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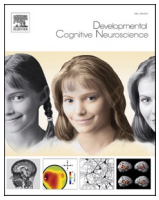

# Associations between behavioral and self-reported impulsivity, brain structure, and genetic influences in middle childhood

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ABSTRACT

Impulsivity undergoes a normative developmental trajectory from childhood to adulthood and is thought to be driven by maturation of brain structure. However, few large-scale studies have assessed associations between impulsivity, brain structure, and genetic susceptibility in children. In 9112 children ages 9–10 from the ABCD study, we explored relationships among impulsivity (UPPS-P impulsive behavior scale; delay discounting), brain structure (cortical thickness (CT), cortical volume (CV), and cortical area (CA)), and polygenic scores for externalizing behavior ($PGS_{EXT}$). Both higher UPPS-P total scores and more severe delay-discounting had widespread, low-magnitude associations with smaller CA in frontal and temporal regions. No associations were seen between impulsivity and CV or CT. Additionally, higher $PGS_{EXT}$ was associated with both higher UPPS-P scores and with smaller CA and CV in frontal and temporal regions, but in non-overlapping cortical regions, underscoring the complex interplay between genetics and brain structure in influencing impulsivity. These findings indicate that, within large-scale population data, CA is significantly yet weakly associated with each of these impulsivity measures and with polygenic risk for externalizing behaviors, but in distinct brain regions. Future work should longitudinally assess these associations through adolescence, and examine associated functional outcomes, such as future substance use and psychopathology.

## 1. Introduction

Impulsivity, frequently characterized as spontaneous actions without prior planning, manifests as a deficiency in self-regulation (Chamberlain and Sahakian, 2007) and is associated with significant mental health disorders, (Ioannidis et al., 2019) including addiction (Kirby and Petry, 2004; MacKillop et al., 2011; Mitchell, 1999). There are many definitions of impulsivity, ranging from comprehensive and multifaceted personality descriptions to more specific interpretations that emphasize objective metrics such as inhibitory control and response inhibition derived from neurocognitive assessments (Beauchaine et al., 2017)., where these assessments may correlate poorly within subject. Consequently, impulsivity is generally regarded as a multi-dimensional concept (Chamberlain et al., 2019; Dalley and Robbins, 2017).

Impulsivity undergoes a characteristic developmental trajectory from childhood to adolescence and into adulthood (Shulman et al., 2016). In early childhood, impulsivity is high, as children are learning to navigate their environment and regulate their behavior. Young children often act without thinking and have difficulty inhibiting impulses. By ages 6–12, in middle childhood, certain facets of impulsivity start to

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decline as cognitive control and self-regulation improves (Tervo-Clemmens et al., 2023a). Children generally become better at following rules, inhibiting impulsive actions, and considering consequences of their behavior (Olson et al., 1999). However, scores on sensation-seeking, risk preference, and reward sensitivity tend to increase from age 10 until mid-adolescence, and to decline thereafter (Steinberg, 2008). Thus, while impulsivity peaks in mid-adolescence, studying youth from immediately prior to this period is important to establish longitudinal trajectories of impulsive behavior. Peak sensation-seeking and risk-taking behavior is typically observed during mid-adolescence, roughly around the ages of 15–18 (Tervo-Clemmens et al., 2023b). The adolescent peak in impulsivity is thought to be related to ongoing development of the prefrontal cortex (PFC) (Casey et al., 2011). In early to middle childhood, the PFC experiences significant maturation in both gray matter and white matter, (Bethlehem et al., 2022; Larsen and Luna, 2018) as cognitive functions continue to improve (Demidenko et al., 2019). Subsequently, as adolescents transition into adulthood, normative declines in impulsive behavior are thought to be driven by maturation of the PFC, (Blakemore and Choudhury, 2006) and in fact, age-related improvement in cognitive control is linked with cortical thinning in children (Kharitonova et al., 2013).

Brain structure can be indexed using measures of cortical area (CA), cortical thickness (CT), and cortical volume (CV), all of which can provide unique clues about how the brain is developing over time. CA refers to the total surface area of the cerebral cortex (e.g., a two-dimensional measure and represents the extent of the cortex's outer surface), while CT refers to the distance between the pial surface (outer layer) and the white matter surface (inner layer) of the cerebral cortex (e.g., three-dimensional measure that provides insight into the thickness of the cortical mantle). CV is a measure combining cortical thickness and surface area, reflecting the overall size of brain regions. During brain development, the cortex undergoes expansion in surface area through processes like gyrification and folding, while CT changes primarily due to migration of neurons to form cortical layers and subsequent synaptic pruning (Gilmore et al., 2018). Thus, in early development, CA, CV and CT may show a positive correlation, but as the brain matures during adolescence, CT decreases while CA and CV continue to increase (Giedd et al., 1999). Few developmental studies have comprehensively related all three measures to neurobehavioral phenotypes.

The prefrontal cortex has been extensively studied as a candidate region for understanding the relationships between morphometry and impulsive traits. In foundational studies, patients with lesions of the ventromedial PFC opted for choices that yielded immediate gains in spite of higher future losses (Bechara et al., 1994). Since then, researchers have been interested in whether features of PFC structure could be a biomarker for impulsive behavior. Structural MRI studies have examined whether gray matter morphometry is linked to impulsivity through techniques like voxel-based (Matsuo et al., 2009) and surface-based morphometry (Hirjak et al., 2017; Holmes et al., 2016). In particular, the PFC, anterior cingulate cortex (ACC), and amygdala have been identified as neural substrates underlying impulse control, (Bechara, 2005) with lesion studies consistently demonstrating that damage to these regions is linked to the inability to control impulses (Bechara, 2005; Berlin and Hollander, 2014). However, although lesion studies show clear directionality, in that lesions cause increased impulsivity, the directionality of associations between normative variations in brain structure and impulsivity is not clear. In adults, increased impulsivity is often associated with decreased CT in PFC regions, (Holmes et al., 2016; Bernhardt et al., 2014; Bjork et al., 2009; Schilling et al., 2012; Tu et al., 2017) but some studies have indicated correlations between impulsivity and larger brain regions, (Cho et al., 2013) and others have shown inconsistent patterns (Grodin et al., 2017; Muhlert and Lawrence, 2015; Wang et al., 2017). Discrepancies may be attributed to differences in sample characteristics, behavioral assessments, imaging techniques, and statistical analyses, (Lai et al., 2019) as well as small sample sizes (Consideration of Sample Size in Neuroscience Studies, 2020).

A critical question in developmental neuroscience is to what extent impulsivity and its parallel brain development are genetically driven during this critical period. Data from twin and adoption studies have demonstrated that impulsivity is heritable, (Bezdjian et al., 2011) but to date, there have been few clear genetic factors associated with impulsivity. Recently, a genome wide association study (GWAS) of 1.5 million people identified genetic associations with traits related to a latent dimension of externalizing liability, (Karlsson Linner et al., 2021) which is linked with impulsivity. Externalizing liability is a component of a larger constellation of phenotypic traits related to externalizing, or outward-directed, behaviors that are often disruptive (e.g., rule-breaking, impulsivity, hyperactively, aggression) (Beauchaine et al., 2017). Thus, to further understand the etiology of impulsive behavior, we assessed potential genetic elements that may be driving a potential association between brain structure and impulsive behavior (Sanchez-Roige et al., 2018).

