score (gF)

dbGaP Study Accession	Variable name	Item question
phv00194007.v1.p1	INT_TYPE	AP=Adult Proband (ages 18 and up); MP= Middle Proband (ages 11-17); MI=Middle Informant; YPI= Young Proband Informant (for ages 8-10)
Attention Deficit Disorder (ADD)		
phv00194008.v1.p1	ADD011	Did you often have trouble paying attention or keeping your mind on your school, work, chores, or other activities that you were doing?
phv00194009.v1.p1	ADD012	Did you often have problems following instructions and often fail to finish school, work, or other things you meant to get done?
phv00194010.v1.p1	ADD013	Did you often dislike, avoid, or put off school or homework (or any other activity requiring concentration)
phv00194011.v1.p1	ADD014	Did you often lose things you needed for school or projects at home (assignments or books) or make careless mistakes in school work or other activities?
phv00194012.v1.p1	ADD015	Did you often have trouble making plans, doing things that had to be done in a certain kind of order, or that had a lot of different steps?
phv00194013.v1.p1	ADD016	Did you often have people tell you that you did not seem to be listening when they spoke to you or that you were daydreaming?
phv00194017.v1.p1	ADD020	Did you often have difficulty sitting still for more than a few minutes at a time, even after being asked to stay seated, or did you often fidget with your hands or feet or wiggle in your seat or were you "always on the go"?
phv00194018.v1.p1	ADD021	Did you often blurt out answers to other people's questions before they finished speaking or interrupt people abruptly?
phv00194019.v1.p1	ADD022	Did you often join other people's conversations or have trouble waiting your turn (e.g., waiting in line, waiting for a teacher to call on you in class)?
Agoraphobia (AGR)		
phv00194035.v1.p1	AGR001	Have you ever been very nervous or afraid of: being in crowds (for example, a classroom, cafeteria, restaurant, or movie theater)?
phv00194036.v1.p1	AGR002	Have you ever been very nervous or afraid of: going to public places (such as a store or shopping mall)?
phv00194037.v1.p1	AGR003	Have you ever been very nervous or afraid of: being in an open field?
phv00194038.v1.p1	AGR004	Have you ever been very nervous or afraid of: going over bridges or through tunnels?
phv00194039.v1.p1	AGR005	Have you ever been very nervous or afraid of: traveling by yourself?
phv00194040.v1.p1	AGR006	Have you ever been very nervous or afraid of: traveling away from home?
phv00194041.v1.p1	AGR007	Have you ever been very nervous or afraid of: traveling in a car?
phv00194042.v1.p1	AGR008	Have you ever been very nervous or afraid of: using public transportation like a bus or SEPTA?
Conduct disorder (CDD)		
phv00194062.v1.p1	CDD001	Was there ever a time when you often did things that got you into trouble with adults like lying or stealing (something worth more than \$5, from family, others, or stores)?
phv00194064.v1.p1	CDD002	Did you ever skip school, stay out at night later than you were supposed to (more than 2 hours), or run away from home overnight?
phv00194066.v1.p1	CDD003	Did you ever set fires, break into cars, or destroy someone else's property on purpose?
phv00194067.v1.p1	CDD004	Do you have a probation officer or have you ever been on probation?
phv00194068.v1.p1	CDD005	Did you often bully others (hitting, threatening or scaring someone who was younger or smaller), threaten or frighten someone on purpose, or often start physical fights with others?
phv00194069.v1.p1	CDD006	Have you ever been physically cruel to an animal or person (on purpose)?
phv00194070.v1.p1	CDD007	Did you ever: try to hurt someone with a weapon (a bat, brick, broken bottle, knife, or gun)?
phv00194071.v1.p1	CDD008	Did you ever: threaten someone?
phv00194072.v1.p1	CDD009	Conduct Disorder: Did you ever: hold someone up?
phv00194073.v1.p1	CDD010	Conduct Disorder: Did you ever: attack someone to steal from them?
phv00194074.v1.p1	CDD011	Did you ever: trick or threaten someone into having sex with you, or did anyone ever accuse you of making them do something sexual?
Depression (DEP)		
phv00194091.v1.p1	DEP001	Has there ever been a time when you felt sad or depressed most of the time?
phv00194092.v1.p1	DEP002	Has there ever been a time when you cried a lot, or felt like crying?
phv00194094.v1.p1	DEP004	Has there ever been a time when you felt grouchy, irritable or in a bad mood most of the time; even little things would make you mad?
phv00194096.v1.p1	DEP006	Has there ever been a time when nothing was fun for you and you just weren't interested in anything?
