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RESEARCH

Cognitive Polygenic Index is Associated with Occupational Complexity over and above Brain Morphometry

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Abstract

Although the impact of occupation on cognitive skills has been extensively studied, there is limited research examining if genetically predicted cognitive score may influence occupation. We examined the association between Cognitive Polygenic Index (PGI) and occupation, including the role of brain measures. Participants were recruited for the Reference Ability Neural Network and the Cognitive Reserve studies. Occupational complexity ratings for Data, People, or Things came from the Dictionary of Occupational Titles. A previously-created Cognitive PGI and linear regression models were used for the analyses. Age, sex, education, and the first 20 genetic Principal Components (PCs) of the sample were covariates. Total cortical thickness and total gray matter volume were further covariates. We included 168 white-ethnicity participants, 20–80 years old. After initial adjustment, higher Cognitive PGI was associated with higher Data complexity (B=-0.526, SE = 0.227, Beta= -0.526 $p = 0.022$, $R^2 = 0.259$) (lower score implies higher complexity). Associations for People or Things were not significant. After adding brain measures, association for Data remained significant (B=-0.496, SE: 0.245, Beta= -0.422, $p = 0.045$, $R^2 = 0.254$). Similarly, for a further, fully-adjusted analysis including all the three occupational complexity measures (B=-0.568, SE = 0.237, Beta= -0.483, $p = 0.018$, $R^2 = 0.327$). Cognitive genes were associated with occupational complexity over and above brain morphometry. Working with Data occupational complexity probably acquires higher cognitive status, which can be significantly genetically predetermined.

Keywords Cognition · Polygenic Indices · Occupation

Introduction

It is well established that middle and late-life occupation plays a significant role to the cognitive status of older age, with specific occupations indicating higher cognitive reserve and, thus, lower risk of cognitive deficits or neurodegeneration (Stern 2012; Boots et al. 2015; Darin-Mattsson et al. 2017; Chapko et al. 2018). Further, in older adults at risk for dementia, higher occupational complexity has been associated with better cognition (Rydström et al. 2022). However, how do we actually choose an occupation? Both early-life education and occupational complexity are predictive factors of dementia, suggesting that strategies for dementia prevention could be implemented at different points throughout life (Hyun et al. 2022). Apart from the environmental factors, is there any genetic factor might being associated with the occupational complexity?. Interestingly, biometric behavioral genetics analyses has shown genetic influences accounting for a large amount of variance in job satisfaction (Li et al. 2016). In a study among twins or brothers, genetics seemed to explain a great variance of occupation (Lichtenstein and Pedersen 1997). More specifically, about 50% of the variance in educational achievement and 40% of the variance in occupational status reflects between-family variance. The aforementioned findings suggest that genes may have a significant impact on the relationship between cognition and occupation. Given the profound influence of occupation on our overall life and

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well-being (Jessen-Winge et al. 2018), it becomes crucial to identify the potential factors that predispose cognitively healthy adults to their chosen professions. However, reports are not always consistent; when incorporating brain measures, occupational complexity does not contribute toward resilience against neuropathology in people at risk for dementia (Rydström et al. 2023).

Polygenic indices (PGI) for cognitive outcomes can help refine our understanding of how the cumulative effect of genetic variation in specific loci may contribute to various traits or life outcomes (Genc et al. 2021). The PGI approach has become a commonly used approach as the number of large-scale genome-wide association meta-analysis studies (GWAS) increase. The PGI used in the current analysis was based on the summary statistics results from a GWAS analyses of 269,867 participants, aimed to identify new genetic and functional links to intelligence (Savage et al. 2018).

Most of the current literature on cognition and occupation focuses on either the association between occupation and education, or occupation and cognitive performance. Little is known about the direct relationship between occupation and cognition-associated genes. In the current study, we examined the association between Cognitive PGI and occupational complexity, in a sample of cognitively healthy adults across age, including brain measures in the analyses. We hypothesized that genetics of cognition will affect occupational complexity, incorporating the role of brain measures.