In the current study, we assessed the relationship between brain structure, impulsivity, and genetic predisposition in the Adolescent Brain Cognitive Development (ABCD) study, the largest longitudinal brain development study in the U.S. ABCD enrolled nearly 12,000 children at ages 9–10 for prospective biennial 3 T MRI scans through adolescence (Barch et al., 2018). Here, we analyze baseline scans obtained at age 9–10, and measures of impulsivity obtained at baseline and year 1 follow-up. For each participant, a polygenic score for a latent dimension of externalizing liability ($PGS_{EXT}$) was calculated to serve as an index of genetic risk for impulsivity (Karlsson Linner et al., 2021). We analyzed two complementary measures of impulsivity: a delay discounting task, which assessed the degree to which a hypothetical reward's subjective value diminishes as the interval to its delivery is increased, (Ainslie, 1975) and self-reported trait impulsivity, measured from the Urgency, Premeditation, Perseverance, Sensation Seeking Impulsive Behavior Scale (UPPS) (Whiteside and Lynam, 2001). For each of these measures of impulsivity, we examined associations, after controlling for demographic, socioeconomic, and technical factors, with all three indices of brain structure: CV, CA, and CT, and for associations with $PGS_{EXT}$. We hypothesized (1) significant associations between frontal brain structures and impulsivity measures, (2) a significant association between impulsivity measures (UPPS-P and delay discounting) and $PGS_{EXT}$, indicating a genetic contribution to impulsivity and self-regulation, and (3) significant associations between $PGS_{EXT}$ and frontal brain regions. As an exploratory aim, we also sought to examine whether any significant relationships between $PGS_{EXT}$ and impulsivity traits were mediated by genetically regulated morphological features in frontal lobe gray matter (Eyler et al., 2011; Opel et al., 2020).

### 1.1. Participants

Analyses here used data from the ABCD study, a longitudinal study of 11,875 participants aged 9–10 years from 22 sites across United States (Barch et al., 2018). Data were obtained from the NIMH Data Archive (NDA), Curated Annual Release 4.0. In brief, 9- to 10-year-old children were recruited from the community, had no contraindications to MRI scanning, and were excluded if they were not fluent in English; had a history of major neurological disorders, traumatic brain injury, or extreme prematurity; or carried a diagnosis of schizophrenia, moderate to severe autism spectrum disorder, intellectual disability, or substance use disorder. Further details of inclusion and exclusion are described elsewhere (Jernigan et al., 2018; Karcher et al., 2018). Most ABCD research sites ceded Institutional Review Board (IRB) approval to a central IRB at the University of California, San Diego, with the remainder obtaining local IRB approval. All parents provided written informed consent and all youth provided assent. Detailed procedures are described in Auchter et al (Auchter et al., 2018).

### 1.2. Assessment of impulsivity

Impulsivity was assessed using the delayed discounting task and the UPPS-P total score. Delay discounting was not available at baseline but was obtained at the 1-year follow-up visit. The delay discounting task required participants to make 42 choices between immediate reward and a $100 hypothetical reward given later (Casey et al., 2018). These include 7 random blocks having 6 choices of time points for reward (6hr, 1 day, 1 week, 1 month, 3 months, 1 year, 5 year). We fit indifference points at each delay interval to a hyperbolic curve, (Mazur, 2013) to yield K value estimates, wherein higher k values corresponded to steeper decay in subjective reward value with delay to delivery, then log transformed due to highly skewed k values (Kohler et al., 2022). The analysis presented here used all participants with delay discounting data (n = 9112). As a sensitivity analysis, we restricted this analysis only to participants whose data passed validity checks for identifying nonsystematic data as suggested by Johnson and Bickel (Johnson and Bickel, 2008)(n = 5893).

The UPPS-P scale was administered at baseline and at Year 2 as a self-report measure of impulsivity. To reduce comparisons, we calculated a UPPS-P Total score at each time point as a total score consisting of the sum of the subscales from Lack of Perseverance, Lack of Premeditation, Negative Urgency, Positive Urgency, and Sensation seeking. We assessed associations between brain structure at baseline with UPPS-P at both baseline and at the Year 2 timepoint.

### 1.3. Assessment of brain structure

Structural MRI (sMRI) scans were obtained from participants on 3 T Siemens, Philips or GE magnets (Casey et al., 2018). We downloaded tabulated minimally processed data from the NDA study for bioRxiv (*Study ID #1944, doi 10.15154/1528507*), which included 11,875 participants with brain regions of interest (ROI), estimated intracranial volumes, (Ducharme et al., 2016) surface hole numbers (SHN), and manual quality control (MQC) (Ducharme et al., 2016). We assessed 34 regions from the right and 34 regions from the left hemisphere within each domain (volume, area, cortical thickness) based on the Desikan-Killiany atlas (Desikan et al., 2006). Based on recent data indicating that variable imaging quality data can affect results, (Ducharme et al., 2016) we used a combination of automated MQC (manual quality control) ratings as well as surface hole numbers (SHN) to exclude poor-quality scans, as higher SHN have predicted worse manual quality control ratings in previous MRI studies and have been proposed as an automated quality control index for use in high-throughput neuroimaging studies. We excluded scans with either 'process failed,' signal dropouts, unusable or presence of large cysts, or with SHN >=62. MQC ratings of either 1 (Requiring minimal edits), 2 (Requiring moderate edits) or 3 (Requiring substantial edits) were included, and SHN was used as covariate.

### 1.4. Assessment of externalizing polygenic scores ($PGS_{EXT}$)

The genome-wide genotype data for ABCD participants were downloaded from the NDA, comprising 733,292 single nucleotide polymorphisms (SNPs) genotyped using the Affymetrix NIDA SmokeScreen Array. We applied standard quality control (QC) procedures as previously described (Lee et al., 2019). Ancestry information was determined through principal component analysis with the 1000 Genomes Project samples. We conducted imputation using the Michigan Imputation Server (v1.5.7) with minimac (v4–1.0.2) and the Haplotype Reference Consortium panel. Haplotype phasing was conducted using eagle (v2.4) with $r^2$ filtering of 0.8. Imputed SNPs after QC yielded a total of 6960, 459 SNPs. The summary statistics of externalizing behaviors were obtained from the latest Externalizing Consortium GWAS, (Karlsson Linner et al., 2021) which utilized multivariate analyses of 1.5 million individuals to identify genetic variants associated with underlying genetic liability shared across behaviors and disorders related to impulse control. All individuals analyzed in the GWAS were of European descent. To mitigate potential confounding due to population stratification, (Hellwege et al., 2017) we generated $PGS_{EXT}$ for 4361, 1362, and 1679 ABCD participants of European, African, and Hispanic American ancestries separately using PRS-CS (v1.1) (Ge et al., 2019). The Bayesian gamma-gamma priors were set to 1 and 0.5. Global shrinkage parameter φ was learned from the data using a Bayesian approach, which suits well for highly polygenic traits with large GWAS sample size. Monte Carlo iterations were set to 1000, with 500 burn-in iterations. Linkage disequilibrium (LD) reference panels were constructed using the 1000 Genomes Project phase 3 samples, adjusting weights of SNPs accounting for LD structure. To adjust for residual within-population stratification, $PGS_{EXT}$ were regressed using the first ten genetic ancestry principal components generated within each ancestry group and were standardized.

