# Cognitive Capacity Genome-wide Polygenic Scores Identify Individuals Resilient to Cognitive Decline in Aging

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# Abstract

The genetic underpinnings of cognitive resilience in aging remains unknown. Predicting an individual's rate of cognitive decline—or cognitive resilience—using genetics will allow personalized intervention for cognitive enhancement and optimal selection of target samples in clinical trials. Here, using genome-wide polygenic scores(GPS) of cognitive capacity as the genomic indicators for variations of human intelligence, we examined the genetic liability of cognitive abilities in the behavioral/cognitive phenome to understand individual phenotypic differences over time. We analyzed the 18-year records of the cross-sectional and longitudinal sociogenomic data of 8,511 European-ancestry adults from the Wisconsin Longitudinal Study (WLS), especially focusing on the cognitive assessments that were repeatedly administered to the participants at their average ages of 64.5 and 71.5. Our linear mixed-effects model identified a significant interaction effect between age and cognitive capacity GPS, which indicates that a higher cognitive capacity GPS significantly correlates with a slower cognitive decline in the domain of *immediate memory recall* (p-value = 1.79E-03, β = 1.86E-01). Also, the phenome-wide analysis identified several significant associations of cognitive capacity GPSs on the cognitive and behavioral phenome, such as *Similarities* task (p-value = 3.59E-74, β = 1.36, 95% CI=(1.22, 1.51)), *Number Series* task(p-value = 2.55E-78, β = 0.94, 95% CI=(0.85, 1.04)), *IQ scores*(p-value = 7.74E-179, β = 1.42, 95% CI=(1.32, 1.51)), *high school class rank (p-value = 3.07E-101, β = 1.86, 95% CI=(1.69, 2.02)*, *Openness* from the BIG 5 personality factor(p-value = 2.19E-14, β = 0.57, 95% CI=(0.42, 0.71)), and social participation of *reading* books (p-value = 2.03E-21, β = 0.50, 95% CI=(0.40, 0.60)), attending cultural events, such as concerts, plays or museums (p-value = 2.06E-23, β = 0.60, 95% CI=(0.49, 0.72)), and *watching TV* (p-value = 4.16E-18, β=-0.48, 95% CI=(-0.59, -0.37)). As the first phenome-wide analysis of cognitive and behavioral phenotypes, this study presents the novel genetic protective effects of cognitive ability on the decline of memory recall in an aging population.


# Introduction

The magnitudes of cognitive decline in aging, a major health concern in contemporary society, differ substantially across individuals[1, 2]. Unraveling the genetic underpinning for individual variations of cognitive decline with aging, particularly those associated with cognitive resilience, could help develop individualized interventions for cognitive decline and allow better sample selection in clinical trials in dementia research. Despite studies reporting the genetic risk factors of accelerated cognitive decline among individuals with dementia[3–5], we know little about the genetic protective factors of cognitive resilience in the normal aging population.

Genome-wide Polygenic Scores (GPS) leverage the fact that most human traits are developed from the aggregated influence of many genetic variants, both common and rare[6–8]. By aggregating the miniscule effects of millions of genetic variants into a single score, GPS allows researchers to stratify individuals by their genomic propensity for a particular trait and to select individuals with extremely high or low GPS for further research. The recent large genome-wide association studies (GWAS) of educational attainment, an often-used proxy phenotype for human intelligence, identified 1,271

independent autosomal loci reaching genome-wide significance[9]. These findings suggest several biological pathways related to brain development or neuron-to-neuron communication contribute to human intelligence. While the GWAS revealed many genetic variants associated with cognitive phenotypes (such as cognitive performance, math ability, highest math class taken)[9–16], the genomic contribution to specific cognitive domains remains unknown, as does their relationship to cognitive changes with aging.

Since general cognitive ability is known to be highly heritable (50–70%) and polygenic[17, 18], we utilize GPS to account for the genome-wide factors underlying cognitive capacity and its secular changes. We leverage the expansive phenotype information of a 50 + year social longitudinal database for phenomewide association studies (PheWAS). The Wisconsin Longitudinal Study (WLS), the longest-running social longitudinal study in the United States[19, 20], encompasses a detailed and broad lifelog of cognition, personality, financial, health, and socioeconomic status. The surveys have repeatedly administered the same cognitive ability tests with the time interval of ~ 10 years in their latest survey rounds, as well as collected the genotype data of the participants, which creates a deep genotype-phenotype catalogue of an individual's cognitive and behavioral traits over their adult lives.

