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"It takes something more than intelligence to act intelligently."

– Fyodor Dostoyevsky, *Crime and Punishment*

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Abstract (149 of 150 words)

Little is known about the genetic architecture of traits affecting educational attainment (EA) other than cognitive ability. We used Genomic Structural Equation Modelling and prior genome-wide association studies (GWASs) of EA (N=1,131,881) and cognitive test performance (N=257,841) to estimate SNP associations with EA variation that is independent of cognitive ability. We identified 157 genome-wide significant loci and a polygenic architecture accounting for 57% of genetic variance in EA. Non-cognitive genetics were enriched in the same brain tissues and cell types as cognitive performance but showed different associations with gray-matter brain volumes. Non-cognitive genetics were further distinguished by associations with personality traits, less risky behavior, and increased risk for certain psychiatric disorders. For socioeconomic success and longevity, non-cognitive and cognitive-performance genetics demonstrated similar-magnitude associations. By conducting a GWAS of a phenotype that was not directly measured, we offer a first view of genetic architecture of non-cognitive skills influencing educational success.

Main Text (3,970 of 4000 Words)

Success in school–and life–depends on skills beyond cognitive ability[1–4]. Randomized trials of early-life education interventions find substantial benefits to educational outcomes, employment, and adult health, even though the interventions have no lasting effects on children's cognitive functions[5,6]. These results have captured attention of educators and policy makers, motivating interest in so-called "non-cognitive skills"[7–9]. Non-cognitive skills suspected to be important for educational success include motivation, curiosity, persistence, and self-control[1,10–13]. However, questions have been raised about the substance of these skills and the magnitudes of their impacts on life outcomes[14].

Twin studies find evidence that non-cognitive skills are heritable[3,15–18]. Genetic analysis could help clarify the contribution of these skills to educational attainment and elucidate their connections with other traits. However, lack of consistent and reliable measurements of non-cognitive skills in existing genetic datasets pose challenges[19].

To overcome these challenges, we designed a GWAS of a latent trait, *i.e.* a trait not measured in any of the genotyped subjects[20]. We borrowed the strategy used in the original analysis of non-cognitive skills within the discipline of economics[21,22]: We defined genetic influences on non-cognitive skills as the genetic variation in educational attainment that was not explained by cognitive skills. We then performed GWAS on this residual "non-cognitive" genetic variation in educational attainment. This approach is a necessarily imperfect representation of the true relationship between cognitive and non-cognitive skills; in human development, cognitive abilities and other skills relevant for educational attainment likely interact dynamically, each influencing the other[23]. Our analysis excludes genetic influences on education-relevant skills that also influence measured cognitive abilities. The value of this imperfect approach is to make a quantity otherwise difficult to study tractable for analysis.

We conducted analysis using Genomic Structural Equation Modeling (Genomic-SEM)[24] applied to published GWAS summary statistics for educational attainment and cognitive performance[25]. Our analysis used these summary statistics to "subtract" genetic influence on cognitive performance from the association of each single-nucleotide polymorphism (SNP) with educational attainment. The remaining associations of each SNP with educational attainment formed a new GWAS of a non-cognitive skills phenotype that was never directly measured. We call this novel statistical approach GWAS-by-subtraction.

We used results from the GWAS-by-subtraction of non-cognitive skills to conduct two sets of analyses. First, we conducted hypothesis-driven analysis using the phenotypic annotation approach[26]. We used genetic correlation and polygenic score analysis to test the hypothesis that non-cognitive skills influence educational and economic attainments and longevity and to investigate traits and behaviors that constitute non-cognitive skills. Second, we conducted hypothesis-free bioinformatic annotation analysis to explore the tissues, cell-types, and brain structures that might distinguish the biology of non-cognitive skills from the biology mediating cognitive influences on educational attainment.

Results

GWAS-by-Subtraction Identifies Genetic Associations with Non-Cognitive Variance in Educational Attainment

The term "non-cognitive skills" was originally coined by economists studying individuals who were equivalent in cognitive ability, but who differed in educational attainment.[22] Our analysis of non-cognitive skills was designed to mirror this original approach: We focused on genetic variation in educational outcomes not explained by genetic variation in cognitive ability. Specifically, we applied Genomic Structural Equation Modeling (Genomic-SEM)[24] to summary statistics from GWASs of educational attainment[25] and cognitive performance[25]. Both phenotypes were regressed on a latent factor representing

genetic variance in cognitive performance (hereafter "*Cog*"). Educational attainment was further regressed on a second latent factor representing the residual genetic variance in educational attainment left over after regressing-out variance related to cognitive performance (hereafter "*NonCog*"). By construction, *NonCog* genetic variance was independent of *Cog* genetic variance (r_g=0). In other words, the *NonCog* factor represents genetic variation in educational attainment that is not accounted for by the *Cog* factor. These two latent factors were then regressed on individual SNPs, yielding a GWAS of the latent constructs *NonCog* and *Cog*. A graphical representation of the model is presented **Figure 1**. Parameters are derived in terms of the observed moments of the joint distribution of educational attainment, cognitive performance and a SNP in **Supplementary Note**.

The *NonCog* latent factor accounted for 57% of total genetic variance in educational attainment. Using the LD Score regression method[27], we estimated SNP-heritability for *NonCog* to be h^2_{NonCog}=.0637 (*SE*=.0021). After conventional GWAS significance threshold correction, GWAS of *NonCog* identified 157 independent genome-wide significant lead SNPs (independent SNPs defined as outside a 250Kb window, or within a 250Kb window and $r^2 < 0.1$). The results from the *NonCog* GWAS are graphed as a Manhattan plot in **Figure 2**. *NonCog* and *Cog* GWAS details are reported in **Supplementary Tables 1, 2, 3 and 4, and Supplementary Figure 1 and Supplementary Note**. In addition, we report a series of sensitivity analyses in the Supplementary Note, Tables, and Figures: analysis of potential biases due to cohort differences, **Supplementary Table 5** and **Supplementary Figures 2-4**; analysis of impact of allowing for positive genetic correlations between *NonCog* and *Cog*, **Supplementary Tables 6** and **7**, **Supplementary Figures 5** and **6**; analysis of impact of allowing for a moderate causal effect of educational attainment on cognitive performance[28], **Supplementary Table 8**, and **Supplementary Figures 7-9**.