### 1.5. Statistical analysis

To ensure replicability of findings, we divided the data in half, using ABCD Reproducible Matched Samples (ARMS), (Feczko et al., 2021) wherein participants in the two samples were matched on nine demographic characteristics (age, site, sex, ethnicity, grade, parental education history, handedness, combined family income and exposure to anesthesia). We performed all analyses using ABCD ARMS-1 (Discovery) and ABCD ARMS-2 (Validation) samples, along with the total (Complete) sample. Linear mixed effect (*lmer*) models were performed for each of 68 brain regions, wherein area (CA), volume (CV) and thickness (CT) were predictors of impulsivity measures (UPPS-P and Delayed Discounting) at baseline. We adjusted for demographics (age, sex, and race-ethnicity), estimated total intracranial volume and SHN. The model also included random effects of site, family id (to control for sibling relationships), and scanner manufacturer, as per ABCD recommendations (Hagler et al., 2019). All the variables in the model were z transformed. For each sMRI phenotype (area, volume, and cortical thickness), we examined 68 regions and 2 impulsivity outcome variables within each dataset (Discovery, Validation, Complete). Therefore, p values were corrected for multiple comparisons within each MRI domain for the three datasets using Benjamini and Hochberg (FDR) method (Benjamini and Hochberg, 1995). Statistical analysis was performed using R (*v 4.2.2*). To maximize the statistical power of the ABCD study by taking advantage of the entirety of the sample and, we report FDR-corrected p values for only the complete dataset. Original (unadjusted) p values are presented for all regions in Tables S1-S13.

For $PGS_{EXT}$ analysis, we calculated the phenotypic variance in impulsivity measures (UPPS-P total and delay discounting k scores) explained by the PGS using $\Delta R^2$ by comparing two linear mixed effects models (*lmer* in *R v.4.2.2*) within each ancestry (European, African, Hispanic American). In the PGS model, $PGS_{EXT}$ was used as an independent variable (predictor), along with each of the impulsivity measures as a dependent variable (outcome). The model included age and sex as covariates (fixed effects) and site as random effects as described above, except we omitted family id because only independent (non-related) participants were included. In the null model, only covariates were used as independent variables. The $\Delta R^2$ was then calculated as the difference of the $R^2$(full model) and $R^2$(null model). The statistical significance of $\Delta R^2$ was calculated using the likelihood ratio test (*lrtest*). Fixed effects meta-analysis of three ancestries was conducted using Inverse variance-weighted average method (*metafor)*. All p values reported in the text are FDR corrected for multiple comparisons.

We also conducted a second PGS model, where $PGS_{EXT}$ was used as a predictor, along with each of the brain regions as the outcome. This model included age, sex, estimated total intracranial volume and SHN as covariates (fixed effects) and scanner manufacturer, site as random effects. Similarly, we calculated the phenotypic variance in brain regions explained by the PGS using $\Delta R^2$ by comparing two linear mixed effects

within each ancestry and the statistical significance of $\Delta R^2$ was calculated using a likelihood ratio test. We performed fixed effects meta-analyses of three ancestries and corrected p values (FDR) for multiple comparisons.

## 2. Results

### 2.1. Participants

The ABCD 4.0 release included 11,572 participants (Discovery and Validation) at baseline. Overall, 2460 participants were excluded from full data for the following reasons: from Site 22 (Mount Sinai, NY) (N= 21) and Site 888 (N=1), due to low count as compared to other sites; presence of cyst >1 $cm^3$ in scans (N= 725); unusable scans, signal dropouts, sans flagged for clinical consultations, unavailability of T1 scans, or failed scan process and with SHN (surface hole number) threshold of 62 or more (N= 1713). Of these excluded scans, 1236 participants were from the Discovery dataset and 1224 participants were from Validation dataset. See Table 1 for a description of included participants, and Fig S1 for a flow chart of excluded participants.

### 2.2. Associations between brain structures and impulsivity

#### 2.2.1. Delay discounting

More severe delay discounting (larger log-transformed k values) was associated with smaller CA in left rostral middle frontal region ($\beta = -0.05$, $p = 0.02$); bilateral middle temporal regions (left: $\beta = -0.05$, $p = 0.02$; right: $\beta = -0.05$, $p = 0.02$), and bilateral superior temporal regions (left: $\beta = -0.04$, $p = 0.04$; right: $\beta = -0.05$, $p = 0.02$) (Figs. 1 A and 2). No significant associations were seen with CV or CT, though generally, greater impulsivity was consistently associated with smaller CV and larger CT (Tables S1-S3, Figs. S2-S3, S9-S10). In a sensitivity analysis of only those participants whose data passed validity checks for identifying nonsystematic data (Johnson and Bickel, 2008)(n = 5893), no additional regions became significant. The associations between larger k values and smaller CA in left rostral middle frontal region, bilateral middle temporal regions, and right superior temporal regions remained significant; however the association between larger k values and smaller CA in the left superior temporal gyrus was no longer significant ($\beta = -0.03$, $p = 0.09$).

**Table 1**
Demographic characteristics.

| | Complete (n = 9112) | Discovery (n= 4550) | Validation (n = 4562) |
|---|---|---|---|
| Measure | Mean (SD) or N (%) | | |
| **Age** | 9.9 (0.6) | 9.9 (0.6) | 9.9 (0.6) |
| **Sex** | | | |
| Female | 4654 (51.1%) | 2354 (51.7%) | 2300 (50.4%) |
| Male | 4453 (48.9%) | 2193 (48.2%) | 2260 (49.5%) |
| NA | 5 (0.1%) | 3 (0.1%) | 2 (0.04%) |
| **Race ethnicity** | | | |
| Hispanic | 1796 (19.7%) | 910 (20.0%) | 886 19.4%) |
| White | 4849 (53.2%) | 2420 (53.2%) | 2429 (53.2%) |
| Black | 1313 (14.4%) | 651 (14.3%) | 662 (14.5%) |
| Asian | 184 (2.0%) | 93 (2.0%) | 91 (2.0%) |
| Not listed | 959 (10.5%) | 471 (10.4%) | 488 (10.7%) |
| NA | 11 (0.1%) | 5 (0.1%) | 6 (0.1%) |
| **Parental Income** | | | |
| Less than $50k | 2404 (26.4%) | 1188 (26.1%) | 1216 (26.7%) |
| $50k through $99,999 | 2397 (26.3%) | 1207 (26.5%) | 1190 (26.1%) |
| $100k or greater | 3546 (38.9%) | 1757 (38.6%) | 1789 (39.2%) |
| NA | 765 (8.4%) | 398 (8.7%) | 367 (8.0%) |
| **Parental marital status** | | | |
| Living with partner | 513 (5.6%) | 246 (5.4%) | 267 (5.9%) |
| Married | 5930 (65.1%) | 2977 (65.4%) | 2953 (64.7%) |
| Never Married | 911 (10.0%) | 450 (9.9%) | 461 (10.1%) |
| Widowed/Divorced/ Separated | 1212 (13.3%) | 604 (13.3%) | 608 (13.3%) |
| NA | 546 (6.0%) | 273 (6.0%) | 273 (6.0%) |
| **Scanner Manufacturer** | | | |
| GE Medical Systems | 2275 (25.0%) | 1120 (24.6%) | 1155 (25.3%) |
| Philips Medical Systems | 1099 (12.1%) | 555 (12.2%) | 544 (11.9%) |
| Siemens | 5725 (62.8%) | 2869 (63.1%) | 2856 (62.6%) |
| NA | 13 (0.1%) | 6 (0.1%) | 7 (0.2%) |
| **SHN (Surface hole number)** | 27.5 (12.0) | 27.4 (11.9) | 27.6 (12.1) |
| **UPPS-P scale Total score** | 40.9(7.7) | 40.9(7.7) | 41.0(7.7) |
| **Log of Delay Discounting** | -2.1(3.3) | -2.1(3.3) | -2.1(3.3) |