Eating disorder (EAT)		
phv00194133.v1.p1	EAT001	Was there ever a time when you felt really fat or heavy, but other people said that you were too thin?
phv00194139.v1.p1	EAT007	Has there been a time when your eating was out of control - you'd eat a large amount of food in a short period of time and could not stop yourself?
Generalized anxiety (GAD)		
phv00194149.v1.p1	GAD001	Have you ever been a worrier?
phv00194150.v1.p1	GAD002	Did you worry a lot more than most children/people your age?
Mania/Hypomania (MAN)		
phv00194185.v1.p1	MAN001	Have there been times when you were much more active, excited or energetic than usual, had problems sitting still, or needed to move around a lot?
phv00194186.v1.p1	MAN002	Has there ever been a time when you felt so full of energy that you couldn't stop doing things and didn't get tired?
phv00194187.v1.p1	MAN003	Has there ever been a time when you felt like you hardly needed sleep?
phv00194188.v1.p1	MAN004	Have there been times when you kept talking a lot, couldn't stop talking, talked faster than usual, had thoughts faster than usual, or had so many ideas in your head that you could hardly keep track of them?
phv00194189.v1.p1	MAN005	Have you ever had a time when you felt much more happy or excited than you usually do when there was nothing special going on?
phv00194190.v1.p1	MAN006	Have you ever had a time when you felt like you could do almost anything?
phv00194191.v1.p1	MAN007	Has there ever been a time when you felt unusually grouchy, cranky, or irritable; when the smallest things would make you really mad?
Obsessive compulsive disorder (OCD)		
phv00194390.v1.p1	OCD001	Have you ever been bothered by thoughts that don't make sense to you, that come over and over again and won't go away, such as concern with harming others/self?
phv00194391.v1.p1	OCD002	Have you ever been bothered by thoughts that don't make sense to you, that come over and over again and won't go away, such as pictures of violent things?
phv00194392.v1.p1	OCD003	Have you ever been bothered by thoughts that don't make sense to you, that come over and over again and won't go away, such as thoughts about contamination/germs/illness?

phv00194393.v1.p1	OCD004	Have you ever been bothered by thoughts that don't make sense to you, that come over and over again and won't go away, such as fear that you would do something/say something bad without intending to?
phv00194394.v1.p1	OCD005	Have you ever been bothered by thoughts that don't make sense to you, that come over and over again and won't go away, such as feelings that bad things that happened were your fault?
phv00194395.v1.p1	OCD006	Have you ever been bothered by thoughts that don't make sense to you, that come over and over again and won't go away, such as forbidden/bad thoughts?
phv00194396.v1.p1	OCD007	Have you ever been bothered by thoughts that don't make sense to you, that come over and over again and won't go away, such as need for symmetry/exactness?
phv00194397.v1.p1	OCD008	Have you ever been bothered by thoughts that don't make sense to you, that come over and over again and won't go away, such as religious thoughts?
phv00194400.v1.p1	OCD011	Have you ever had to do something over and over again - that would have made you feel really nervous if you couldn't do it, like: cleaning or washing (for example, your hands, house)?
phv00194401.v1.p1	OCD012	Have you ever had to do something over and over again - that would have made you feel really nervous if you couldn't do it, like: counting?
phv00194402.v1.p1	OCD013	Have you ever had to do something over and over again - that would have made you feel really nervous if you couldn't do it, like: checking (for example, doors, locks, ovens)?
phv00194403.v1.p1	OCD014	Have you ever had to do something over and over again - that would have made you feel really nervous if you couldn't do it, like: getting dressed over and over again?
phv00194404.v1.p1	OCD015	Have you ever had to do something over and over again - that would have made you feel really nervous if you couldn't do it, like: going in and out a door over and over again?
phv00194405.v1.p1	OCD016	Have you ever had to do something over and over again - that would have made you feel really nervous if you couldn't do it, like: ordering or arranging things?
phv00194406.v1.p1	OCD017	Have you ever had to do something over and over again - that would have made you feel really nervous if you couldn't do it, like: doing things over and over again at bedtime, like arranging the pillows, sheets, or other things?
phv00194407.v1.p1	OCD018	Have you ever saved up so many things that people complained or they got in the way
phv00194408.v1.p1	OCD019	Do you feel the need to do things just right (like they have to be perfect)?