Phenotypic Annotation Analysis Elucidates Behavioral, Psychological and Psychiatric Correlates of Non-Cognitive Skills Genetics

Our phenotypic annotation analyses proceeded in two steps. First, we conducted polygenic score (PGS) and genetic correlation (rG) analysis to test if our GWAS-by-subtraction succeeded in identifying genetic influences that were important to educational attainment and also distinct from genetic influences on cognitive ability. Second, we conducted PGS and rG analyses to explore how *NonCog* related to a network of phenotypes that psychology and economics research suggests might form the basis of non-cognitive influences on educational attainment.

***NonCog* genetics are distinct from cognitive performance and are important to education, socioeconomic attainment, and longevity.** To establish if the Genomic-SEM GWAS-by-subtraction succeeded in isolating genetic variance in education that was independent of cognitive function, we compared genetic associations of *NonCog* and *Cog* with educational attainment and cognitive test performance. Results for analysis of education and cognitive test phenotypes are graphed in **Figure 3**.

We conducted PGS analysis of educational attainment in the Netherlands Twin Register[29] (NTR), National Longitudinal Study of Adolescent to Adult Health[30] (AddHealth), Dunedin Longitudinal Study[31], E-Risk[32], and Wisconsin Longitudinal Study[33] (WLS) cohorts (meta-analysis N=24,056; cohorts descriptions in **Supplementary Tables 9** and **10** and **Supplementary Note**). PGS effect-sizes were the same for *NonCog* and *Cog* (*NonCog* β=.24 (*SE*=.03), *Cog* β=.24 (*SE*=.02), p_{diff}=.702; all PGS results are reported in **Supplementary Tables 11** and **12**). We conducted complementary genetic correlation analysis using Genomic SEM and GWAS summary statistics from a hold-out-sample GWAS of educational attainment (**Supplementary Note**). This analysis allowed us to compute an out-of-sample genetic correlation of NonCog with educational attainment. *NonCog* showed a stronger

genetic correlation with educational attainment as compared to *Cog* (*NonCog* r_g =.71 (*SE*=.02), *Cog* r_g=.57 (*SE*=.02), p_{diff} < .0001; all genetic correlation results are reported in **Supplementary Tables 13** and **14**).

We conducted PGS analysis of cognitive test performance in the NTR, Texas Twin Project[34], Dunedin, E-Risk, and WLS cohorts (combined *N*=11,351). The goal of our GWAS-by-subtraction analysis was to exclude, as much as possible, genetic variance in cognitive ability from genetic variance in skills relevant for education. Consistent with this goal, effect-sizes for *NonCog* PGS associations with full-scale IQ were smaller by half as compared to *Cog* PGS associations (*NonCog* β=.17 (*SE*=.02), *Cog* β=.29 (*SE*=.03); p_{diff}<.0001). But, the non-zero correlation between the NonCog PGS and full-scale IQ is a reminder that the cognitive performance GWAS used in our GWAS-by-subtraction analyses does not capture the entirety of genetic influences on all forms of cognitive tests measured at all points in the lifespan. Additional PGS analysis of IQ subscales are reported in **Supplementary Figure 10** and **Supplementary Tables 11** and **12**.

We conducted complementary genetic correlation analysis using results from a published GWAS of childhood IQ[35]. Parallel to PGS analysis, the *NonCog* genetic correlation with childhood IQ was smaller by more than half as compared to the *Cog* genetic correlation (*NonCog* r_g=0.31 (*SE*=.06), *Cog* r_g=0.75 (*SE*=.08), p_{diff_fdr}<.0001). Of the total genetic correlation between childhood IQ and educational attainment, 31% of the covariance was explained by *NonCog* and 69% by *Cog*.

We next examined downstream economic and health outcomes associated with greater educational attainment.[36,37] In PGS analysis in the AddHealth and Dunedin cohorts (*N*=6,358), *NonCog* and *Cog* PGSs showed similar associations with occupational attainment (*NonCog* β=.21 (*SE*=.01), *Cog* β=.21 (*SE*=.01), p_{diff}=.902). In genetic correlation analysis, *NonCog* showed a similar relationship to income[38] as *Cog* (*NonCog* r_g=.62, (*SE*=.04), *Cog*

r_g=.62 (*SE*=.04), p_{diff_fdr}=.947) and a stronger relationship with neighborhood deprivation[38], a measure related to where a person can afford to live (*NonCog* r_g=-.51 (*SE*=.05), *Cog* r_g=-.32 (*SE*=.04), p_{diff_fdr}=.001). In Genomic-SEM analysis, *NonCog* explained 53% of the genetic correlation between educational attainment and income and 65% of the genetic correlation between educational attainment and neighborhood deprivation (**Supplementary Table 15**).

We conducted genetic correlation analysis of longevity based on GWAS of parental lifespan[39]. Genetic correlations were stronger for *NonCog* as compared to *Cog* (*NonCog* r_g=.37 (*SE*=.03); *Cog* r_g=.27 (*SE*=.03); p_{diff_fdr}=.024). In Genomic-SEM analysis, *NonCog* explained 61% of the genetic correlation between educational attainment and longevity.

In sum, *NonCog* and *Cog* genetics showed similar relationships with educational attainment and its long-term outcomes, despite *NonCog* genetic having a much weaker relationship to measured cognitive test performance than *Cog* genetics. These findings broadly support the hypothesis that non-cognitive skills distinct from cognitive abilities are an important contributor to success across the life course.

We next conducted a series of genetic correlation analyses to explore the network of phenotypes to which *NonCog* was genetically correlated. To develop understanding of the substance of non-cognitive skills, we tested where in that network of phenotypes genetic correlations with *NonCog* diverged from genetic correlations with *Cog*. Our analysis was organized around four themes: decision making preferences, health-risk and fertility behaviors, personality traits, and psychiatric disorders. Results of genetic correlation analyses are graphed in **Figure 4** and in **Supplementary Figure 11**. Results are reported in **Supplementary Table 14**.