Methods

Participants were recruited for two studies: the Reference Ability Neural Network (RANN) and the Cognitive Reserve (CR) study. The RANN study was designed to identify networks of brain activity uniquely associated with performance across adulthood for each of the four following reference abilities: memory, fluid reasoning, speed of processing and vocabulary (Habeck et al. 2016). The CR study was designed to elucidate the neural underpinnings of CR and the concept of brain reserve (Stern 2012). Both studies share similar recruitment procedures and data collection. All participants were native English speakers, right-handed, with at least a fourth-grade reading level. To be included in the study, participants had to also be free of any major neurological or psychiatric condition that could affect their cognitive status. Careful screening excluded participants with MCI or dementia. A score equal or greater than 130 was required on the Mattis Dementia Rating Scale (Mattis 1988) for the inclusion in the study. Moreover, participants had to have no or minimal complaints on a questionnaire about their functionality (Blessed et al. 1968). Both studies have been approved by the Institutional Review Board (IRB) of Columbia University. More detailed information can be found in previous publications (Stern 2009, 2012; Stern et al. 2014; Habeck et al. 2016, 2017; Razlighi, Habeck et al. 2017). The total baseline sample for RANN&CR was $N = 528$. For the purposes of the current analyses, we included participants who had complete data on the measures used for our hypothesis, and where White-ethnicity.

Occupational data

Participants were asked to provide the occupation of the longest duration during their lifetime. As described in a previous publication of our group (Habeck et al. 2019), for the description of occupational data, we used descriptors from the Dictionary of Occupational Titles (DOT) https://occupationalinfo.org/appendxb_1.html (United States Employment Service. Dictionary of Occupational Titles). Every job requires a worker to function in relation to three major categories: Data, People, and Things (Gadermann et al. 2014). The DOT classifies occupational complexity with Data, People, and Things (United States Employment Service. Dictionary of Occupational Titles, Smart et al. 2014). The complexity ratings range from 0 to 6, 0–8, and 0–7 for data, people, and things, respectively, with lower values indicating higher complexity. As described in the DOT, there are specific identifications of each category, referred to as Worker Functions. The definitions of Worker Functions are as follows: "Data: Information, knowledge, and conceptions, related to data, people, or things, obtained by observation, investigation, interpretation, visualization, and mental creation. Data are intangible and include numbers, words, symbols, ideas, concepts, and oral verbalization." "People: Human beings; also, animals dealt with on an individual basis as if they were human." "Things: Inanimate objects as distinguished from human beings, substances, or materials; and machines, tools, equipment, work aids, and products. A thing is tangible and has shape, form, and other physical characteristics" (United States Employment Service. Dictionary of Occupational Titles). Occupational data were standardized prior to the analyses.

Genotyping

Each participant had venous blood drawn during their visit at Columbia University. DNA samples were obtained through whole blood extraction. Genotyping was performed using Omni 1 M chips, according to Illumina procedures. Genotype calling was performed using GenomeStudio v.1.0. Quality control was applied to both DNA samples and SNPs. Specifically, samples were removed from further analysis if they had call rates below 95%, sex discrepancies

and relatedness (kinship coefficient more than 0.125). To account for population structure, we computed the top 20 Principal Components (PCs) of the whole sample using Plink software and we used the 20 PCs as covariates in our analysis (Purcell et al. 2007).

GWAS Imputation

GWAS data for all study participants was imputed using the Haplotype Reference Consortium (HRC v1.1) panel through the Michigan Imputation online server (Das et al. 2016). The HRC is a reference panel of 64,976 human haplotypes at 39,235,157 SNPs constructed using whole genome sequence data from 20 studies of predominantly European ancestry (McCarthy et al. 2016). Imputed dosages for a total of 6,280,331 SNPs with MAF > 0.05, HWE p value > 1e–6 and a missing rate < 10% were used for PGI computation. PGI scoring was performed using PRSice software (Choi and O'Reilly, 2019) following the clumping and thresholding (C + T) approach, as originally described by the International Schizophrenia Consortium (Prive et al., 2019) (Tsapanou et al. 2023).

Polygenic Index: We composed the PGI from summary statistics from a recent GWAS metanalysis of cognitive performance including $n = 269{,}867$ participants, from 14 independent European cohorts (Savage et al. 2018). Different measures of intelligence were assessed in each cohort but were all operationalized to index a common latent g factor, the general intelligence factor or Spearman's g, representing multiple cognitive functioning dimensions. The majority of the samples were adults, 18–60 years old ($n = 204{,}228$), and when they stratified the participants according to age-groups (children, young adults, older adults, adults), results did not show any specific age-dependent effect suggesting that the same SNPs are important across age-groups.