Oppositional defiant disorder (ODD)		
phv00194431.v1.p1	ODD001	Was there a time when you often did things that got you into trouble with adults such as losing your temper, arguing with or talking back to adults, or being grouchy or irritable with them?
phv00194432.v1.p1	ODD002	Was there a time when you often got into trouble with adults for refusing to do what they told you to do or for breaking rules at home/school?
phv00194434.v1.p1	ODD003	Did you often annoy other people on purpose or blame other people for your mistakes (excluding siblings)?
phv00194436.v1.p1	ODD005	Did you ever get into trouble for getting even with other people by doing things to hurt them, telling lies about them, or messing up their things?
phv00194437.v1.p1	ODD006	Were you often irritable or grouchy, or did you often get angry because you thought that things were unfair?
Panic disorder (PAN)		
phv00194448.v1.p1	PAN001	Have you ever had an attack like this?
phv00194449.v1.p1	PAN003	Has there ever been a time when all of a sudden you felt very, very scared or uncomfortable - and your chest hurt, you couldn't catch your breath, your heart beat very fast, you felt very shaky, and sweaty/tingly/numb in your hands or feet?
phv00194450.v1.p1	PAN004	Has there ever been a time when all of a sudden, you felt that you were losing control, something terrible was going to happen, that you were going crazy, or going to die?
Specific phobia (PHB)		
phv00194468.v1.p1	PHB001	have you ever been very nervous or afraid of animals or bugs, like dogs, snakes, or spiders?
phv00194469.v1.p1	PHB002	have you ever been very nervous or afraid of being in really high places, like a roof or tall building?
phv00194470.v1.p1	PHB003	have you ever been very nervous or afraid of water or situations involving water, such as a swimming pool, lake, or ocean?
phv00194471.v1.p1	PHB004	have you ever been very nervous or afraid of storms, thunder, or lightning?
phv00194472.v1.p1	PHB005	have you ever been very nervous or afraid of doctors, needles, or blood?
phv00194473.v1.p1	PHB006	have you ever been very nervous or afraid of closed spaces, like elevators or closets?
phv00194474.v1.p1	PHB007	have you ever been very nervous or afraid of flying or airplanes?
phv00194475.v1.p1	PHB008	have you ever been very nervous or afraid of any other things or situations?
Psychosis (PSY)		
phv00194490.v1.p1	PSY001	Have you ever heard voices when no one was there?
phv00194507.v1.p1	PSY020	Has there ever been anything unusual about the way things smelled or felt or looked?
phv00194518.v1.p1	PSY029	Have you ever seen visions or seen things which other people could not see?
phv00194531.v1.p1	PSY050	Have you ever smelled strange odors other people could not smell?
phv00194539.v1.p1	PSY060	Have you ever had strange feelings in your body like things were crawling on you or someone touching you and nothing or no one was there?
phv00194546.v1.p1	PSY071	Have you ever believed in things and later found out they weren't true, like people being out to get you, or talking about you behind your back, or controlling what you do or think?
Post-traumatic stress (PTD)		
phv00194609.v1.p1	PTD001	Have you ever been in a flood or a tornado or an earthquake or a hurricane or some other natural disaster where you thought you were going to die or be seriously hurt?
phv00194610.v1.p1	PTD002	Have you ever been in a situation where you thought you or someone close to you was going to be killed or be hurt very badly (e.g. family violence)?
phv00194611.v1.p1	PTD003	Have you ever been attacked by somebody or badly beaten?
phv00194612.v1.p1	PTD004	Have you ever been very upset by someone forcing you to do something sexual?
phv00194614.v1.p1	PTD006	Have you ever been threatened with a weapon?
phv00194615.v1.p1	PTD007	Have you ever been in a bad accident?
phv00194616.v1.p1	PTD008	Other than television or at the movies, have you ever seen or heard somebody get killed or get hurt very badly or die?
phv00194617.v1.p1	PTD009	Have you ever been very upset by seeing a dead body or by seeing pictures of the dead body of somebody you knew well?
General probes (SCR)		
phv00194639.v1.p1	SCR001	Have you ever talked to a counselor, psychologist, social worker, psychiatrist or some other professional about your feelings or problems with your mood or behaviors?
phv00194644.v1.p1	SCR006	Are you currently taking medication because of your emotions and/or behaviors?
phv00194645.v1.p1	SCR007	Have you ever had to go to a hospital and stay overnight because of problems with your mood, feelings, or how you were acting?
Separation anxiety (SEP)		
phv00194654.v1.p1	SEP500	Since you were 5 years old, has there ever been a time when you had a lot of worries about your (attachment figures) and were very upset or got sick (for example, felt sick to your stomach, headaches, thrown-up) when you were away from him/her?
phv00194656.v1.p1	SEP508	Has there ever been a time when you wanted to stay home from school or not go to other places (for example, sleep-overs) without your (attachment figures)?