***NonCog* genetics were associated with decision-making preferences.** In economics, non-cognitive influences on achievement and health are often studied in relation to decision-making preferences[40–43]. *NonCog* was genetically correlated with higher tolerance

of risks [44] (r_g=.10 (*SE*=.03)) and willingness to forego immediate gratification in favor of a larger reward at a later time[45] (delay discounting r_g=-.52 (*SE*=.08)). In contrast, *Cog* was genetically correlated with generally more cautious decision-making characterized by lower levels of risk tolerance (r_g=-.35 (*SE*=.07), p_{diff_fdr}<.0001) and delay discounting (r_g=-.35 (*SE*=.07), p_{diff_fdr}=.082).

***NonCog* genetics were associated with less health-risk behavior and delayed fertility.** An alternative approach to studying specific non-cognitive skills is to infer individual differences in non-cognitive skills from patterns of health-risk behavior. *NonCog* was genetically correlated with less health-risk behavior as indicated by analysis of obesity[46], substance use[44,47–50], and sexual behaviors and early fertility[44,51,52] (r_g range .2-.5), with the exception that the r_g with alcohol use was not different from zero and r_g with cannabis use was positive. Genetic correlations for *Cog* were generally in the same direction but of smaller magnitude.

***NonCog* genetics were associated with a broad spectrum of personality characteristics linked with social and professional competency.** In psychology, non-cognitive influences on achievement are conceptualized as personality traits, *i.e.* patterns of stable individual differences in emotion and behavior. The model of personality that has received the most attention in genetics is a five-factor model referred to as the Big-5. Genetic correlation analysis of the Big-5 personality traits[53–55] revealed *NonCog* genetics were most strongly associated with Openness to Experience (being curious and eager to learn; r_g=.30 (*SE*=.04)) and were further associated with a pattern of personality characteristic of changes that occur as people mature in adulthood[56]. Specifically, *NonCog* showed a positive r_g with Conscientiousness (being industrious and orderly; r_g=.13 (*SE*=.03)), Extraversion (being enthusiastic and assertive; r_g=.14 (*SE*=.03)), and Agreeableness (being polite and compassionate; r_g=.14 (*SE*=.05)), and negative r_g with Neuroticism (being emotionally

volatile; r_g=-.15 (*SE*=.04)). Genetic correlations of *Cog* with Openness to Experience and Neuroticism were similar to those for *NonCog* ($p_{diff\_fdr\text{-}Openness}$=.040, $p_{diff\_fdr\text{-}Neuroticism}$=.470). In contrast, genetic correlations of *Cog* with Conscientiousness, Extraversion, and Agreeableness were in the opposite direction (r_g=-.25 to -.12, p_{diff_fdr}<.0005). PGS analysis of personality traits is reported in **Supplementary Table 12, Supplementary Figure 12** and **Supplementary Note**.

***NonCog* genetics were associated with higher risk for multiple psychiatric disorders.** In clinical psychology and psychiatry, research is focused on mental disorders. Mental disorders are generally associated with impairments in academic achievement and social role functioning.[57,58] However, positive genetic correlations with educational attainment and creativity have been reported for some disorders[59,60]. We therefore tested *NonCog* r_g with psychiatric disorders based on published case-control GWAS of mental disorders[61–67]. *NonCog* was associated with *higher* risk for multiple clinically-defined disorders including anorexia nervosa (r_g=.26 (*SE*=.04)), obsessive-compulsive disorder (r_g=.31 (*SE*=.06)), bipolar disorder (r_g=.27 (*SE*=.03)), and schizophrenia (r_g=.26 (*SE*=.02)). Genetic correlations between *Cog* and psychiatric disorders were either smaller in magnitude (anorexia nervosa r_g=.08 (*SE*=.03), p_{diff_fdr}<.001; obsessive-compulsive disorder r_g=.05 (*SE*=.05), p_{diff_fdr}=.002) or in the opposite direction (bipolar disorder r_g=-.07 (*SE*=.03), p_{diff_fdr}<.001; schizophrenia r_g=-.22 (*SE*=.02), p_{diff_fdr}<.001). Both *NonCog* and *Cog* showed negative genetic correlations with attention-deficit/hyperactivity disorder (*NonCog* r_g=-.37 (*SE*=.03), *Cog* r_g=-.37 (*SE*=.04), p_{diff_fdr}=.947).

In sum *NonCog* genetics were associated with phenotypes from economics and psychology thought to mediate non-cognitive influences on educational success. These associations contrasted with associations for *Cog* genetics, supporting distinct pathways of influence on achievement in school and later in life. Opposing patterns of association were

also observed for psychiatric disorders, suggesting that the unexpected positive genetic correlation between educational attainment and mental health problems uncovered in previous studies[60,68,69] arises from non-cognitive genetic influences on educational attainment.

Biological Annotation Analyses Reveal Shared and Specific Neurobiological Correlates

The goal of biological annotation of GWAS discoveries is to elucidate molecular mechanisms mediating genetic influences on the phenotype of interest. Our biological annotation analysis proceeded in two steps. First, we conducted enrichment analysis to test if some tissues and cell-types were more likely to mediate *NonCog* and *Cog* heritabilities than others. Second, we conducted genetic correlation analysis to explore how *NonCog* and *Cog* genetics related to different brain structures.

***NonCog* and *Cog* genetics were enriched in similar tissues and cells.** We tested whether common variants in genes specifically expressed in 53 GTEx tissues[70] or in 152 tissues captured in a previous aggregation of RNA-seq studies[71,72] were enriched in their effects on *Cog* or *NonCog*. Genes predominantly expressed in the brain rather than peripheral tissues were enriched in both *NonCog* and *Cog* (**Supplementary Table 16**).

To examine expression patterns at a more granular level of analysis, we used MAGMA[73] and stratified LD score regression[74] to test enrichment of common variants in 265 nervous system cell-type-specific gene-sets[75] (**Supplementary Table 17**). In MAGMA analysis, common variants in 95 of 265 gene-sets were enriched for association with *NonCog*. The enriched cell-types were predominantly neurons (97%), with enrichment most pronounced for telencephalon-projecting neurons, di- and mesencephalon neurons, and to a lesser extent, telencephalon interneurons (**Supplementary Figure 13** and **Table 18**). Enrichment for *Cog* was similar to *NonCog* (correlation between *Z*-statistics *Pearson's*

297 r=.85) and there were no differences in cell-type-specific enrichment, suggesting that the
298 same types of brain cells mediate genetic influences on *NonCog* and *Cog* (**Supplementary**
299 **Figure 14**). Stratified LDSC results were similar to results from MAGMA (**Supplementary**
300 **Note, Supplementary Figure 15, and Supplementary Table 19**).