#### 2.2.2. Baseline UPPS-P

As expected, total UPPS-P score and delay discounting measures were positively correlated, though low in magnitude (Pearson's $r = 0.050$, $p < 0.01$). Generally, smaller CA predicted higher UPPS-P scores (Figs. 1 A and 2). In the left hemisphere, greater scores were associated with smaller CA in the cuneus ($\beta = -0.03$, $p < 0.05$), middle temporal ($\beta = -0.04$, $p = 0.03$) and insula regions ($\beta = -0.04$, $p < 0.05$); in the right hemisphere, with banks of superior temporal sulcus ($\beta = -0.04$, $p = 0.03$), caudal middle frontal ($\beta$ =-0.04, $p = 0.02$), and frontal pole regions ($\beta = -0.04$, $p = 0.03$); and bilaterally in postcentral (left: $\beta = -0.04$, $p < 0.05$; $\beta = -0.04$ $p = 0.04$), precentral (left: $\beta = -0.04$,$p = 0.02$; right: $\beta = -0.04$ p= 0.03), rostral middle frontal (left: $\beta = -0.05$, $p < 0.05$; right: $\beta = -0.04$ p= 0.03), superior frontal (left: $\beta = -0.04$, $p = 0.04$; right: $\beta = -0.04$ p= 0.03), and superior temporal (left: $\beta = -0.06$, $p = 0.01$; right: $\beta = -0.04$ $p = 0.03$) regions (Figs. 1 B and 2). Smaller CVs in these regions also predicted greater UPPS-P scores (Fig S4), however, no correlations between impulsivity and parcel CV survived multiple comparison corrections. No associations were seen with CT, though generally, larger CT trended toward greater impulsivity (Figs. S5, S8-S10).

#### 2.2.3. Year 2 UPPS-P

Associations of Year 2 UPPS-P and baseline brain structures were similar in direction and magnitude to the UPPS-P at baseline, with smaller CA predicting higher Year 2 UPPS-P scores. In the left hemisphere, greater scores were associated with smaller CA in the transverse temporal gyrus ($\beta = -0.03$, p =0.04), superior frontal gyrus ($\beta = -0.05$ $p = 0.01$), rostral middle frontal regions ($\beta = -0.06$, $p = 0.004$), precentral gyrus ($\beta = -0.05$, $p = 0.01$), paracentral gyrus ($\beta = -0.04$, $p < 0.05$), and lateral occipital regions ($\beta = -0.04$, $p < 0.05$); in the right hemisphere, with posterior cingulate ($\beta = -0.04$, $p = 0.04$), caudal middle frontal ($\beta$ =-0.05, $p = 0.01$), and caudal anterior cingulate regions ($\beta = -0.03$, $p = 0.04$); and bilaterally in superior temporal (left: $\beta = -0.05$, $p = 0.01$; right: $\beta = -0.05$ $p = 0.01$) and precentral gyrus (left: $\beta = -0.05$, p =0.01; $\beta = -0.06$ $p = 0.006$). Smaller CVs in these regions also predicted greater UPPS-P Year 2 scores (Figs. S7, S9-S10), however, no correlations between impulsivity and CV survived multiple comparison corrections. No associations were seen with CT, though generally, as with baseline measures, larger CT trended toward greater impulsivity (Figs. S8-S10).

### 2.3. Externalizing polygenic scores ($PGS_{EXT}$) are associated with impulsivity and brain structure

#### 2.3.1. Delay discounting

Meta-analysis across three ancestries confirmed that greater $PGS_{EXT}$ was significantly associated with increased impulsivity measured by delay discounting in the complete dataset ($\beta_{\text{meta-analyzed}} = 0.028$, $p$ =.036). However, there were no significant associations between $PGS_{EXT}$ and delay discounting within ancestry-specific datasets (Tables S7-S10).

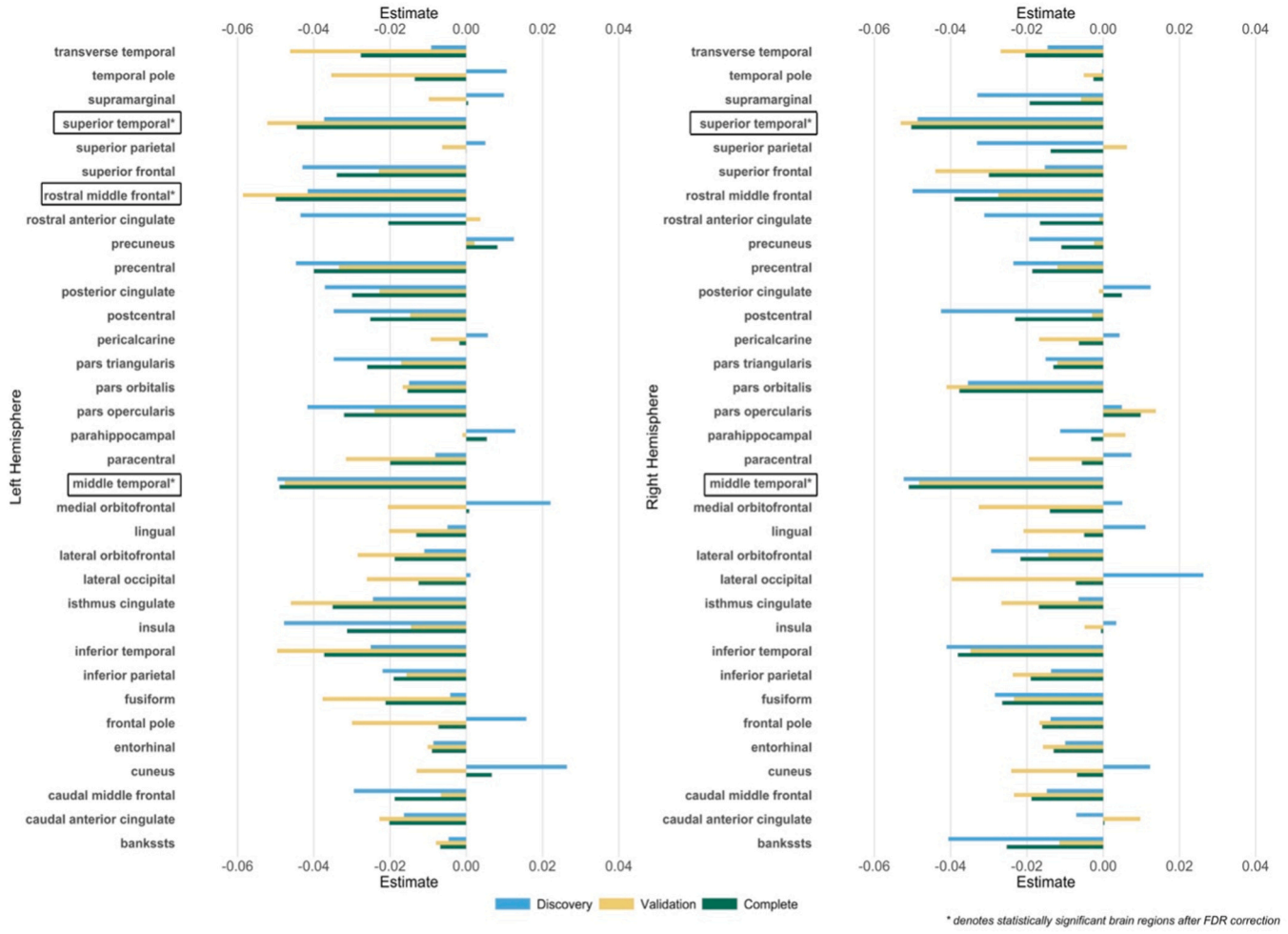


**Fig. 1. A.** Associations between Baseline Cortical Areas and Year 1 Delay Discounting. Asterisk indicates significance after FDR correction for multiple comparisons. In each plot, the effect size, defined as the standardized regression coefficient, is shown for each brain region. Estimates for Discovery (blue), Validation (yellow), and Complete (green) datasets are shown. **B**. Associations between Baseline Cortical Areas and Baseline Total UPPS-P score. **Forest Plots of Associations between Baseline Cortical Areas and Baseline UPPS-P Total Scores.** Asterisk indicates significance after FDR correction for multiple comparisons. In each plot, the effect size, defined as the standardized regression coefficient, is shown for each brain region. Please note, when correcting for twin status, the left postcentral gyrus and left cuneus regions no longer passed FDR correction for significance. Estimates for Discovery (blue), Validation (yellow), and Complete (green) datasets are shown.