Herein, we hypothesize that the polygenic influence of the cognitive capacity can explain certain patterns of cognitive abilities and their declines in aging as well as other socio-behavioral phenotypes that might be affected by genetics of cognitive abilities. We tested the associations between longitudinal observations of individual cognitive/behavioral phenomes and the GPSs of four different cognitive phenotypes (educational attainment, cognitive performance, math ability, highest math class taken) with a focus on the secular changes of cognitive test scores. The approach was designed to systematically address the following research questions: firstly, whether a certain cognitive domain is more impacted by polygenic influence than other cognitive domains; secondly, whether individuals with different GPS show different patterns of cognitive decline in aging; and, thirdly, the extents to which phenotypic variances of behavioral/cognitive phenotypes can be explained by genetic liability of cognitive capacities.

## Materials And Methods

# Data

The WLS is based on 10,317 individuals surveyed in 1957 – representing a 1/3 random sample of Wisconsin high school graduates that year – with a randomly-selected sibling empaneled later. The study has collected 27,000 + phenotypic variables of the participants, ranging from cognition, personality, financial, socioeconomic to genotype data during 6 waves of data collection over 60 years. The cohort is representative of non-Hispanic White Americans who completed at least 12 years of high school education in the United States. The participants had undergone an in-person, telephone structured interviews or a mail-in questionnaires for each survey round after providing informed consent. All instruments and operations were approved by the Institutional Review Board of the University of Wisconsin-Madison.

# Genotype data and quality control process

In 2007–2008, saliva samples were collected by mail or home-interview, and 9,019 individuals were successfully genotyped at the Johns Hopkins University center for inherited disease research (CIDR) using the Illumina HumanOmniExpress-24 v.1.1 array designed to human genome build 37/hg19. The subsequent quality control process filtered individuals with (i) genotype missingness rate > 0.05 in all chromosomes, (ii) mismatch between recorded sex and genetically determined sex, (iii) high genetic relatedness with other individual (> 0.025), (iv) outlier in heterozygosity/homozygosity test, and (v) non-European ancestry outliers. Non-European individuals were identified by visually inspecting the principal component analysis (PCA) plot of the covariance matrix of the WLS genotype data with 1000 Genome populations. Additionally, SNPs with (i) genotype call rate < 0.95, (ii) Hardy-Weinberg exact test p-value < 1.0E-05, and (iii) minor allele frequency < 0.01 were excluded from the data, resulting in 607,469 autosomal SNPs in 8,527 European-ancestry individuals to be considered for further analysis. The data was then imputed to the Haplotype Reference Consortium (HRC) v1.1 European reference panel[21] and resulted in 39,127,657 variants. The detailed imputation and QC report is available separately[22, 23].

# Construction of Cognitive Capacity GPS

A set of cognitive ability-related GPSs were constructed based on four large-scale GWAS MTAG summary statistics on educational attainment (EA, n = 1,131,881), cognitive performance (CP, n = 257,841), self-reported math ability (MA, n = 564,698), and highest-level math class taken (HM, n = 430,445) from Lee et al[9]. GPS were calculated with PLINK 1.9[24] using the SNP weights adjusted for linkage disequilibrium using *LDpred* software[25]. All SNP weights were obtained from cognitive GWAS discovery samples that did not contain the WLS participants. The completed set of GPSs was available from the WLS website upon request[19].

Outcome Measures

# 1) Cognitive Phenotypes

The cognition of the participants was assessed longitudinally using various tasks and structured questionnaires throughout the survey period of 60 + years. Our analysis used the participants' cognition data from the four WLS survey rounds (taken in 1957, 1992–1994, 2003–2003, 2011). The WLS data included *IQ scores* of the participants from the Henmon-Nelson Test of Mental Ability with 90 items collected in their high school junior years in 1957, which measured general verbal, quantitative, and spatial knowledge[26–28], and their *high school class rank* percentile which is based on the mean grade taken throughout the high school courses. The years of education (*Educational attainment*) were calculated from the highest educational degree held by each participant at their middle age. We also included the cognition component of the Health Utilities Index 3 (*HUI3 cognition level*) which asked the subjects about their self-perceived cognitive status at the time of interview.

Beginning in 1992–1994, 10 types of cognitive tasks were systematically proposed to the subjects at three time points over a 18–19 year period; *Similarities* (administered at survey timepoint 1/2/3), *Letter*

*Fluency* (timepoint 2/3), *Category Fluency* (timepoint 2/3), *Immediate Recall* (timepoint 2/3), *Delayed Recall* (timepoint 2/3), *Digit Ordering* (timepoint 2,3), *Number Series* (timepoint 3), *Linguistic Function* (timepoint 3), including two health literacy assessment: *Newest Vital Sign (NVS) Health Literacy Assessment* (timepoint 3) and *Short Test of Functional Health Literacy in Adults (STOFHLA)* (timepoint 3). The phenotypes selected for phenome-wide analysis were marked as *italic* and their measurement criteria are available in the **Supplementary Material**. All the raw scores were z-scored for the analysis.

