Concept Paper Template

Provisional Paper Title: Development and evaluation of a polygenic score for non-cognitive skills

Proposing Author: DW Belsky

Author's Email: dbelsky@duke.edu

P.I. Sponsor: TE Moffitt & A Caspi
(if the proposing author is a student or colleague of an original PI)

Today's Date: August 15, 2018

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:

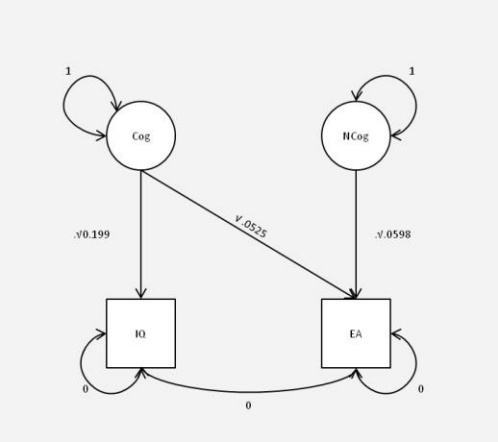
To develop and evaluate a novel genetic measurement of an inherited tendency to develop non-cognitive skills influencing life course socioeconomic attainment.

Expanded Background & Significance. Success in school and socioeconomic attainment in adulthood are important determinants of healthy lifespan (1). Understanding the etiology of this pattern of achievement is therefore of public health significance (2). In life-course longitudinal studies, individual differences in cognitive skills and other skills loosely referred to under the umbrella of "non-cognitive skills" influence success in school and beyond (3–5). Individual differences in cognitive and so-called non-cognitive skills are heritable (6, 7). Recently, genome-wide association studies of educational attainment and cognitive test performance have begun to outline the molecular basis of this heritability (8). Polygenic scores, summary measures of tiny-effect genetic influences from across the whole genome (9), can be derived from these GWAS and, in independent samples, predict educational and economic outcomes as well as individual differences in cognitive and non-cognitive skills (10–14). These data suggest education GWAS discoveries reflect genetics influencing both cognitive and non-cognitive skill development. At present, it is not possible to study these genetics separately; the educational attainment polygenic score measures their combined influence on success in school. Having available measurements of genetics that uniquely affect development of either cognitive or non-cognitive skills would enhance opportunities to investigate independent etiologies and sequelae of cognitive and non-cognitive skills.

Data analysis methods:

Stage 1. Development
We propose to use the new Genomic Structural Equation Modeling (GSEM) suite of methods (15) to derive a GWAS of non-cognitive skills from published GWAS results for the phenotypes of educational attainment and cognitive test performance. We will use GSEM to approximate an analysis which effectively runs a GWAS of educational attainment with a covariate for cognitive test performance. The residual genetic coefficients from this model, by construction, reflect genetic influences on non-cognitive skills influencing educational attainment. GSEM will actually produce two novel sets of GWAS summary statistics. One set will reflect genetic influences shared between education and cognitive test performance. The second set will reflect genetic influences on education that are not shared with cognitive test performance, i.e. "non-cognitive" summary statistics.

The structural equation path diagram can be visualized below (path coefficients from preliminary analysis)



Development analyses will be conducted by the laboratories of M Nivard & Elliott Tucker-Drob at the Vrije University Amsterdam and the University of Texas at Austin. *Development analyses involve only GWAS summary data and will not involve any Dunedin Data.*

Stage 2. Validation

We will conduct analyses of 4 polygenic scores:
EA3 – based on the original education GWAS summary statistics (8)
IQ – based on original GWAS of cognitive test performance (16)
Cog – based on the overlap between EA3 and IQ GWAS
NonCog – based on genetics unique to EA3 GWAS and that do not overlap with IQ GWAS

We will conduct 3 sets of analyses using E-Risk and Data:

1) Test correlations among derived polygenic scores
2) Test correlations of derived polygenic scores with
    a. Educational attainment - measured as in (12)
    b. IQ – measured in childhood (wfsiq713) as and at age 38 (wfsiq38).
        i. We propose analysis of WAIS subtests and potential follow-up in CANTAB tests because the GWAS of cognitive test performance consists mostly of samples with cognitive tests of "fluid" intellectual functions (such as are measured by the WAIS Matrix Reasoning and Digit-Symbol Coding sub-tests). Therefore, a possible outcome of our GSEM analysis is that we will parse the EA3 GWAS results into a component reflecting primarily fluid intellectual functions and a component that comprises some combination of so-called "crystalized" cognitive functions (such as are measured by the WAIS Information subtest) and non-cognitive skills.
    c. Self Control – measured as in (3)
    d. Big 5 Personality Traits – measured at age 38 (Big 5 variables)
3) Test multivariate associations of derived polygenic scores with the outcomes in (2)

We will conduct parallel analyses of similar phenotypes in the Add Health Study, the Texas Twin Study, and, pending approval from the Study PIs, the E-Risk Study and other studies.

The primary objective of validation analysis is to test if derived NonCog PGS associations with non-cognitive phenotypes (personality, self-control) are stronger than NonCog PGS associations with cognitive phenotypes (IQ, potentially WAIS subtests/ CANTAB scales). In parallel, we will test of Cog PGS associations with cognitive phenotypes are stronger than Cog PGS associations with non-cognitive phenotypes. A secondary objective is to compare effect-sizes for the two polygenic scores for cognitive and non-cognitive phenotypes and for educational attainment. A caveat to this secondary objective is that statistical power is not equivalent for derivation for the cognitive and non-cognitive PGSs, so results will not permit strong inference about the genetic architecture of the phenotypes. However, these analyses will shed light on how these polygenic scores should be interpreted in future analyses.

Validation analyses using Dunedin data will be conducted by DW Belsky with collaboration from TE Moffitt, A Caspi, K Sugden, D Corcoran, and J Prinz.

Stage 3. Phenotypic Annotation
Phenotypic annotation analysis will test associations of newly derived polygenic scores with outcomes in school and beyond using data from studies with follow-up into adulthood.

We propose analysis of social mobility in the Dunedin Study following the analysis in (12).

Variables needed at which ages:

Childhood Self-Control from Moffitt et al. 2011 PNAS (3) [lsc311]].
Childhood IQ [wfsiq713]
Adult IQ [wfsiq38] (would prefer avg of 38-45 when available)
Age-38 WAIS subscales (would prefer avg of 38-45 when available)
Childhood SES [sesav115]
Adulthood SES [sesHiHmk38, sesHi38]
Educational Attainment [Educ263238]
Big 5 ratings [BF variables – asking for guidance re: research worker vs. informant vs. combined ratings; happy to follow precedent, e.g. Israel et al. 2014 JPSP]

Significance of the Study (for theory, research methods or clinical practice):

The significance of this project is primarily for research. A genetic measurement of non-cognitive skills could be used to test (a) how non-cognitive skills develop, including potential "genetic nurture" effects; (b) the extent to which non-cognitive skills influence performance on measurements of academic skills/abilities and cognitive tests; (c) the importance of non-cognitive skills to life attainments, health behaviors, and healthy lifespan.

References cited:

1. Adler NE, Rehkopf DH (2008) U.S. Disparities in Health: Descriptions, Causes, and Mechanisms. *Annu Rev Public Health* 29(1):235–252.

2. Berkman LF, Kawachi I, Glymour MM (2014) *Social epidemiology* (Oxford University Press).

3. Moffitt TE, et al. (2011) A gradient of childhood self-control predicts health, wealth, and public safety. *Proc Natl Acad Sci U S A* 108(7):2693–2698.

4. Strenze T (2007) Intelligence and socioeconomic success: A meta-analytic review of longitudinal research. *Intelligence* 35:401–426.

5. Deary I J, Strand S, Smith P, Fernandes C (2007) Intelligence and educational achievement. *Intelligence* 35(1):13–21.