phv00194657.v1.p1	SEP509	When you knew that you were going to be away from home or (attachment figure(s)), did you get very upset and worry (e.g., when you learned (attachment figure(s)) were going on an upcoming trip or night out)?
phv00194658.v1.p1	SEP510	Did you ever worry/have bad dreams about something terrible happening to you or your (attachment figures) so that you would not see them again?
phv00194659.v1.p1	SEP511	Were you scared to be alone in your room (or any place in your house) or did you need your (attachment figure(s)) to stay with you while you fell asleep?
Structural interview for prodromal symptoms (SIP)		
phv00194672.v1.p1	SIP001	TROUBLE WITH FOCUS AND ATTENTION Severity Scale
phv00194674.v1.p1	SIP003	I think that I have felt that there are odd or unusual things going on that I can't explain.
phv00194675.v1.p1	SIP004	I think that I might be able to predict the future.
phv00194676.v1.p1	SIP005	I may have felt that there could possibly be something interrupting or controlling my thoughts, feelings, or actions.
phv00194677.v1.p1	SIP006	I have had the experience of doing something differently because of my superstitions.
phv00194678.v1.p1	SIP007	I think I may get confused at times whether something I experience or perceive may be real or may be just part of my imagination or dreams.
phv00194679.v1.p1	SIP008	I have thought that it might be possible that other people can read my mind, or that I can read others' minds
phv00194680.v1.p1	SIP009	I wonder if people may be planning to hurt me or even may be about to hurt me.
phv00194681.v1.p1	SIP010	I believe that I have special natural or supernatural gifts beyond my talents and natural strengths.
phv00194682.v1.p1	SIP011	I think I might feel like my mind is "playing tricks" on me.
phv00194683.v1.p1	SIP012	I have had the experience of hearing faint or clear sounds of people or a person mumbling or talking when there is no one near me.
phv00194684.v1.p1	SIP013	I think that I may hear my own thoughts being said out loud.
phv00194685.v1.p1	SIP014	I have been concerned that I might be "going crazy."
phv00194698.v1.p1	SIP027	Do people ever tell you that they can't understand you?
phv00194699.v1.p1	SIP028	Do people ever seem to have difficulty understanding you?
phv00194700.v1.p1	SIP030	Changes in speech, disorganized communication, tangential speech Severity Scale
phv00194702.v1.p1	SIP032	Do you ever feel a loss of sense of self or feel disconnected from yourself or your life?
phv00194703.v1.p1	SIP033	Has anyone pointed out to you that you are less emotional or connected to people than you used to be?
phv00194704.v1.p1	SIP035	Changes in perception of self, others, or the world in general: Severity Scale
phv00194706.v1.p1	SIP037	EXPRESSION OF EMOTION: Severity Scale
phv00194707.v1.p1	SIP038	Within the past 6 months, are you having a harder time getting your work or schoolwork done?
phv00194708.v1.p1	SIP039	Within the past 6 months, are you having a harder time getting normal activities done?
phv00194709.v1.p1	SIP041	Occupational Functioning Severity Scale
phv00194711.v1.p1	SIP043	Avolition Severity Scale
Social Anxiety (SOC)		
phv00194713.v1.p1	SOC001	was there ever a time in your life when you felt afraid or uncomfortable or really, really shy with people, like meeting new people, going to parties, or eating or drinking, writing or doing homework in front of others?
phv00194714.v1.p1	SOC002	was there ever a time in your life when you felt afraid or uncomfortable talking on the telephone or with people your own age who you don't know very well?
phv00194715.v1.p1	SOC003	was there ever a time in your life when you felt afraid or uncomfortable when you had to do something in front of a group of people, like speaking in class?
phv00194716.v1.p1	SOC004	was there ever a time in your life when you felt afraid or uncomfortable acting, performing, giving a talk/speech, playing a sport or doing a musical performance, or taking an important test or exam (even though you studied enough)?
phv00194717.v1.p1	SOC005	was there ever a time in your life when you felt afraid or uncomfortable because you were the center of attention and were concerned something embarrassing might happen and you felt very afraid or felt uncomfortable?
Depression (DEP)		
phv00194734.v1.p1	SUI001	Have you ever thought a lot about death or dying?
phv00194735.v1.p1	SUI002	Have you ever thought about killing yourself?

Supplementary Figure 3: List of the 129 clinical variables that entered the independent component analysis