#### 2.3.2. *UPPS-P*

Meta-analysis across three ancestries confirmed that greater $PGS_{EXT}$ was significantly associated with increased UPPS-P score in all datasets ($\beta_{\text{meta-analyzed}} = 0.095 - 0.099$, $p < 0.001$) (Table 2; Fig. 3). Ancestry-specific results indicated that significant associations were primarily driven by participants of European ancestry ($\beta = 0.102 - 0.137$, $p < 0.001$). $PGS_{EXT}$ explained 1.1–1.9% of variability in UPPS-P score within this group (Log likelihood ratio p-value <0.05 within European ancestry). No individually significant associations were seen for participants of African ancestries.

Fig. 3. Associations between Polygenic Scores for Externalizing Liability ($PGS_{EXT}$) and UPPS-P and Delay Discounting Scores across Complete, Discovery, and Validation Datasets

#### 2.3.3. *$PGS_{EXT}$ and brain structure*

Meta-analysis across three ancestries confirmed that greater $PGS_{EXT}$ was significantly associated with smaller CA in right hemisphere (lateral orbitofrontal ($\beta_{\text{meta-analyzed}} = -0.03$, $p = .004$), and paracentral regions ($\beta_{\text{meta-analyzed}} = -0.05$, $p = 0.002$)), and with smaller CV in left hemisphere (rostral anterior cingulate ($\beta_{\text{meta-analyzed}} = -0.04$, $p = 0.025$)). Greater $PGS_{EXT}$ was also significantly associated with smaller CV in the right hemisphere (inferior temporal ($\beta_{\text{meta-analyzed}} = -0.03$, $p = 0.04$), lateral orbitofrontal ($\beta_{\text{meta-analyzed}} = -0.04$, $p = 0.02$), and paracentral regions ($\beta_{\text{meta-analyzed}} = -0.04$, $p = 0.03$)). See Table 3 for a summary of significant findings across analyses.

#### 2.3.4. *Mediation of $PGS_{EXT}$ relationship with impulsivity by brain morphology*

Because brain regions with morphology that correlated with $PGS_{EXT}$ were distinct from brain regions found to be associated with impulsivity; therefore, a mediation analysis could not be conducted.

## 3. Discussion

This study investigated associations among impulsivity, measured by delay discounting and the UPPS-P self-report scale, and indices of brain structure after controlling for overall brain size, including CT, CV, and CA, and polygenic scores in a large sample of children from the ABCD study. Findings showed that higher self-reported impulsivity, indexed by the UPPS-P, was related to smaller CA throughout brain regions involved in cognitive control, sensory processing, motor function, emotional regulation, and social behavior. Delay discounting was also associated with smaller CAs, though in fewer regions. These associations were generally widespread yet small in magnitude. Finally, findings revealed

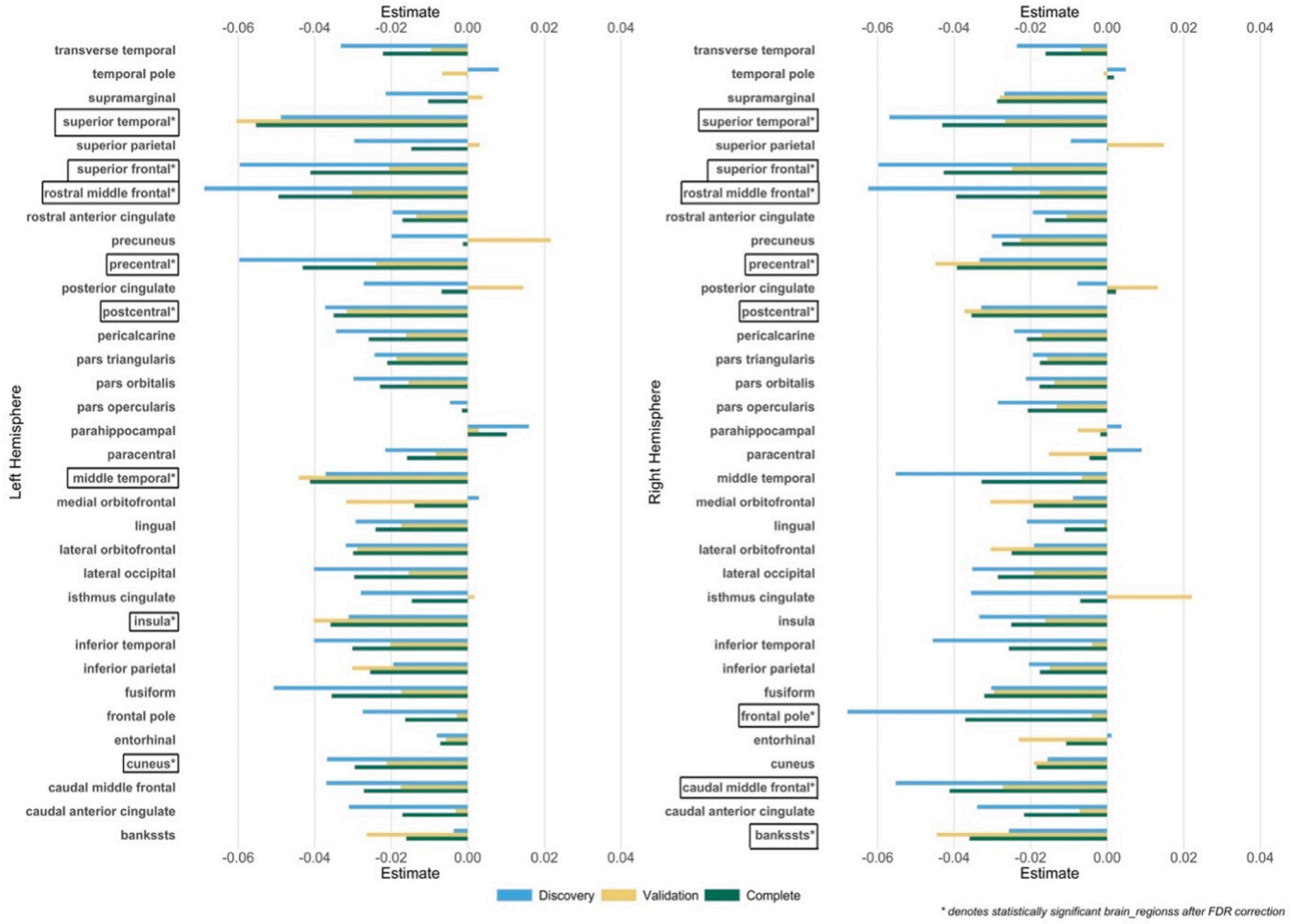


**Fig. 1.** (*continued*).

a significant genetic association between externalizing polygenic scores ($PGS_{EXT}$) and UPPS-P scores, and likewise, associations between $PGS_{EXT}$ and smaller CA and CV, in related yet distinct regions. Findings suggest that $PGS_{EXT}$ could influence the growth, maturation, and functional organization of these brain regions during critical developmental periods, though further research is needed to understand how these genetic predispositions translate into observed developmental outcomes.