In our analyses, we included all SNPs, regardless of p-value. To ensure that only independent markers were included in the computed PGI, we conducted LD clumping using an R^2 threshold of 0.1 and a 250 kb sliding window. Markers within the Major Histocompatibility Complex (MHC) LD region on chromosome 6 (chr6:27–33 Mb, hg19) were also excluded from the PGI due to the presence of complex patterns of long-range linkage disequilibrium within this region. For each remaining SNP, we computed the weighted count of cognition-associated alleles (0, 1, or 2), with the weights determined by the coefficient estimated in the GWAS. We then computed the average weighted count across all SNPs to form the PGI. The PGI computation was performed using the PRSice software (Choi and O'Reilly 2019). For interpretation reasons, PGI values were normalized by z-transformed.

Structural MRI Scan and Image Processing

MRI images were acquired on a 3.0T Philips Achieva Magnet. Each scan used 240 mm field of view. The parameters for EPI acquisition were TE/TR (ms) 20/2000; Flip Angle 72°; In-plane resolution (voxels) 112 × 112; Slice thickness/gap (mm) 3/0; Slices 41.

We selected two neural phenotypes for analysis based on existing literature establishing association with between brain morphometry and cognitive test performance: gray matter volume (GM) (mm^3) (Yoon et al. 2017), and cortical thickness (CT) (mm) (Ehrlich et al. 2012; Tuladhar et al. 2015). T1 scans for each participant were reconstructed with FreeSurfer (v5.1.0) software for human brain imaging analysis (http://surfer.nmr.mgh.harvard.edu). The accuracy of FreeSurfer's subcortical segmentation and cortical parcellation (31, 32) has been reported to be comparable to manual labeling. Each participant's white and gray matter boundaries, as well as gray matter and cerebral-spinal-fluid boundaries, were visually inspected slice by slice, and manual control points were added in case of any visible discrepancy. Boundary reconstruction was repeated until satisfactory results for every participant were reached. The subcortical structure borders were plotted by TkMedit visualization tools and compared against the actual brain regions. In case of discrepancy, they were corrected manually. FreeSurfer's subcortical segmentation and cortical parcellation has been shown to have comparable accuracy to manual labeling (Fischl et al. 2002; Fischl 2012). We measured GM volume based on the total gray-matter volume reported by FreeSurfer. We measured regional CT from values computed by standard FreeSurfer parcellation (Desikan et al. 2006). We measured total CT as the average of values across both hemispheres.

Statistical Analysis

Linear regression models were used for the association between the Cognitive PGI and occupation. Prior to the main analysis we explored the association between global cognition as measured through the neuropsychological assessment and occupational complexity, unadjusted and then, adding age, sex, and education as covariates. For the main analysis, age, sex, years of education, and the first 20 genetic Principal Components (PCs) were initially used as covariates. Subsequently, GM and CT were added in the statistical analyses. In secondary analysis, linear regression was performed for the association between Cognitive PGI and occupation, adding in the model all the three occupational complexity measures, along with the covariates (age, sex, education, PCs, GM, and CT). Age, years of education, PCs, and the two brain measures were used as continuous

Table 1 Characteristics of our sample; $N = 168$ cognitively healthy, white-ethnicity adults

Characteristics	
Age, years, Mean (SD)	56.9 (15.5)
Education, years, Mean (SD)	16.4 (2.27)
Sex, women, N (%)	82 (48.8)
GM, Mean (SD)	6.25 (0.59)
CT, Mean (SD)	0.63 (0.24)
Total, N	168

variables, while sex was used as dichotomous. For interpretation reasons, PGI and the three occupational categories values were normalized by z-transformations.

Descriptive and linear regression analyses were performed using SPSS 26 (SPSS, Chicago, Illinois, USA). Nominally significant alpha values were defined as $p < 0.05$.