# 2) Behavioral Phenotypes

Personality traits of the participants were assessed with the Big 5 Factor Model of Personality inventory test[29] in the WLS 1992–1994 collection wave. The five personality traits are known as one of the most common and influential models in the field of personality research and to stay relatively stable over the lifetime. The Big 5 Factor Model of Personality test describes an individual's personality in terms of five basic dimensions: *Extraversion, Openness, Neuroticism, Conscientiousness, and Agreeableness*. A higher score on each scale indicates the person has higher tendencies and behaviors representing the personality.

Time spent on different types of social participations were asked to the subjects and self-reported in hours per week or year. We compared the participation time spent on various kinds of social activities including *reading, writing letters, watching movies/TV, light or vigorous physical activity(alone or together), doing crafts, hunting/fishing, playing a crossword puzzle/other word game*, or *attending cultural events*, etc. The description of each social participation type is provided in the **Supplementary Material**. To correct for outliers with extreme hours of certain activities, we took the natural logarithm of the reported hours for each activity and used for the analysis.

In addition, we included two occupational standing variables collected in the WLS 2003–2005 wave based on their current or last employment information. *Occupational Education Score* represented a numeric value to the types of industry or class-of-worker categories based on the 1990 US Census data, which indicates a percentage of persons who had at least a year of college education, ranging from 0 to 999. *Occupational Income Score* was from the 1990-basis occupational earning scores, which represent the percentage of persons in the 1990 US Census data in an industry or class-of-work category who earned more than $14.30/hour in 1989, ranging from 37 to 876.

As spouse IQ data of the participants were available, we also included the variable for the analysis, hypothesizing that the behavior of assortative mating is associated with the GPSs of cognitive abilities. Previous literature suggested the psychiatric hypothesis of assortative mating in academic achievements and IQ [30–34].

Statistical Analysis

# 1) Cognitive/Behavioral PheWAS

Linear regression was used to investigate the associations between the four types of cognitive capacity GPS (EA, CP, HM, MA) and the normalized variables of the cognitive and behavioral phenotypes. We adjusted for biological sex, age and the first 10 PCs of genetic ancestry and estimate each GPS' significance (p-value), effect size (β), 95% confidence interval (CI), and proportion of variance explained ($R^2$) for the target outcomes.

# 2) Cognitive changes

Among aforementioned cognitive assessments, we have selected 7 repetitive measures administered to the participants with an average 6.5-year interval and investigated its interaction effects with cognitive capacity GPSs as the participants aged: *Similarities*, *Letter Fluency*, *Category Fluency*, *Immediate Recall*, *Delayed Recall*, *Digit Ordering* and *HUI3 cognition level* (timepoint 2/3). Linear mixed-effects regressions were nested by individual ID and each survey round (random effect) and included the following fixed covariates in the analysis: age at the survey time point, biological sex, first 10 ancestrally-informative principal components(PC1-10) of genotype data and years of education. Bonferroni-correction was used to adjust for multiple testing and the scores were normalized except for an ordinal variable, *HUI3 cognition level*. We hypothesized that the contribution of genetic factors to cognitive phenotypes are associated with different degree of cognitive decline in certain cognitive domain. The analyses were performed in R 3.5.1 environment, and linear mixed-effect model was run with lme4 package[35].

## Results

# Participant Demographics

Our study included 8,511 European-ancestry individuals with DNA genotype data, behavioral questionnaire data and cognitive assessment data available, including 7 different cognitive ability tasks which were administered repetitively with an average 6.5-year interval (SD = 1.25 year). The average age of the study participants was 48.6 years at the time of the first round of cognitive assessment (WLS survey round 4, 1992–1994, SD = 15.4 years), 64.2 years at the second assessment (WLS survey round 5, 2003–2005, SD = 4.1 years), and 70.7 years at the time of the last assessment (WLS survey round 6, 2011, SD = 4.2 years). The sample was 51.8% female, 47.8% completed high school education or less than one year of college (number of years of education), 78.2% were born in Wisconsin, USA.

PheWAS of Cognitive GPSs in the Cognitive/Behavioral Phenome

# 1) Cognitive Phenotypes

Across all of the PheWAS results, *IQ score* showed the strongest associations with the four cognitive GPSs in terms of p-value and the increase proportion of variance explained (strongest with CP GPS, p-value = 7.74E-179, β = 1.42, 95% CI=(1.32, 1.51)) **(**Fig. 1, Table 1, **Supplementary Table 1)**. The variance of *IQ scores* explained by CP GPS was 10.4% (Adjusted $R^2$) whereas the baseline covariate model without GPS variable explained 0.8% of *IQ score* variance.