301 The absence of differences in cell-type specific enrichment is surprising given that
302 *NonCog* and *Cog* are genetically uncorrelated. We therefore used the TWAS/Fusion tool[76] to
303 conduct gene-level analysis. This analysis revealed a mixture of concordant and discordant
304 gene effects on *NonCog* and *Cog* consistent with the genetic correlation of zero
305 (**Supplementary Note, Supplementary Figure 16,** and **Supplementary Table 20**).

306 ***NonCog* and *Cog* genetics show diverging associations with total and regional**
307 **brain volumes.** EA has previously been found to be genetically correlated with greater total
308 brain volume[77,78]. We therefore used a GWAS of regional brain volume to compare the r_g of
309 *NonCog* and *Cog* with total brain volume and with 100 regional brain volumes (99 gray
310 matter volumes and white matter volume) controlling for total brain volume (**Supplementary**
311 **Table 21**)[79]. For total brain volume, genetic correlation was stronger for *Cog* as compared to
312 *NonCog* (*Cog* r_g=.22 (*SE*=.04), *NonCog* r_g=.07 (*SE*=.03), p_{diff}=.005). Total gray matter
313 volume, controlling for total brain volume, was not associated with either *NonCog* or *Cog*
314 (*NonCog*: r_g=.07 (*SE*=.04); *Cog*: r_g=.06 (*SE*=.04)). For total white matter volume, conditional
315 on total brain volume, genetic correlation was weakly negative for *NonCog* as compared to
316 *Cog* (*NonCog* r_g= -.12 (*SE*=.04), *Cog* (r_g=-.01 (*SE*=.04), p_{diff}=.04).

317 *NonCog* was not associated with any of the regional gray-matter volumes after FDR
318 correction. In contrast, *Cog* was significantly associated with regional gray-matter volumes
319 for the bilateral fusiform, insula and posterior cingulate (r_g range .11-.17), as well as left
320 superior temporal (r_g=.11 (*SE*=.04)), left pericalcarine (r_g=-.16 (*SE*=.05)) and right superior
321 parietal volumes (r_g=-.22 (*SE*=.06)) (**Figure 5**).

Finally, we tested genetic correlation of *NonCog* and *Cog* with white matter tract integrity as measured using diffusion tensor imaging (DTI)[80]. Analyses included 5 DTI parameters in each of 22 white matter tracts (**Supplementary Table 22**). *NonCog* was positively associated with the mode of anisotropy parameter (which denotes a more tubular, as opposed to planar, water diffusion) in the corticospinal tract, retrolenticular limb of the internal capsule, and splenium of the corpus callosum (**Figure 5**). But all correlations were small ($.10<r_g<.14$) and we detected no genetic correlations that differed between *NonCog* and *Cog* (**Supplementary Note**).

Discussion

GWAS of non-cognitive influences on educational attainment (EA) identified 157 independent loci and polygenic architecture accounting for more than half the genetic variance in EA. In genetic correlation and PGS analysis, these non-cognitive (*NonCog*) genetics showed similar magnitude of associations with EA, economic attainment and longevity to genetics associated with cognitive influences on EA (*Cog*). As expected, *NonCog* genetics had much weaker associations with cognition phenotypes as compared to *Cog* genetics. These results contribute new GWAS evidence in support of the hypothesis that heritable non-cognitive skills influence educational attainment and downstream life-course economic and health outcomes.

Phenotypic and biological annotation analyses shed light on the substance of heritable non-cognitive skills influencing education. Economists hypothesize that preferences that guide decision-making in the face of risk and delayed rewards represent non-cognitive influences on educational attainment. Consistent with this hypothesis, *NonCog* genetics were associated with higher risk tolerance and lower time discounting. These decision-making preferences are associated with financial wealth, whereas opposite preferences are

hypothesized to contribute to a feedback loop perpetuating poverty[81]. Consistent with results from analysis of decision-making preferences, *NonCog* genetics were also associated with healthier behavior and later fertility.

Psychologists hypothesize that the Big Five personality characteristics of conscientiousness and openness are the two "pillars of educational success"[2,3,82]. Our results provide some support for this hypothesis, with the strongest genetic correlation evident for openness. But they also show that non-cognitive skills encompass the full range of personality traits, including agreeableness, extraversion, and the absence of neuroticism. This pattern mirrors the pattern of personality change that occurs as young people mature into adulthood[56]. Thus, non-cognitive skills share genetic etiology with what might be termed as "mature personality". The absolute magnitudes of genetic correlations between *NonCog* and individual personality traits are modest. This result suggests that the personality traits described by psychologists capture some, but not all genetic influence on non-cognitive skills.

Although the general pattern of findings in our phenotypic annotation analysis indicated non-cognitive skills were genetically related to socially desirable characteristics and behaviors, there was an important exception. Genetic correlation analysis of psychiatric disorder GWAS revealed positive associations of *NonCog* genetics with schizophrenia, bipolar disorder, anorexia nervosa, and obsessive-compulsive disorder. Previously, these psychiatric disorders have been shown to have a positive r_g with EA, a result that has been characterized as paradoxical given the impairments in educational and occupational functioning typical of serious mental illness. Our results clarify that these associations are driven by non-cognitive factors associated with success in education. These results align with the theory that clinically-defined psychiatric disorders represent extreme manifestations of

dimensional psychological traits, which might be associated with adaptive functioning within the normal range[83–85].

Finally, biological annotation analyses suggested that genetic variants contributing to educational attainment not mediated through cognitive abilities are enriched in genes expressed in the brain, specifically in neurons. Even though *NonCog* and *Cog* were genetically uncorrelated, variants in the same neuron-specific gene-sets were enriched for both traits. Although we found some evidence of differences between *NonCog* and *Cog* in associations with gray matter volumes, moderate sample sizes in neuroimaging GWAS mean these results must be treated as preliminary, requiring replication with data from larger-scale GWAS of white-matter and gray-matter phenotypes. Limited differentiation of *NonCog* and *Cog* in biological annotation analyses focused at the levels of tissue and cell type highlights need for finer-grained molecular data resources to inform these analyses and the complementary value of phenotypic annotation analyses focused at the level of psychology and behavior.