### 3.1. Brain structures and impulsivity

Our investigation into the UPPS-P revealed that smaller CA in several frontal regions (frontal pole, rostral and caudal middle frontal, superior frontal gyrus and precentral gyrus) were associated with impulsivity, supporting our hypotheses of the importance of frontal lobe structures in impulsive behavior, and extending this association into middle childhood. Delay discounting showed similar results, though generally with smaller effect sizes. Likewise, smaller CV, and greater CT, were generally related to greater impulsivity, although none survived multiple comparison corrections.

The opposite associations between impulsivity and each of CA/CV versus CT are not surprising. As the brain matures during adolescence, CT decreases due to synaptic pruning while CA and CV continue to increase (Giedd et al., 1999). Thus, increases in impulsivity may be associated with a more 'immature' neurobiological state. Because we controlled for age in our analyses, data indicate that children who are more impulsive have a less mature developmental profile than less impulsive peers. Though many individual associations were not statistically significant, the overall pattern of greater CT and smaller CA and CV was highly consistent across measures and brain regions, particularly for the UPPS-P.

These results are consistent with other developmental studies. Impulsivity has shown a robust connection with attention-deficit/hyperactivity disorder, a condition associated with both increased impulsivity and by morphological variations in regions of the prefrontal cortex and other cortical areas (Nakao et al., 2011; Valera et al., 2007). A large study of adolescents, age 14 (n = 1620), reported reduced volume of the OFC in those with greater impulsivity (Schilling et al., 2013a) (though a study in the same sample also reported that elevated impulsivity correlated with reduced CT in the superior frontal cortex, (Schilling et al., 2013b) indicating that associations between impulsivity and CT may change across adolescence). Further, our CA/CV findings were supported by a large meta-analysis of 30 (mostly adult) studies of brain structure (gray matter volume) and trait impulsivity, (Pan et al., 2021) which found that impulsivity was negatively correlated with regional GMV proportional to total brain size in four clusters, including the left middle frontal and left superior temporal regions, regions implicated in our analyses.

In addition to hypothesized frontal regions, we also found that reduced CA in temporal regions (middle temporal gyrus, banks of the superior temporal sulcus, and superior temporal gyrus), in addition to the postcentral gyrus, insula, and cuneus, were associated with increased impulsivity measured by the UPPS-P. These regions are involved in various processes, such as sensory input and language, social perception, auditory and visual processing, sensory, and emotional responses, (Casey et al., 2008) suggesting broader neural basis for impulsivity beyond the frontal regions of the brain. While speculative,

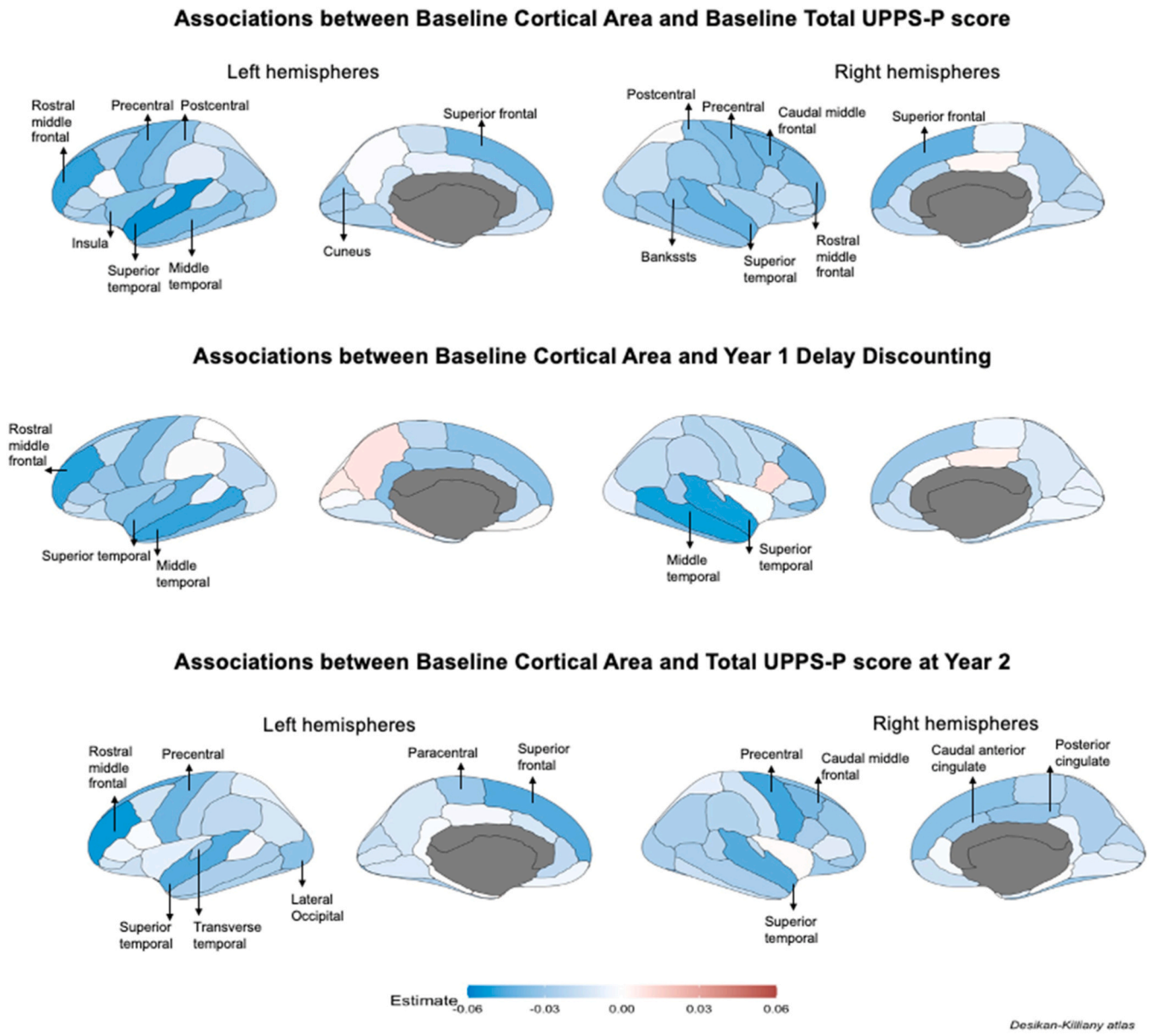


**Fig. 2.** Estimates of associations between CA and indices of impulsivity (delay discounting k and UPPS-P at baseline and Year 2) for the complete dataset, plotted on the Desikan-Killiany brain atlas. The color gradient (ranging from blue to red) across the maps indicates strength of this association, with blue likely indicating a negative association and red indicating a positive association. Significant cortical areas after multiple comparison correction are labeled in the left and right hemisphere from the complete dataset.

one account for this positive relationship between impulsivity and sensory structures would be in the greater "stimulus-driven" behavior (including auditory) (Bubl et al., 2015) clinically described in persons with ADHD-like tendencies. The widespread but small reductions in CA associated with impulsivity also provide evidence to support recent work with multivariate prediction models that aggregate the small effects across the cortex and produce a summary score of behavioral prediction, (Byington et al., 2023) in order to discover brain-phenotype associations that may be widespread rather than regionally specific.