The years of *educational attainment* measure (strongest with EA GPS, p-value = 1.62E-129, β = 1.73, 95% CI=(1.59, 1.87)) and *high school class rank* (strongest with EA GPS, p-value = 3.07E-101, β = 1.86, 95% CI= (1.69, 2.02)) were also significantly associated with all of four cognitive GPSs, following *IQ score*. The variance of *high school class rank* explained by EA GPS was 17.1% (Adjusted $R^2$) whereas the baseline covariate model without GPS variable explained 9.2% of *high school class rank* variance.

Among the cognitive tasks, the *Similarities* task presented the strongest p-value significance and positive effect sizes with cognitive GPSs in all the three rounds (strongest between timepoint3 *Similarities* and EA GPS, p-value = 3.59E-74, β = 1.36, 95% CI=(1.22, 1.51)). Cognitive GPSs also showed robust associations with *Number Series* (strongest with HM GPS, p-value = 2.55E-78, β = 0.94, 95% CI=(0.85, 1.04)) and *Digit Ordering* tasks (strongest with CP GPS, p-value = 8.63E-41, β = 0.78, 95% CI=(0.67, 0.89)) across different types of cognitive GPS. Several cognitive tasks were also consistently and significantly associated across the cognitive GPSs with positive effect sizes, including *Letter Fluency* (strongest association between timpoint3 *Letter Fluency* and CP GPS, p-value = 5.01E-30, β = 0.61, 95% CI=(0.50, 0.71)), *Category Fluency* (strongest association between timpoint3 *Category Fluency* with EA GPS, p-value = 2.03E-18, β = 0.95, 95% CI=(0.74, 1.16)), *Immediate Recall* (strongest association between timpoint3 *Immediate Recall* with EA GPS, p-value = 5.29E-22, β = 0.80, 95% CI=(0.64, 0.96)), *Delayed Recall* (strongest association between timpoint3 *Delayed Recall* with CP GPS, p-value = 5.00E-15, β = 0.45, 95% CI=(0.34, 0.56)), *NVS Health Literacy assessments* (strongest with CP GPS, p-value = 2.28E-29, β = 0.92, 95% CI=(0.76, 1.07)), which indicates genetic contribution to cognitive abilities are positively correlated to higher cognitive scores of several assessments (Table 1).

# 2) Behavioral Phenotypes

Among the Big 5 Personality traits, all the four GPS associations of *Openness* (strongest with EA GPS, p-value = 2.19E-14, β = 0.57, 95% CI=(0.42, 0.71)) met phenome-wide significance with positive effect sizes. In addition to *Openness*, HM and MA GPSs presented significant associations with *Neuroticism* (strongest with MA GPS, p-value = 1.92E-06, β=-0.32, 95% CI=(-0.45, -0.19)), showing negative effect sizes.

Social participation of *reading* books, magazines, newspapers or other reading material (strongest with EA GPS, p-value = 2.03E-21, β = 0.50, 95% CI=(0.40, 0.60)) and *attending cultural events* (strongest with EA GPS, p-value = 2.06E-23, β = 0.60, 95% CI=(0.49, 0.72)) presented phenome-wide significant associations across the cognitive GPSs with positive directions. Notably, social participation of *watching TV watching TV* (strongest with EA GPS, p-value = 4.16E-18, β=-0.48, 95% CI=(-0.59, -0.37)) and *fishing/hunting* (strongest with EA GPS, p-value = 1.72E-11, β=-0.59, 95% CI=(-0.77, -0.42)) showed significant negative associations with all the cognitive GPSs. Other phenome-wide significant activities included *writing letters* (strongest with EA GPS, p-value = 2.28E-11, β = 0.32, 95% CI=(0.23, 0.41)), working on *crosswords or word games* (strongest with CP GPS, p-value = 1.27E-10, β = 0.39, 95% CI=(0.27, 0.51)), and *vigorous physical activities (alone)* (strongest with EA GPS, p-value = 7.39E-10, β = 0.61, 95% CI=(0.42, 0.80)) (Table 1, Fig. 1).

Occupational education scores (strongest with EA GPS, p-value = 4.77E-61, β = 1.22, 95% CI=(1.08, 0.36)) and occupational income scores (strongest with EA GPS, p-value = 3.50E-37, β = 0.90, 95% CI=(0.76, 1.03)) presented positive relationships across all the cognitive GPSs. The association of *Spouse IQ* did not reach the phenome-wide significance with any of the cognitive GPSs. Full PheWAS results of the phenome-wide significant associations are available in **Supplementary Table 1**.