Results

A total of 168 White-only participants had complete data on both genetic and occupational information. Age ranged from 20 to 80 years old, with an average of 16 years of education (see Table 1). Global cognition was associated with Data both in the unadjusted model (B=-0.017, SE: 0.076, Beta=-0.217, $p = 0.005$, $R^2 = 0.047$) and the adjusted one (B=-0.226, SE: 0.089, Beta=-0.226, $p = 0.012$, $R^2 = 0.100$). Associations between global cognition and the categories of Things and People were not significant. There were significant associations between the Cognitive PGI and occupational complexity in Data, using the covariates of age, sex, education, and PCs (B=-0.526, SE = 0.227, Beta= -0.526 $p = 0.022$, $R^2 = 0.259$), such that higher Cognitive PGI was associated with higher Data complexity (see Fig. 1). Association for People or Things was not significant (B = 0.238, SE = 0.230, Beta = 0.238, $p = 0.564$, $R^2 = 0.242$, and B=-0.388, SE = 0.241, Beta=-0.388, $p = 0.145$, $R^2 = 0.168$ accordingly). Even after adding brain morphometry in the covariates, associations remained significant for Data (B=-0.496, SE: 0.245, Beta=-0.422, $p = 0.045$, $R^2 = 0.254$), while, the associations for People (B = 0.315, SE: 0.242, Beta = 0.267, $p = 0.195$, $R^2 = 0.273$) or Things (B=-0.394, SE: 0.257, Beta=-0.336, $p = 0.127$, $R^2 = 0.173$ remained non-significant). For exploratory reasons, we also performed further analysis examining the association between Cog PGI and the three occupational categories without including the covariate "education", in all models. Results remained significant only for the association with Data, adjusted for age, sex, and the PCs (B=-0.573, SE: 0.232, Beta= -0.573, $p = 0.015$), and for age, sex, PCs, and the brain measures (B=-0.540, SE: 0.250, Beta= -0.459, $p = 0.032$). Results indicate the strong role of the cognitive genetics to occupational complexity.

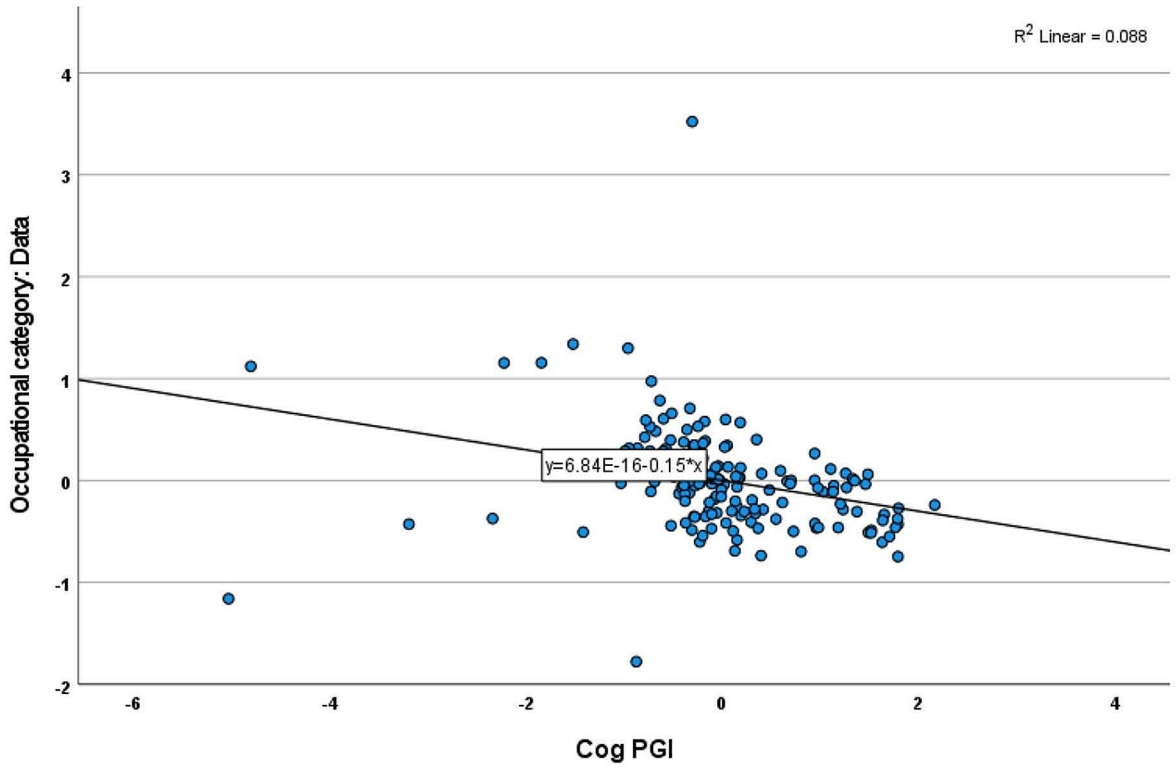

Fig. 1 Scatterplot for the association between Cog PGI and Data Occupational category, after adjustments for PCs, age, sex, and education (standardized predicted value). Lower Data value indicates higher complexity