We acknowledge limitations. Cognitive and non-cognitive skills develop in interaction with one another. For example, the dynamic mutualism hypothesis[86] proposes that non-cognitive characteristics shape investments of time and effort, leading to differences in the pace of cognitive development[87,88]. But in Genomic-SEM analysis, the *NonCog* factor is, by construction, uncorrelated with genetic influences on adult cognition as measured in the *Cog* GWAS. Our statistical separation of *NonCog* from cognition is thus a simplified representation of development. Longitudinal studies with repeated measures of cognitive and candidate non-cognitive skills are needed to study their reciprocal relationships across development[89,90]. Our statistical separation of *NonCog* from cognition is also incomplete. The ability to control statistically for any variable, genetic or otherwise, depends on how well and comprehensively that variable is measured[91]. The tests of cognitive performance included in

396 the *Cog* GWAS likely do not capture all genetic influences on all forms of cognitive ability
397 across the lifespan[92,93]. Despite these limitations, our simplified and incomplete statistical
398 separation of *NonCog* from *Cog* allowed us to test if heritable traits other than cognitive
399 ability influenced educational attainment and to explore what those traits might be.
400 Because our analysis was based on GWAS of educational attainment, non-cognitive
401 genetics identified here may differ from non-cognitive genetics affecting other
402 socioeconomic attainments like income, or traits and behaviors that mediate responses to
403 early childhood interventions, to the extent that those genetics do not affect educational
404 attainment. Parallel analysis of alternative attainment phenotypes will clarify the specificity
405 of discovered non-cognitive genetics.
406 In the case of GWAS of educational attainment, the included samples were drawn
407 mainly from Western Europe and the U.S., and participants completed their education in the
408 late 20th and early 21st centuries. The phenotype of educational attainment reflects an
409 interaction between an individual and the social system in which they are educated.
410 Differences across social systems, including education policy, culture, and historical context,
411 may result in different heritable traits influencing on educational attainment[94]. Results
412 therefore may not generalize beyond the times and places GWAS samples were collected.
413 Generalization of the *NonCog* factor is also limited by restriction of included GWAS
414 to individuals of European ancestry. Lack of methods for integrating genome-scale genetic
415 data across populations with different ancestries[95,96] requires this restriction, but raises threats
416 to external validity. GWAS of other ancestries and development of methods for trans-
417 ancestry analysis can enable analysis of (*Non)Cog* in non-European populations.
418 Within the bounds of these limitations, results illustrate the application of Genomic-
419 SEM to conduct GWAS of a phenotype not directly measured in GWAS databases. This
420 application could have broad utility beyond the genetics of educational attainment. The

GWAS-by-subtraction method allowed us to study a previously hard-to-interpret residual value. Our analysis provides a first view of the genetic architecture of non-cognitive skills influencing educational success. These skills are central to theories of human capital formation within the social and behavioral sciences and are increasingly the targets of social policy interventions. Our results establish that non-cognitive skills are central to the heritability of educational attainment and illuminate connections between genetic influences on these skills and social and behavioral science phenotypes.

Methods

Meta-analysis of educational attainment GWAS

We reproduced the Social Science Genetic Association Consortium (SSGAC) 2018 GWAS of educational attainment[25] by meta-analyzing published summary statistics for *N*=766,345 (www.thessgac.org/data) with summary statistics obtained from 23andMe, Inc. (N=365,538). We included SNPs with sample-size > 500,000 and MAF > 0.005 in the 1000 Genomes reference set (10,101,243 SNPs). We did not apply genomic control, as standard errors of publicly available and 23andMe summary statistics were already corrected[25]. Meta-analysis was performed using METAL[97].

GWAS-by-subtraction

The objective of our GWAS-by-subtraction analysis was to estimate, for each SNP, the association with educational attainment that was independent of that SNP's association with cognition (hereafter, the *NonCog* SNP effect). We used Genomic-SEM[24] in R 3.4.3 to analyze GWAS summary statistics for the educational attainment and cognitive performance phenotypes in the SSGAC's 2018 GWAS (Lee et al. 2018[25]). The model regressed the educational-attainment and cognitive-performance summary statistics on two latent variables,

Cog and *NonCog* (**Figure 1**). *Cog* and *NonCog* were then regressed on each SNP in the genome. This analysis allowed for two paths of association with educational attainment for each SNP. One path was fully mediated by *Cog*. The other path was independent of *Cog* and measured the non-cognitive SNP effect, *NonCog*. To identify independent hits with p <5e-8 (the customary p-value threshold to approximate an alpha value of 0.05 in GWAS), we pruned the results using a radius of 250 kb and an LD threshold of r^2 <0.1 (**Supplementary Tables 1 to 3**). We explore alternative lead SNPs and loci definition in **Supplementary Table 4**. The parameters estimated in a GWAS-by-subtraction, and their derivation in terms of the genetic covariance are described in **Supplementary Note** (model specification) and practical analysis steps are described in **Supplementary Note** (SNP filtering). The effective sample size of the NonCog and Cog GWAS was estimated to 510 795 and 257 700 respectively, see **Supplementary Note.** We investigate biases from unaccounted-for heterogeneity in overlap across SNPs in the EA and CP GWAS and describe possible strategy to deal with it (**Supplementary Note**). We investigate potential biases due to cohort differences in SNP heritability in **Supplementary Note**. We evaluate the consequences of modifying r_g(*NonCog*, *Cog*)=0 by evaluating r_g = 0.1, 0.2 or 0.3 and we investigate the consequences of a violation of the assumed causation between CP and EA in **Supplementary Note**.

Genetic correlations

We use Genomic-SEM to compute genetic correlations of *Cog* and *NonCog* with other education-linked traits for which well-powered GWAS data were available (SNP-h^2 z-statistics >2; **Supplementary Table 13**) and to test if genetic correlations with these traits differed between *Cog* and *NonCog*. Specifically, models tested the null hypothesis that trait genetic correlations with *Cog* and *NonCog* could be constrained to be equal using a chi-

squared test with FDR adjustment to correct for multiple testing. The FDR adjustment was conducted across all genetic correlation analyses reported in the article excluding the analyses of brain volumes described below. Finally, we used Genomic-SEM analysis of genetic correlations to estimate the percentage of the genetic covariance between educational attainment and the target traits that was explained by *Cog* and *NonCog* using the model illustrated in **Supplementary Figure 17**.