# Cognitive GPSs correlate with the changes of Immediate Recall

Our linear mixed effect model identified the significant age-x-GPS interaction effect in the changes of *Immediate Recall* task with the participants' age. All four kinds of cognitive capacity GPS showed significant interaction effects with participants' age (Age:GPS) for the *Immediate Recall* test scores (strongest with EA GPS, p-value = 1.79E-03, β = 1.86E-01) **(**Table 2**)**. Their positive effect sizes suggest that an individual who has higher EA GPS tend to show less changes in cognitive assessments as an individual ages.

Compared to the individuals in the lowest GPS quartile (EA GPS mean=-0.480), individuals in the highest GPS quartile (EA GPS mean=-0.089) showed less decrease in Immediate Recall score changes in later survey rounds. Slope of participants' age in the lowest GPS quartile (β= -1.97E-01, 95% CI=(-0.231, -0.163), p-value of slope = 8.61E-31) distinctively showed more intense decrease compared to the highest GPS quartile group (β=-1.24E-01, 95% CI=(-0.158, -0.090), p-value of slope = 6.67E-13) **(**Fig. 2**(a)).** The pseudo-$R^2$ of our linear mixed models in explaining Immediate Recall by cognitive capacity GPS was up to 0.063 with fixed effects and 0.170 with both fixed and random effects (both with EA GPS).

To visually depict the degree of cognitive changes according to GPS, we divided the cohort into 4 quartiles based on the GPS of each individual and analyzed the average phenotypic changes of each group over time. The average Immediate Recall task scores of the individuals in the highest GPS quartile were 0.044 (z-score) at timepoint 2 (average age of participants 64.5), and increased to 0.073 (z-score) at timepoint 3 (average age 71.5) (1.65 fold increase). In contrast, the average task scores of the individuals in the lowest GPS quartile were − 0.031 (z-score) at timepoint 2 and decreased to -0.077 (z-score) at timepoint 3 (2.48 fold decrease) **(**Fig. 2**(b))**.

# Discussion

In this study, we assessed the genetic influences of general cognitive abilities on cognitive and behavioral phenome using a combinational approach of GPS-based PheWAS on longitudinal observations in the aging population. We hypothesized that the contribution of genetic factors to cognitive capacities are associated with certain cognitive or behavioral phenotypes, and even different degree of cognitive decline in certain cognitive domains.

Our study identified that the effect of the age-x-GPS interactions were significantly positive across all four cognitive capacity GPSs **(**Table 2**)**, and individuals with a higher cognitive GPS presented a slower

trajectory of memory decline than those with a lower GPS (Fig. 2(a)). This result indicates that the portions of cognitive ability under genetic influence may serve as a 'buffer' against memory decline in aging. These observations align well with existing studies on the protective effect of education and intelligence on the occurrence of dementia[36]. A close relationship between early-life education and intelligence with cognitive decline have been reported for dementia and AD[37]. Even though it is not yet clear how early-life education and intelligence moderate the risk for dementia, our findings suggest that individual variations of memory decline are closely associated with polygenic influences of cognitive abilities.

Among the repeated assessments of 7 cognitive domains with an average 6.5-year interval, a decline of *immediate memory recall* in aging significantly correlated with the cognitive GPS but not the other cognitive domains did. Memory recall, assessed by *immediate* and *delayed recall* tests of words, is hippocampus dependent[38–40]. We did not observe the significant interaction effect in the domain of delayed recall. It is interesting that the discovered genetic protective effect exerted specifically on the hippocampus-related immediate memory recall. There are two implications worth noting. Firstly, given the specificity of the correlations among various cognitive domains, the genetic protective factor of immediate memory decline may be mediated via the hippocampus. Indeed, the hippocampus is the primary mediator of interventions for the cognitive wellness or dementia, such as aerobic fitness[41], diet[42], and medication[43–45]. This is closely related to the unique role of the hippocampus in neurogenesis and synaptic plasticity[46, 47]. Future research should thus test whether the hippocampus and hippocampal network underlies the genetic projective effect on immediate memory decline, but not in delayed recall, and if so seek to elucidate the mechanisms involved. Secondly, given the role of the hippocampal memory impairment in the pathophysiology of Alzheimer's disease (AD), our finding may lead to the potential link of the inherited genetic factor of cognitive resilience to the individual differences in hippocampal degeneration, as well as memory decline in AD[48, 49]. Testing this link will allow better stratification of AD and monitoring the course of the disease by the individual-specific genetic profiles of cognitive resilience.