### 3.2. Polygenic scores for externalizing and impulsivity

We observed significant associations between $PGS_{EXT}$ and trait impulsivity as assessed using the UPPS-P scale, particularly in individuals of European and Hispanic-American ancestry. The consistency of these associations across the Complete, Discovery, and Validation datasets underscores the robustness of these findings. The positive beta values indicate that a higher genetic risk for externalizing traits correlates with increased impulsivity scores, explaining a significant yet modest amount of variability in impulsivity across datasets. The absence of significant associations among participants from African ancestral backgrounds is not surprising, given that the Externalizing Consortium GWAS used to generate $PGS_{EXT}$ consisted of European individuals and highlights the importance of obtaining more diverse samples in GWAS studies to further our understanding of genetic contributors to complex traits and behaviors. We note that the race/ethnicity of the participants in the ABCD study explicitly mirrors that of the U.S., (Compton et al., 2019) indicating that the limitations were likely due to limitations in the GWAS analysis. Further research is warranted to understand mediating mechanisms that underpin the genetic contribution to impulsivity, as well as to increase diversity in genomics studies to ensure the generalizability of genetic associations across populations.

We note that our genetic analyses indicate that the UPPS-P self-report scale shows a stronger association than the delay discounting task

**Table 2**
Associations Between Externalizing Polygenic Scores and UPPS-P Across Ancestries.

| Data | Genetic Ancestry | Estimate | SE | P value | P value (FDR corrected) | R2 full model (%) | R2 null model (%) | Delta R2 (%) | P value (LRT) |
|---|---|---|---|---|---|---|---|---|---|
| Complete | European | 0.120 | 0.017 | <0.001 | | 4.367 | 2.898 | 1.470 | <0.001 |
| | African | 0.029 | 0.033 | 0.383 | | 2.219 | 2.147 | 0.073 | 0.382 |
| | Hispanic American | 0.083 | 0.028 | 0.004 | | 3.110 | 2.449 | 0.660 | 0.004 |
| | **Meta-analyzed** | **0.098** | **0.013** | **<0.001** | **<0.001** | | | | |
| Discovery | European | 0.137 | 0.024 | <0.001 | | 5.211 | 3.313 | 1.898 | <0.001 |
| | African | -0.001 | 0.047 | 0.988 | | 2.832 | 2.837 | -0.006 | 0.998 |
| | Hispanic American | 0.041 | 0.040 | 0.308 | | 2.859 | 2.706 | 0.154 | 0.309 |
| | **Meta-analyzed** | **0.095** | **0.019** | **<0.001** | **<0.001** | | | | |
| Validation | European | 0.102 | 0.023 | <0.001 | | 3.627 | 2.546 | 1.081 | <0.001 |
| | African | 0.053 | 0.048 | 0.271 | | 1.883 | 1.637 | 0.245 | 0.266 |
| | Hispanic American | 0.122 | 0.040 | 0.002 | | 3.534 | 2.066 | 1.467 | 0.002 |
| | **Meta-analyzed** | **0.099** | **0.019** | **<0.001** | **<0.001** | | | | |

Complete, discovery, and validation datasets across European, African, and Hispanic American genetic ancestries. Estimate (standardized beta), Standard Error (SE), P value (unadjusted), P value (FDR corrected: adjusted P value with False Discovery Rate), P value (LRT: likelihood ratio test), R2 full model (%): variability explained by PGS and covariates, R2 null model (%): variability explained by covariates, Delta R2 (%): R2 (full model) - R2 (null model) variability explained by PGS.

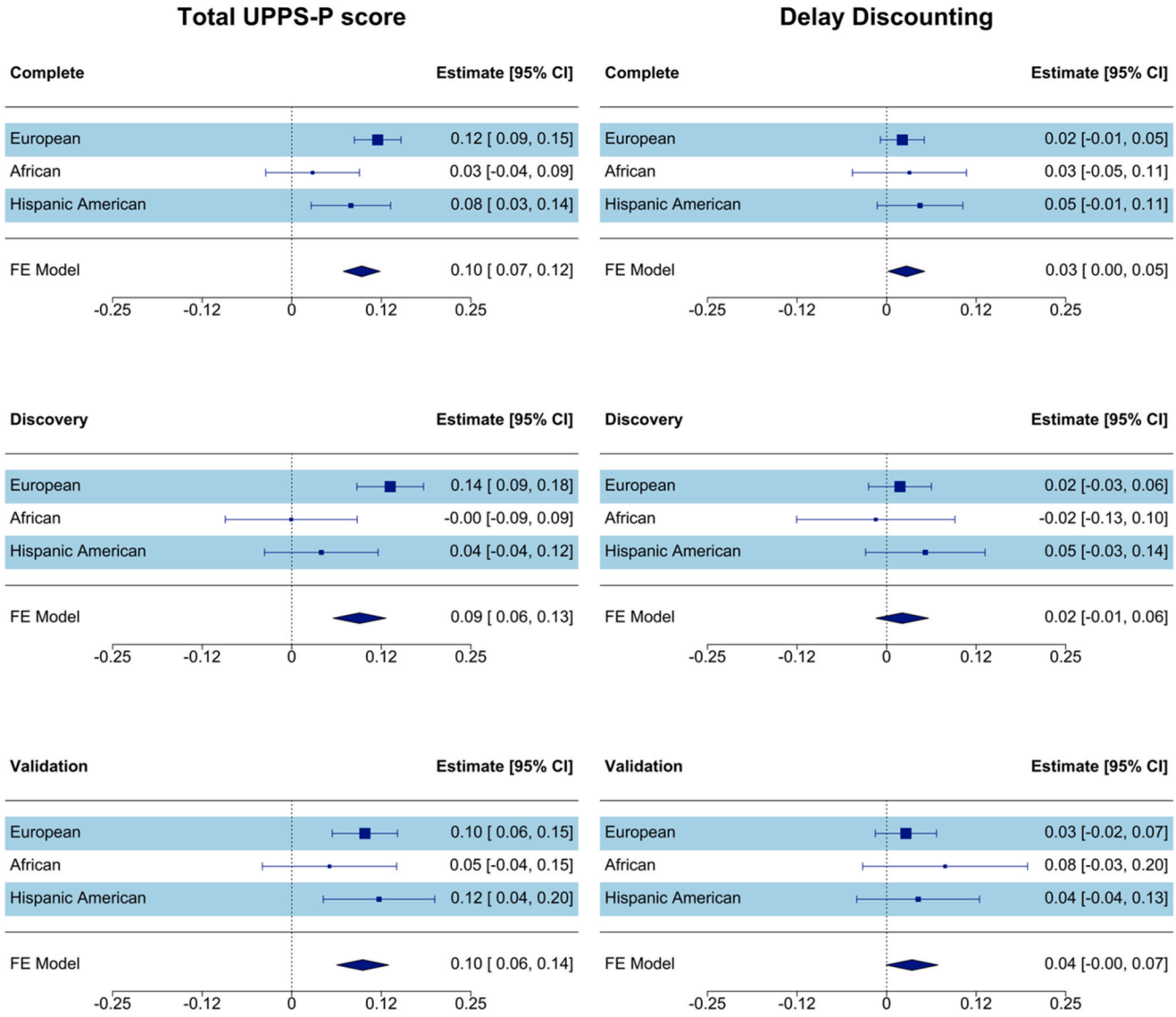


**Fig. 3.** Each plot includes estimates for European, African, and Hispanic American populations. For each group, the plots show an estimate point and a 95% Confidence Interval (CI). FE Model indicates a Fixed Effects model. Horizontal lines represent the confidence intervals, with the square indicating the estimate's point value.