Polygenic score analysis

Polygenic score analyses were conducted in data drawn from six population-based cohorts from the Netherlands, the U.K., the U.S., and New Zealand: (1) the Netherlands Twin Register (NTR)[29,98], (2) E-Risk[32], (3) the Texas Twin Project[34], (4) the National Longitudinal Study of Adolescent to Adult Health (AddHealth)[30,99], dbGaP accession phs001367.v1.p1; (5) Wisconsin Longitudinal Study on Aging (WLS)[33], dbGaP accession phs001157.v1.p1; and (6) the Dunedin Multidisciplinary Health and Development Study[31]. **Supplementary Tables 9 and 10** describe cohort-specific metrics, **we include** a short description of the cohorts' populations and recruitment in **Supplementary Note**. Only participants with European ancestry were included in the analysis, due to the low portability of PGS between different ancestry populations. Polygenic scores were computed with Plink based on weights derived using the LD-pred[100] software with an infinitesimal prior and the 1000 Genomes phase 3 sample as a reference for the LD structure. LD-pred weights were computed in a shared pipeline to ensure comparability between cohorts. Each outcome (*e.g.*, IQ score) was regressed on the *Cog* and *NonCog* polygenic scores and a set of control variables (sex, 10 principal components derived from the genetic data and, for cohorts in which these quantities varied, genotyping chip and age), using Stata 14 for WLS, Stata 15 for E-Risk and the Dunedin Study, and R (versions 3.4.3 and newer) for NTR, AddHealth, and the Texas Twin

Project. In cohorts containing related individuals, non-independence of observations from relatives were accounted for using ~~mixed linear models (MLM),~~ generalized estimation equations (GEE), or by clustering of standard errors at the family level. We used a random effects meta-analysis to aggregate the results across the cohorts. This analysis allows a cohort-specific random intercept. Individual cohort results are in **Supplementary Table 11** and meta-analytic estimates in **Supplementary Table 12**.

Biological annotation

Enrichment of tissue-specific gene expression. We used gene-sets defined in Finucane et al. 2018[101] to test for the enrichment of genes specifically expressed in one of 53 GTEx tissues[70], or 152 tissues captured by the Franke et al. aggregation of RNA-seq studies[71,72]. This analysis seeks to confirm the role of brain tissues in mediating *Cog* and *NonCog* influences on educational attainment. The exact analysis pipeline used is available online (https://github.com/bulik/ldsc/wiki/Cell-type-specific-analyses).

Enrichment of cell-type specific expression. We leveraged single cell RNA sequencing (scRNA-seq) data of cells sampled from the mouse nervous system[75] to identify cell-type specific RNA expression. Zeisel et al.[75] sequenced cells obtained from 19 regions in the contiguous anatomical regions in the peripheral sensory, enteric, and sympathetic nervous system. After initial QC, Zeisel et al. retained 492,949 cells, which were sampled down to 160,796 high quality cells. These cells were further grouped into clusters representing 265 broad cell-types. We analyzed the dataset published by Zeisel et al. containing mean transcript counts for all genes with count >1 for each of the 265 clusters (**Supplementary Table 17**). We restricted analysis to genes with expression levels above the 25th percentile. For each gene in each cell-type, we computed the cell-type specific proportion of reads for the gene (normalizing the expression within cell-type). We then computed the proportion of

proportions over the 265 cell-types (computing the specificity of the gene to a specific cell-type). We ranked the 12,119 genes retained in terms of specificity to each cell-type and then retained the 10% of genes most specific to a cell-type as the "cell-type specific" gene-set. We then tested whether any of the 265 cell-type specific gene-sets were enriched in the *Cog* or *NonCog* GWAS. This analysis sought to identify specific cell-types and specific regions in the brain involved in the etiology of *Cog* and *NonCog*. We further computed the difference in enrichment for *Cog* and *NonCog* to test if any cell types were specific to either trait. For these analyses, we leveraged two widely used enrichment analysis tools: MAGMA[73] and stratified LD score regression[74] with the European reference panel from 1000 Genomes Project Phase 3 as SNP location and LD structure reference, Gencode release 19 as gene location reference and the human-mouse homology reference from MGI (http://www.informatics.jax.org/downloads/reports/HOM_MouseHumanSequence.rpt).

MAGMA. We used MAGMA (v1.07b[73]), a program for gene-set analysis based on GWAS summary statistics. We computed gene-level association statistics using a window of 10kb around the gene for both *Cog* and *NonCog*. We then used MAGMA to run a competitive gene-set analysis, using the gene p-values and gene correlation matrix (reflecting LD structure) produced in the gene-level analysis. The competitive gene-set analysis tests whether the genes within the cell-type-specific gene-set described above are more strongly associated with *Cog*/*NonCog* than other genes.

Stratified LDscore regression. We used LD-score regression to compute LD scores for the SNPs in each of our "cell-type specific" gene-sets. Parallel to MAGMA analysis, we added a 10kb window around each gene. We ran partitioned LD-score regression to compute the contribution of each gene-set to the heritability of *Cog* and *NonCog*. To guard against inflation, we use LD score best practices, and include the LD score baseline model

(baselineLD.v2.2) in the analysis. We judged the statistical significance of the enrichment based on the p-value associated with the tau coefficient.

Difference in enrichment between *Cog* and *NonCog*. To compute differences in enrichment we compute a standardized difference between the per-annotation enrichment for *Cog* and *NonCog* as*:*

$$Z_{diff} = \frac{e_{Cog} - e_{NonCog}}{sqrt(se_{Cog}^2 + se_{NonCog}^2 - 2 * CTI * se_{Cog} * se_{NonCog})} \quad \text{(Equation 1)}$$

Where e_{Cog} is the enrichment of a particular gene-set for *Cog*, e_{NonCog} is the enrichment for the same gene-set for *NonCog*, se_{Cog} is the standard error of the enrichment for *Cog*, se_{NonCog} is the standard error of the enrichment for *NonCog*, and CTI is the LD score cross-trait intercept, a metric of dependence between the GWASs of *Cog* and *NonCog*.
We investigated the significance of the difference between Cog and NonCog tau coefficient with Equation 1 as well as by computing jackknifed standard errors. From the jackknifed estimates of the coefficient output by the LDSC software, we computed the jackknifed estimates and standard errors of the difference between *Cog* and *NonCog* tau coefficients, as well as a z-statistic for each annotation.