Our PheWAS identified several phenome-wide associations between cognitive capacity GPSs and cognitive assessments. The *Similarities* task from WAIS, *Number Series* task and *Digit Ordering* task showed strongest associations across the four cognitive capacity GPSs in terms of effect size (β) and p-value (Fig. 1, Fig. 1). These findings suggest that the cognitive components required to successfully complete the *Similarities*, *Number Series*, or *Digit Ordering* tasks might strongly overlap with genetic components of cognitive capacities primarily exhibited by the domain of fluid intelligence. We assume that the series of cognitive components involved in the *Similarities* and *Number series* tasks, such as logical memory, symbol search, and reasoning, might be closely linked to early-life cognition, all of which may serve as phenotypic indicators for fluid intelligence. Our findings are backed up by the previous knowledge that fluid intelligence is considered to be more dependent on biological influences and less dependent on past learning experiences than crystalized intelligence[50].

Our analysis identified several phenome-wide significant associations of cognitive capacity GPSs with several early-life cognitive phenotypes including *IQ scores, educational attainment*, or *high school class rank*. The significant genetic association between cognitive capacity and *IQ scores* or *educational attainment* has been well established in several GWAS studies on human intelligence[9, 13–16]. IQ scores of the WLS respondents were derived from the Henmon-Nelson test of mental ability, which is regarded as a general measure of overall intelligence, capturing both fluid and crystallized intelligence.

PheWAS of the behavioral phenome identified several behavioral traits having high relatedness to the genetic factors of cognitive capacity. All of the tested cognitive capacity GPSs positively correlated with *Openness* among the Big 5 Personality factors, and some GPSs negatively correlated with *Neuroticism* **(Supplementary Table 1).** The finding presents an interesting cross-trait hypothesis in which the variances of personality dimensions may be partially explained by genomic components of cognitive capacity, or vice versa. 'Openness' could be regarded as the attitude and tendency to explore, detect, understand, and appreciate complicated patterns of new information through both the senses and in the abstract[51]. Previous studies support our findings, concluding that an overall open-minded attitude might positively influence the long-term variances of cognitive abilities with willingness to explore [52].

No significant associations between Spouse IQ and cognitive abilities were identified, which indicates that the behavioral associations between assortative mating and cognitive abilities is unclear. In addition, a strong relationship between occupational income and several cognitive capacity GPS were found, which supports the existing studies on a strong association between general mental ability and job performance [53].

A few limitations of this study should be noted. The WLS had two time points for measuring changes in their cognitive assessments with an average 6.5 year interval. Adding more cognitive measurements through time will strengthen our findings by more thoroughly monitoring cognitive changes over the lifetime. Also, the unexplored impact of other sociodemographic variables such as socioeconomic status, educational environment, lifestyles, or family structure, should be considered to better connect our theorical findings with phenome-wide expression of cognitive abilities. In addition, we used European-ancestry specific summary statistics for constructing the cognitive capacity GPSs and applied them to participants with European-ancestry. Researchers should note that the translational application to non-European individuals could be different, and the results should be interpreted with caution. Future investigation is needed to elucidate heterogeneity between ancestry groups for the genetic underpinnings of cognitive abilities. Our findings could serve as the first cognitive-phenome map that describes the functional boundaries of human cognition from a genetic perspective, and the map could be further expanded with the advanced phenotyping of human cognition and behavior traits.

## Declarations

# Disclosures

The authors have no conflicts to declare.

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# Author Contributions

YYJ, JC, JF, and MGH designed the study; YYJ, JF, and MGH acquired genotype and/or phenotype data; YYJ performed statistical analyses; YYJ, JC, JF and MGH interpreted the results; YYJ and JC drafted the manuscript; YYJ, JC, JF, and MGH critically reviewed the manuscript; YYJ and MGH obtained the funding