Table 2 Associations between cognitive PGI and the three occupational complexity measures, in the different adjustments' analyses

Cognitive PGI	Data	People	Things
PCs only	**B=-0.598, SE: 0.231, Beta=-0.598, $p=0.011$, $R^2=209$**	**B = 0.142, SE: 0.245, Beta = 0.142, $p=0.564$, $R^2=0.113$**	**B=-0.351, SE: 0.239, Beta=-0.351, $p=0145$, $R^2=0.150$**
Age, sex, education, PCs	**B=-0.526, SE = 0.227, Beta=-0.526 p = 0.022, R2 = 0.259**	B = 0.238, SE = 0.230, Beta = 0.238, $p=0.564$, R2 = 0.242	B=-0.388, SE = 0.241, Beta=-0.388, $p=0.145$, R2 = 0.168
Age, sex, education, PCs, GM, CT	**B=-0.496, SE: 0.245, Beta=-0.422,p = 0.045, R2 = 0.254**	B = 0.315, SE: 0.242, Beta = 0.267, $p=0.195$, R2 = 0.273	B=-0.394, SE: 0.257, Beta=-0.336, $p=0.127$, R2 = 0.173
Age, sex, education, PCs, GM, CT, Data, People, Things	**B=-0.568, SE = 0.237, Beta=-0.483,p = 0.018, R2 = 0.327**	B = 0.349, SE: 0.225, Beta = 0.297, $p=0.124$, $R^2=0.405$	B=-0.239, SE: 0.253, Beta=-0.204, $p=0.346$

In the fully adjusted analysis including all the three occupational complexity measures, the association between Cognitive PGI and Data remained significant (B=-0.568, SE = 0.237, Beta= -0.483, $p=0.018$, $R^2=0.327$) (see Table 2).

Discussion

These findings suggest that genetic variation associated with cognition is also related to occupational complexity of cognitively healthy adults, over and above brain morphometry. One possibility is that there is a direct relationship between specific cognition-associated genes and occupational skills. Alternately, people with genetic variation associated with better cognition are more likely to acquire the cognitive skills needed in high-Data occupations through education and training. Higher complexity Data occupations such as synthesizing, coordinating, and analyzing, might depend on the executive function abilities, which are needed to combine working memory, monitoring, planning etc. (Stern et al. 1996; Puente et al. 2015).

Our results suggest that a specific genetic disposition captured by the Cognitive PGI predisposes for occupations that require these abilities. However, the Cognitive PGI might not contribute significantly to the development and maintenance of the other occupational demands summarized as People and Things. This might indicate that other factors, such as emotional intelligence or behavioral styles, might be more important for these aspects of occupation.

While the relationship between occupation and cognitive skills has been studied extensively, to our knowledge, this is the first study to examine if genetic polygenic indices for cognition is related to the nature of occupation. The PGI has the advantage of examining the cumulative genetic contribution of many different genes instead of unique ones, providing more robust and parsimonious explanation of the cognitive variance than single SNPs. Further, we included data on brain morphometry, based on MRI scans. However, some limitations to this study should be noted. The occupation information was based on self-reports from the participants and was limited to the one occupation engaged in for the longest time, limiting the validity of the results. Further, available data only yielded a relatively small sample size, possibly affecting the statistical power of the study to detect small but potentially meaningful effects. Including a wide age-range in a genetics' analysis study could be also considered a limitation, since there is a variability in genetics influence over the lifespan. The environment can play a crucial role in modulating the effects of genetic factors on cognition. Lifespan development is influenced by a complex interplay of genetics and environment, and the impact of this interaction might change with age. While measured genotypes through PGIs provide valuable insights into the genetic underpinnings of occupational complexity, they currently capture a smaller portion of the variance compared to twin estimates of heritability. There's still a considerable amount of variance left to characterize, pointing to the complex interplay of genetic, environmental, and perhaps epigenetic factors in shaping occupational outcomes. Advances in genetic research and methodologies may gradually close this gap, enhancing our understanding of how genetics contributes to occupational complexity.

In summary, people with higher Cognitive PGI were more likely to engage in occupations with higher Data demands, accounting for their brain morphometry. This suggests that genetic variation associated with cognition may predispose individuals for occupational complexity.

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Declarations

Competing interests The authors declare no competing interests.

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