**Table 3**
Summary of Brain Regions Significantly Associated with Delay Discounting, UPPS-P, and Polygenic Score for Externalizing Liability ($PGS_{EXT}$).

| | DELAY DISCOUNTING | | | UPPS-P | | | $PGS_{EXT}$ | | |
|---|---|---|---|---|---|---|---|---|---|
| Lobe | *Region* | *HEM.* | *MEAS.* | *Region* | *HEM.* | *MEAS.* | *Region* | *HEM.* | *MEAS.* |
| FRONTAL | Rostral Middle Frontal | L | CA | Rostral Middle Frontal | L,R | CA | Lateral Orbitofrontal | R | CA, CV |
| | | | | Superior Frontal | L,R | CA | Rostral Anterior Cingulate | L | CV |
| | | | | Precentral Gyrus | L,R | CA | | | |
| | | | | Caudal Middle Frontal | R | CA | | | |
| | | | | Frontal Pole | R | CA | | | |
| TEMPORAL | Middle Temporal Gyrus | L,R | CA | Middle Temporal Gyrus | L | CA | Inferior Temporal Gyrus | R | CV |
| | Superior Temporal Gyrus | L,R | CA | Superior Temporal Gyrus | L,R | CA | | | |
| | | | | Superior Temporal Sulcus | R | CA | | | |
| PARIETAL | | | | Postcentral Gyrus | L,R | CA | Paracentral Gyrus | R | CA, CV |
| SUBCORTICAL | | | | Insula | L | CA | | | |
| OCCIPITAL | | | | Cuneus | L | CA | | | |

HEM, hemisphere; MEAS, measure; L, left, R, right; CA, cortical area; CV, cortical volume. All significant measures indicated that greater measures of impulsivity (by delay discounting, UPPS-P or greater PGS scores) were associated with smaller CA or CV.

with $PGS_{EXT}$. It is possible that in middle childhood, a self-report scale like UPPS-P may be a more robust measure of impulsivity than delay discounting for hypothetical monetary rewards, which may be a confusing task to some children. The current pattern of results may likewise reflect previous reports suggesting low correspondence between laboratory and self-reported impulsivity and/or differential reliability among the measures, where self-report measures may have higher reliability (Cyders and Coskunpinar, 2011). Moreover, research has indicated that trait-like capture of neurobehavioral tendencies from psychometric instruments can show greater relationships with real-world psychosocial outcomes than laboratory performance impulsivity measures (Barkley and Murphy, 2010). Future studies can continue to measure these associations as children enter adolescence, to determine whether delay discounting is more predictive of biological measures in older children and adolescents.

### 3.3. Polygenic scores for externalizing and brain structure

This study provides evidence that PGS is significantly associated with brain structure in children. Specifically, higher genetic susceptibility to externalizing behaviors ($PGS_{EXT}$) were associated with smaller areas and volumes in the lateral orbitofrontal cortex, paracentral regions, rostral anterior cingulate, and inferior temporal regions, which are involved in functions such as decision-making, emotional regulation, and cognitive processing (Casey et al., 2008). Our findings offer insights into how genetic factors might influence brain structure across vital developmental stages. Contrary to our initial hypotheses, the brain features that correlated with $PGS_{EXT}$ were in parcels distinct from those whose morphology correlated with impulsivity. This precluded our planned mediation analysis, suggesting that the relationship between $PGS_{EXT}$ and impulsivity may not operate through morphological brain development detectable by conventional structural MRI. Furthermore, it is important to recognize that polygenic scores for externalizing behaviors reflect a broad spectrum of phenotypic traits, including but not limited to impulsivity. These externalizing traits, often characterized by disruptive, outward-directed behaviors, may explain the differentiation in brain regions associated with the polygenic scores and impulsivity measures. As more precisely defined PGS for impulsivity become available, future research should examine the nuanced relationships between genetics, brain structures and impulsivity. Additionally, exploring brain function through functional MRI in relation to $PGS_{EXT}$ and impulsivity may unveil whether impulsivity is mediated by genetic influences on neurotransmitter function (Forbes et al., 2009) or other mechanisms not observable in gross brain morphology. More broadly, diverging patterns between narrow band impulsivity-defined phenotypes (e.g., delay discounting, UPPS-P) and externalizing genetic risk emphasize the complex and likely multi-faceted nature of impulsivity neurobiology.

### 3.4. Conclusions

This study has notable strengths, including a large sample size, adjustments for covariates in demographics and neuroimaging quality metrics, and the inclusion of different indices of brain structure (CA, CV, CT). This report also adds rigor to the literature, in investigating the effect sizes in both discovery and validation datasets. This study also has limitations, including analyses of structural data only one time point, and the focus on only two measures of impulsivity. Further, we note that most associations in this report were significant only in the complete dataset, but not in the discovery or validation datasets, though effect sizes were similar in all. Future studies may benefit from integrating longitudinal timepoints of scans, incorporating functional neuroimaging data, and exploring subsets of children with different characteristics (e.g., those with psychopathology). Future work could assess these associations into adolescence and adulthood, capturing more advanced stages of brain development, and assess how structural differences map onto functional outcomes.

In conclusion, findings indicate that brain structure, notably CA, is associated with impulsivity in middle childhood, with higher scores relating to smaller areas in a widespread network of brain regions critical for decision-making, emotional regulation, and cognitive processing. Findings also indicate that $PGS_{EXT}$ is a predictor of trait impulsivity in the ABCD sample, particularly when measured with the UPPS-P self-report scale, and influences brain structure in frontal and temporal regions. However, morphology in brain regions correlating with $PGS_{EXT}$ were distinct from those correlating with impulsivity measures, perhaps reflecting the multidimensional nature of externalizing disorders. Overall, consistent with other ABCD brain data findings, (Dick et al., 2021) associations amongst measures in this study were small. This reflects complexity in neurobehavioral conceptualizations of impulsivity and also underscores the importance of large samples to discover meaningful brain-behavior relationships in heterogeneous cohorts such as ABCD (Marek et al., 2022). That is, the analyses here test for associations in population data, with a broad and more inclusive sampling frame than targeted clinical cohorts. As such, the results from the current work should be interpreted from the perspective of developing psychiatric neuroimaging tools towards clinical prediction in population data (Tervo-Clemmens et al., 2023c). It is possible that larger effect sizes would be present with refined phenotypes and careful consideration of particularly high-risk cohorts, and thus, parallel studies with targeted longitudinal cohorts and refined phenotyping may improve effect sizes, and are also critically important towards a comprehensive understanding of neuroimaging correlates of impulsivity.

## Data Availability

Data used in this manuscript were obtained from the Adolescent

Brain and Cognitive Development (ABCD; https://abcdstudy.org) study and can be found in the National Institute of Mental Health Data Archive. Data access can be obtained through a request at the following link https://nda.nih.gov/abcd/request-access. Data use certification was obtained for this study.

Code for analyses is available at https://gitlab.partners.org/jk1330/abcd_impulsivity/-/tree/main/Brain%20regions%20project/Final%20Scripts/Complete_Discovery_Validation_age_sex_scanner_Scripts?ref_type=heads

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## CRediT authorship contribution statement

**Jodi Gilman:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Methodology, Conceptualization. **Phil H. Lee:** Writing – review & editing, Validation, Data curation, Conceptualization. **Joshua L. Roffman:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Brandon T. Sanzo:** Writing – review & editing, Methodology, Formal analysis. **Kevin Potter:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Brenden Tervo-Clemmens:** Writing – review & editing, Validation, Supervision, Resources, Conceptualization. **Jasmeen Kaur:** Writing – review & editing, Visualization, Methodology, Formal analysis. **Randi M. Schuster:** Writing – review & editing. **A. Eden Evins:** Writing – review & editing, Conceptualization. **James M. Bjork:** Writing – review & editing, Supervision.

## Declaration of Competing Interest

All authors declare no competing interests.

## Data availability

Data and code are shared in the manuscript file.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2024.101389.

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