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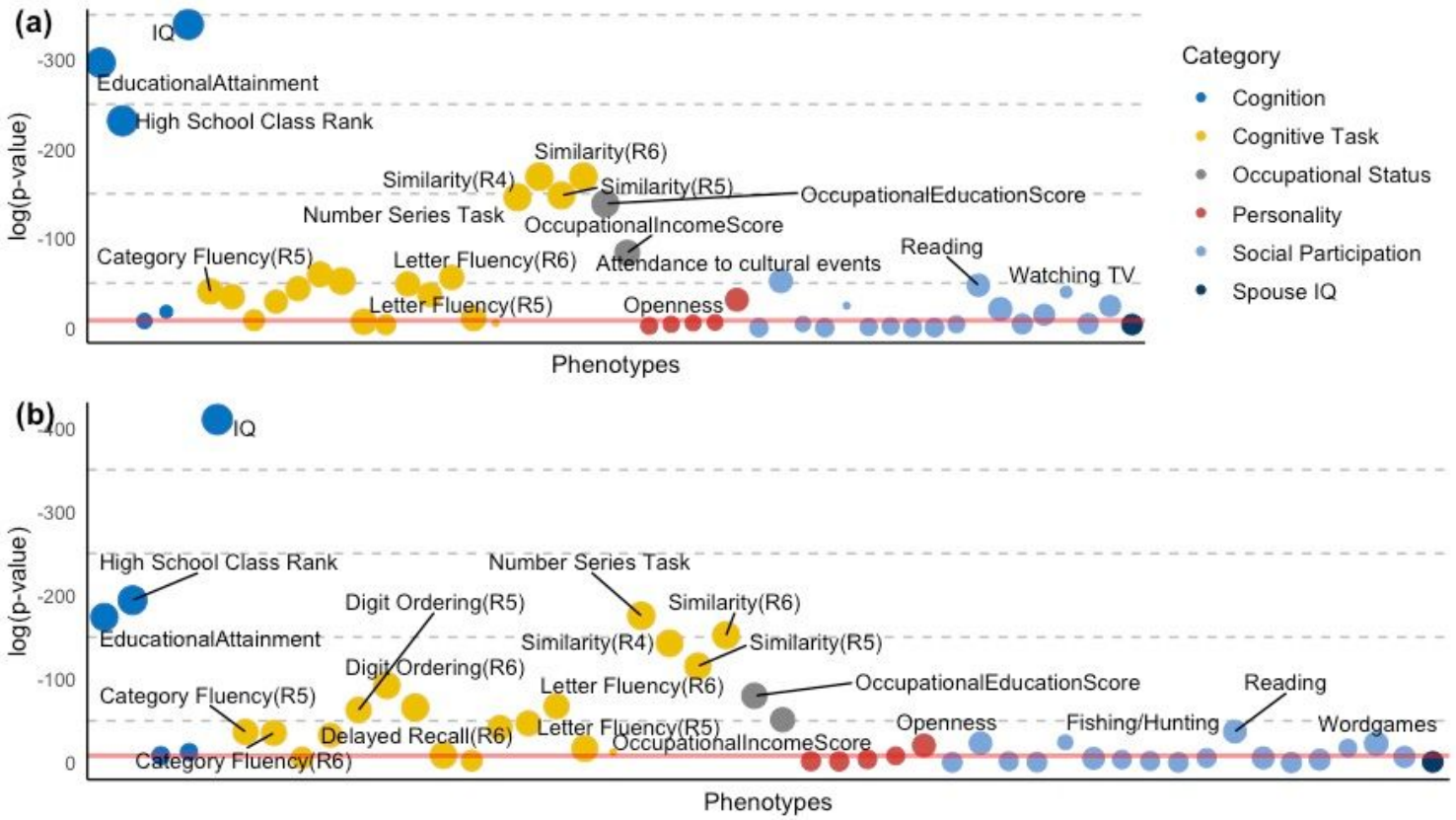
# Tables