Enrichment of gene expression in the brain. We performed a transcriptome-wide association study (TWAS) using Gusev et al.[76] (FUSION: http://gusevlab.org/projects/fusion/). We used pre-computed brain-gene-expression weights available on the FUSION website, generated from 452 human individuals as part of the CommonMind Consortium. We then superimposed the bivariate distribution of the results of the TWAS for *Cog* and *NonCog* over the bivariate distribution expected given the sample overlap between EA and CP (the GWAS on which our GWAS of *Cog* and *NonCog* are based, see **Supplementary Note**).

Brain modalities

Brain volumes. We conducted genetic correlation analysis of brain volumes using GWAS results published by Zhao et al.[79]. Zhao et al. performed GWAS of total brain volume and 100 regional brain volumes, including 99 gray matter volumes and total white matter volume (**Supplementary Table 21**). Analyses included covariate adjustment for sex, age, their square interaction and 20 principle components. Analyses of regional brain volumes additionally included covariate adjustment for total brain volume. GWAS summary statistics for these 101 brain volumes were obtained from https://med.sites.unc.edu/bigs2/data/gwas-summary-statistics/. Summary statistics were filtered and pre-processed using Genomic SEM's "munge" function, retaining all HapMap3 SNPs with allele frequency >.01 outside the MHC region. We used Genomic-SEM to compute the genetic correlations between *Cog*, *NonCog* and brain volumes. Analyses of regional volumes controlled for total brain volume. For each volume, we tested if correlations differed between *Cog* and *NonCog*. Specifically, we used a chi-squared test to evaluate the null hypothesis that the two genetic correlations were equal. We used FDR adjustment to correct for multiple testing. The FDR adjustment is applied to the results for all gray matter volumes for *Cog* and *NonCog* separately.

White matter structures. We conducted genetic-correlation analysis of white-matter structures using GWAS results published by Zhao et al.[80]. Zhao et al. performed GWAS of diffusion tensor imaging (DTI) measures of the integrity of white-matter tracts. DTI parameters were derived for fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), and mode of anisotropy (MO). Each of these parameters were measured for 22 white matter tracts of interests (**Supplementary Table 22**) resulting in 110 GWAS. GWAS summary statistics for these 110 GWAS were obtained from https://med.sites.unc.edu/bigs2/data/gwas-summary-statistics/. Summary statistics were

filtered and processed using Genomic SEM's "munge" function; retaining all HapMap3 SNPs with allele frequency >.01 outside the MHC region. For each white matter structure, we tested if genetic correlations differed between *Cog* and *NonCog*. Specifically, we used a chi-squared test to evaluate the null hypothesis that the two genetic correlations were equal. We used FDR adjustment to correct for multiple testing. As these different diffusion parameters are statistically and logically interdependent, having been derived from the same tensor, FDR adjustment was applied to the results for each type of white matter diffusion parameter separately. FDR correction was applied separately for *Cog* and *NonCog*.

Additional Resources

A FAQ on why, how and what we studied is available here: https://medium.com/@kph3k/investigating-the-genetic-architecture-of-non-cognitive-skills-using-gwas-by-subtraction-b8743773ce44

A tutorial on how to perform GWAS-by-subtraction: http://rpubs.com/MichelNivard/565885

Additional resources to Genomic SEM software:

- A wiki including numerous tutorials: https://github.com/MichelNivard/GenomicSEM/wiki
- A Genomic SEM user group for specific questions relating to models and software: https://groups.google.com/g/genomic-sem-users
- A venue to report technical issues: https://github.com/MichelNivard/GenomicSEM/issues

Code availability

Code used to run the analyses is available at: https://github.com/PerlineDemange/non-cognitive

A tutorial on how to perform GWAS-by-subtraction: http://rpubs.com/MichelNivard/565885
All additional software used to perform these analyses are available online.

Data Availability

GWAS summary data for *NonCog* & *Cog* (excluding 23andMe) have been deposited in the GWAS Catalog with accession numbers GCST90011874 and GCST90011875 respectively (*NonCog* GWAS: ftp://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90011874, *Cog* GWAS: ftp://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90011875)

For 23AndMe dataset access, see https://research.23andme.com/dataset-access/.
Part of the National Longitudinal Study of Adolescent to Adult Health (Add Health) data is publicly available and can be downloaded at the following link: https://data.cpc.unc.edu/projects/2/view#public_li. For restricted access data, details of the data sharing agreement and data access requirements can be found at the following link: https://data.cpc.unc.edu/projects/2/view
The Dunedin study datasets reported in the current article are not publicly available due to lack of informed consent and ethical approval, but are available on request by qualified scientists. Requests require a concept paper describing the purpose of data access, ethical approval at the applicant's university, and provision for secure data access. We offer secure access on the Duke, Otago and King's College campuses. All data analysis scripts and results files are available for review. https://moffittcaspi.trinity.duke.edu/research-topics/dunedin
The E-Risk Longitudinal Twin Study datasets reported in the current article are not publicly available due to lack of informed consent and ethical approval, but are available on request by qualified scientists. Requests require a concept paper describing the purpose of data access, ethical approval at the applicant's university, and provision for secure data access. We offer

secure access on the Duke and King's College campuses. All data analysis scripts and results files are available for review. https://moffittcaspi.trinity.duke.edu/research-topics/erisk

Netherlands Twin Register data may be accessed, upon approval of the data access committee, email: ntr.datamanagement.fgb@vu.nl.

Researchers will be able to obtain Texas Twins data through managed access. Requests for managed access should be sent to Dr. Elliot Tucker-Drob (tuckerdrob@utexas.edu) and Dr. Paige Harden (harden@utexas.edu), joint principal investigators of the Texas Twin Project.