6. Polderman TJC, et al. (2015) Meta-analysis of the heritability of human traits

based on fifty years of twin studies. *Nat Genet* 47(7):702–709.

7. Tucker-Drob EM, Briley DA, Engelhardt LE, Mann FD, Paige K (2016) Genetically-mediated associations between measures of childhood character and academic achievement. *J Pers Soc Psychol* 111(5):790–815.

8. Lee JJ, et al. (2018) Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nat Genet* 50(8):1112–1121.

9. Dudbridge F (2013) Power and Predictive Accuracy of Polygenic Risk Scores. *PLOS Genet* 9(3):e1003348.

10. Belsky DW, et al. (2016) The Genetics of Success: How Single-Nucleotide Polymorphisms Associated With Educational Attainment Relate to Life-Course Development. *Psychol Sci* 27(7):957–972.

11. Wertz J, et al. (In Press) Genetics and crime: Integrating new genomic discoveries into psychological research about antisocial behavior. *Psychol Sci*.

12. Belsky DW, et al. (2018) Genetic analysis of social-class mobility in five longitudinal studies. *Proc Natl Acad Sci*:201801238.

13. de Zeeuw EL, et al. (2014) Polygenic scores associated with educational attainment in adults predict educational achievement and ADHD symptoms in children. *Am J Med Genet Part B Neuropsychiatr Genet Off Publ Int Soc Psychiatr Genet* 165B(6):510–520.

14. Plomin R, von Stumm S (2018) The new genetics of intelligence. *Nat Rev Genet*.

15. Grotzinger AD, et al. (2018) Genomic SEM Provides Insights into the Multivariate Genetic Architecture of Complex Traits. *bioRxiv*:305029.

16. Savage JE, et al. (2018) Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat Genet* 50(7):912–919.

Data Security Agreement

Provisional Paper Title	Development & Evaluation of a Polygenic Score for Non-Cognitive Skills
Proposing Author	DW Belsky
Today's Date	August 15, 2018

Please keep one copy for your records and return one to the PI Sponsor

Please initial your agreement

DWB	I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent)
DWB	My project is covered by Duke or Otago ethics committee OR I have /will obtain ethical approval from my home institution.
DWB	I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: a) encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) b) password-protected c) configured to lock-out after 15 minutes of inactivity AND d) has an antivirus client installed as well as being patched regularly.
DWB	I will not "sync" the data to a mobile device.
DWB	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact Professor Moffitt or Caspi. (919-684-6758, tem11@duke.edu, ac115@duke.edu)
DWB	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
DWB	I will not post data online or submit the data file to a journal for them to post. *Some journals are now requesting the data file as part of the manuscript submission process. The Dunedin Study Members have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to Terrie or Avshalom for strategies for achieving compliance with data-sharing policies of journals.*
DWB	I will delete all data files from my computer after the project is complete. Collaborators and trainees may not take a data file away from the office. The data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.

Signature: DWB

CONCEPT PAPER RESPONSE FORM

A

Provisional Paper Title	Development & Evaluation of a Polygenic Score for Non-Cognitive Skills
Proposing Author	DW Belsky
Other Contributors	TE Moffitt, A Caspi, R Poulton, K Sugden, D Corcoran, J Prinz, B Williams, and J Wertz as part of a team of investigators also including B Domingue, M Nivard, KP Harden, E Tucker-Drob, and others.
Potential Journals	PNAS, Nature Human Behavior, Psychological Science
Today's Date	August 15, 2018
Intended Submission Date	June 1, 2019

Please keep one copy for your records and return one to the proposing author

B. To be completed by potential co-authors:

	Approved
	Not Approved
	Let's discuss, I have concerns

Comments:

Please check your contribution(s) for authorship:

	Conceptualizing and designing the longitudinal study
	Conceptualizing and collecting one or more variables
	Data collection
	Conceptualizing and designing this specific paper project
	Statistical analyses
	Writing
	Reviewing manuscript drafts
	Final approval before submission for publication
	Acknowledgment only, I will not be a co-author

Signature:

_____