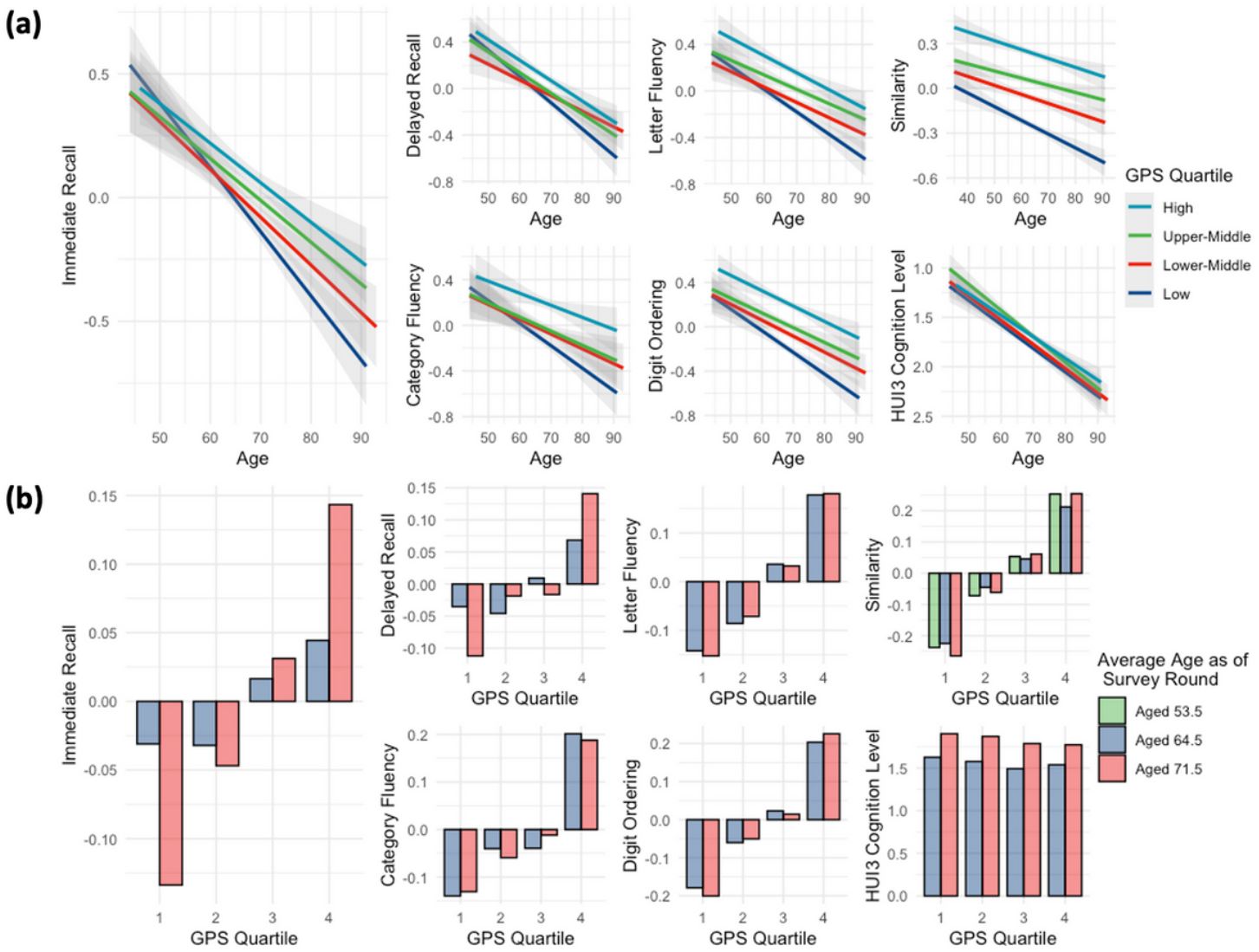
Tables 1 and 2 are available in the Supplementary Files.

# Figures




## Figure 1

PheWAS plots of (a) Educational attainment (EA), and (b) Cognitive Performance (CP) GPS in the cognitive/behavioral phenome of the WLS participants. The cognitive/behavioral phenotypes were presented on x-axis. The phenotype variables were retrieved from the WLS survey data, primarily from the cognition and social participation modules in 1957, 1992-1994, 2003-2005 and 2011 waves. The red line represents the phenome-wide significance level [ log10 of the Bonferroni corrected p-value for multiple testing corrections (alpha = 0.05 / (48 tested phenotypes * 4 GPS) = 2.60E-04). The size of each point is proportional to the effect size of each cognitive capacity GPS-phenotype association. (a) PheWAS plot of Educational Attainment (EA) GPS (b) PheWAS plot of Cognitive Performance (CP) GPS




## Figure 2

Graphical results of our linear mixed-effect model analysis showing that individuals with a higher cognitive GPS presented a slower trajectory of memory decline than those with a lower GPS. Changes in seven cognitive assessments (immediate recall task, category fluency task, digit ordering task, delayed recall task, letter fluency task, similarities task, and health utility index (HUI) level 3 cognition level) and interaction effects of CP GPS were shown. The selected seven cognitive assessments were repeatedly administered to 8,511 European ancestry individuals between the average age of mid-50s (survey timepoint 1) and mid-70s (survey timepoint 3). (a) Interaction plots showing the different slopes of age-dependent interaction effects by cognitive capacity GPS on the cognitive assessments. The X-axis indicates the age of the WLS participants at survey timepoint, while the y-axis indicates each cognitive assessment score (z-scored). The four lines indicates different slopes of individuals' cognitive changes stratified by GPS. The gray area represents 95% confidence interval of each slope. Similarities task were the only tasks that were repeatedly administered to the participants since timepoint 1 (Average participants' age 48.6). (b). Bar plots showing the stratification performance of cognitive capacity GPS in each cognitive assessment modules. Quartile 1 on the x-axis includes the individuals with lowest

cognitive GPS (bottom 25%) and Quartile 4 includes the individuals the individuals with the highest. The number on y-axis represented the average phenotypic scores by each GPS quartile.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- JooHayesWLSSupplementaryMaterialNPPfinal.docx
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