Wisconsin Longitudinal study data can be requested following this form: https://www.ssc.wisc.edu/wlsresearch/data/Request_Genetic_Data_28_June_2017.pdf

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Author Contributions

Conceived and designed the experiment: D.W.B., K.P.H., M.G.N., P.D., M.M. conceived the idea for the study with assistance from E.M.T-D., B.W.D., P.B, C.M., J.W. **Analyzed the data:** P.D., M.M., T.T.M., P.B., B.W.D., D.W.B., D.C., K.S., S.R.C., M.G.N., A.A., H.I. **Wrote the paper:** D.W.B., K.P.H., M.G.N., M.M., P.D., E.M.T-D. with helpful contributions from P.B., B.W.D., S.R.C. All authors contributed to interpretation of data, provided critical feedback on manuscript drafts and approved the final draft.

Competing Interests

The authors declare no competing interests.

Figure legends

Figure 1. GWAS-by-subtraction Genomic-SEM model

Cholesky model as fitted in Genomic SEM, with path estimates for a single SNP included as illustration. SNP, Cognitive performance (CP) and Educational attainment (EA) are observed variables based on GWAS summary statistics. The genetic covariance between CP and EA is estimated based on GWAS summary statistics for CP and EA. The model is fitted to a 3x3 observed variance-covariance matrix (i.e. SNP, CP, EA). Cog and Non-Cog are latent (unobserved) variables. The covariances between CP and EA and between Cog and NonCog are fixed to 0. The variance of the SNP is fixed to the value of 2pq (p = reference allele frequency, q = alternative allele frequency, based on 1000 Genomes phase 3). The residual variances of CP and EA are fixed to 0, so that all variance is explained by the latent factors. The variances of the latent factors are fixed to 1. The observed variables CP and EA were regressed on the latent variables resulting in the estimates for the path loadings: λCog-

CP=.4465; λCog-EA=.2237; λNonCog-EA=.2565. The latent variables were then regressed on each SNP that met QC criteria.

Figure 2. Manhattan plot of SNP associations with *NonCog*

Plot of the -$\log_{10}$(*p*-value) associated with the Wald test (two-sided) of β_{NonCog} for all SNPs, ordered by chromosome and base position. Purple triangles indicate genome-wide significant ($p < 5e10^{-8}$) and independent (within a 250Kb window and $r^2 < .1$) associations. The red dashed line marks the threshold for genome-wide significance ($P = 5 \times 10^{-8}$), and the black dashed line the threshold for nominal significance ($P = 1 \times 10^{-5}$).

Figure 3. Polygenic prediction and genetic correlations with IQ and educational achievement

a. Genetic correlations of NonCog and Cog with Educational Attainment, Highest Math Class Taken, Self-reported Math Ability and Childhood IQ. The dots represent genetic correlations estimated using Genomic SEM. Correlations with *NonCog* are in orange; with *Cog* in blue. Error bars represent 95% CIs. Exact estimates and p-values are reported in Supplementary Table 14. For analysis of genetic correlations with educational attainment, we re-ran the Genomic-SEM model to compute *NonCog* and *Cog* using summary statistics that omitted the 23andMe sample from the educational attainment GWAS. We then used the 23andMe sample to run the GWAS of educational attainment. Thus, there is no sample overlap in this analysis.
b. Effect-size distributions from meta-analysis of *NonCog* and *Cog* polygenic score associations with cognitive test performance and educational attainment. Outcomes were regressed simultaneously on *NonCog* and *Cog* polygenic scores. Effect-sizes entered into the meta-analysis were standardized regression coefficients interpretable as Pearson *r*. Exact estimates and p-values are reported in **Supplementary Table 12**. Samples and measures are detailed in **Supplementary Tables 9-10**. Traits were measured in different samples: Educational Attainment was measured in the AddHealth, Dunedin, E-Risk, NTR and WLS samples (N=24,056); Reading Achievement and Mathematics Achievement were measured in the AddHealth, NTR, and Texas-Twin samples (N=9,274 for reading achievement; N=10,747 for mathematics achievement); Cognitive test performance (IQ) was measured in the Dunedin, E-Risk, NTR, Texas Twins and WLS samples (N=11,351). The densities were obtained by randomly generating normal distributions where the meta-analytic estimate was included as the mean and the meta-analytic standard error as the standard deviation.

Figure 4. Estimates of genetic correlations with *NonCog*, *Cog* and Educational Attainment

Genetic correlations of *NonCog*, *Cog*, and EA with selected phenotypes. The dots represent genetic correlations estimated in Genomic SEM. Correlations with *NonCog* are in orange; with *Cog* in blue; with EA in gray. Error bars represent 95% CIs. Red stars indicate a statistically significant (FDR corrected p-value < 0.05, two tailed test) difference in the magnitude of the correlation with *NonCog* versus *Cog*. Exact p-values for all associations are reported in **Supplementary Table 14**. The FDR correction was applied based on all genetic correlations tested (including in **Supplementary Figure 11**). The difference test is based on a chi-squared test associated with a comparison between a model constraining these two correlations to be

identical, versus a model where the correlations are freely estimated. Source GWAS are listed in **Supplementary Table 13.**

Figure 5. Genetic correlations with regional gray matter volumes and white matter tracts
a. Cortical patterning of FDR-corrected significant genetic correlations with regional gray matter volumes for *Cog* versus *NonCog*, after correction for total brain volume. Regions of interest are plotted according to the Desikan-Killiany-Tourville atlas[102], shown on a single manually-edited surface (http://mindboggle.info[103]). Exact estimates and p-values are reported in **Supplementary Table 21**. *Cog* showed significant associations with gray matter volume for the bilateral fusiform, insula and posterior cingulate, the left superior temporal and left pericalcarine and right superior parietal volumes. *NonCog* was not associated with any of the regional brain volumes.
b. White matter tract patterning of FDR-corrected significant genetic correlations with regional mode of anisotropy (MO) for *Cog* versus *NonCog*. White matter tract probability maps are plotted according to the Johns Hopkins University DTI atlas (https://identifiers.org/neurovault.image:1401[104]). Exact estimates and p-values are reported in **Supplementary Table 21**. *Cog* was not associated with regional MO. *NonCog* showed significant associations with MO in the corticospinal tract, the retrolenticular limb of the internal capsule and the splenium of the corpus callosum.