Dual-systems models of the genetic architecture of impulsive personality traits: neurogenetic evidence of distinct but related factors

Alex P. Miller[1] 🆔 and Ian R. Gizer[2] 🆔

[1]Department of Psychiatry, School of Medicine, Washington University in St. Louis, St. Louis, MO, USA and
[2]Department of Psychological Sciences, University of Missouri, Columbia, MO, USA

Abstract

Background. Dual-systems models, positing an interaction between two distinct and competing systems (i.e. top-down self-control, and bottom-up reward- or emotion-based drive), provide a parsimonious framework for investigating the interplay between cortical and subcortical brain regions relevant to impulsive personality traits (IPTs) and their associations with psychopathology. Despite recent developments in multivariate analysis of genome-wide association studies (GWAS), molecular genetic investigations of these models have not been conducted.
Methods. Using IPT GWAS, we conducted confirmatory genomic structural equation models (GenomicSEM) to empirically evaluate dual-systems models of the genetic architecture of IPTs. Genetic correlations between dual-systems factors and relevant cortical and subcortical neuroimaging phenotypes (regional/structural volume, cortical surface area, cortical thickness) were estimated and compared.
Results. GenomicSEM dual-systems models underscored important sources of shared and unique genetic variance between top-down and bottom-up constructs. Specifically, a dual-systems genomic model consisting of sensation seeking and lack of self-control factors demonstrated distinct but related sources of genetic influences ($r_g = 0.60$). Genetic correlation analyses provided evidence of differential associations between dual-systems factors and cortical neuroimaging phenotypes (e.g. lack of self-control negatively associated with cortical thickness, sensation seeking positively associated with cortical surface area). No significant associations were observed with subcortical phenotypes.
Conclusions. Dual-systems models of the genetic architecture of IPTs tested were consistent with study hypotheses, but associations with relevant neuroimaging phenotypes were mixed (e.g. no associations with subcortical volumes). Findings demonstrate the utility of dual-systems models for studying IPT genetic influences, but also highlight potential limitations as a framework for interpreting IPTs as endophenotypes for psychopathology.

Research has shown that impulsive personality traits (IPTs) confer transdiagnostic risk for psychopathology with an important role in disorders of the externalizing spectrum (e.g. substance use disorders, conduct disorder, antisocial personality disorder; Creswell, Wright, Flory, Skrzynski, & Manuck, 2019; Johnson, Carver, & Joormann, 2013). Broadly, IPTs are characterized by lack of self-control and forethought of behavioral consequences in response to more temporally salient external stimuli or internal impulses (Whiteside & Lynam, 2001). Twin and genome-wide association studies (GWAS) have demonstrated that IPTs are heritable, though estimates vary across specific traits under study (Bezdjian, Baker, & Tuvblad, 2011; Friedman et al., 2020; Sanchez-Roige et al., 2019). Neuroimaging studies also suggest heterogeneity in the neural correlates of IPTs but support a general pattern of differential brain morphology with cortical regions involved in cognitive control and attention (orbitofrontal cortex), subcortical regions involved in reward- and emotion-processing (ventral striatum, amygdala), and connections between these regions relevant to both (mesocorticolimbic and frontostriatal pathways; Johnson, Elliott, & Carver, 2020; Pan *et al.*, 2021).

In aggregate, the described studies support the hypothesis that IPTs may serve as useful endophenotypes for externalizing psychopathology (Cyders, Coskunpinar, & VanderVeen, 2016; Jonas & Markon, 2014). The endophenotype approach argues that studying genetic influences underlying intermediate constructs that confer risk for a manifest disorder may help identify shared neurobiological and genetic factors underlying that disorder (Hall & Smoller, 2010). Conceptualizations of IPTs, however, exhibit substantial heterogeneity, that while meaningful, contributes to a lack of clarity regarding relations between IPTs and clinical presentations (Strickland & Johnson, 2021). Similarly, the indiscriminate use of

multidimensional IPTs as endophenotypes in genetic studies may hamper the ability to identify causal loci. To address this, we argue that molecular genetic investigations of IPT models rooted in developmental and neurobiological frameworks, such as dual-systems models (Shulman et al., 2016b), can be used to develop, evaluate, and refine conceptualizations of IPTs as endophenotypes for psychopathology.

Dual-systems models posit that impulsive behaviors are the result of two complementary neurobiological systems associated with distinct neural substrates acting in dynamic tension to influence behavior: (1) a bottom-up system, involving activation of subcortical regions (ventral striatum, amygdala) involved in reward (e.g. sensation seeking) and/or emotion-based drive (e.g. urgency), and (2) a top-down system, involving activation of prefrontal cortical regions (PFC; orbitofrontal cortex) involved in effortful control and forethought (e.g. self-control; Carver & Johnson, 2018; Shulman et al., 2016b). Notably, dual-systems models align empirical neurocognitive observations with developmental theory (Steinberg et al., 2008). The transition from adolescence to adulthood is characterized by a developmental 'spike' in risky, impulsive behaviors driven by rapid increases in sensitivity to reward and affective salience (sensation seeking, urgency; Lopez-Vergara, Spillane, Merrill, & Jackson, 2016; Shulman, Harden, Chein, & Steinberg, 2016a) paired with relatively slower maturation of PFC regions that govern inhibition, planning, and self-control.

Post-GWAS investigations of dual-systems models can provide novel empirical support for these models and assessment of their constituent constructs and potentially aid in their refinement. Further, parsing genetic liability for increased bottom-up approach behaviors or lack of top-down cognitive control has the potential to identify unique risk pathways to psychopathology consistent with the endophenotype approach. Nonetheless, behavior genetic studies conducted to date suggest this may be difficult as prior twin research examining genetic influences for distinct top-down and bottom-up IPTs have indicated overlap between the two systems resulting from shared genetic factors (Ellingson et al., 2018; Ellingson, Vergés, Littlefield, Martin, & Slutske, 2013; Hur & Bouchard, 1997). Though not explicitly testing dual-systems models, recent GWAS have shown that traits putatively characterizing top-down lack of self-control (lack of premeditation, non-planning impulsivity) are highly genetically correlated with each other and uncorrelated with putative bottom-up reward-based traits (sensation seeking; Gustavson et al., 2020; Sanchez-Roige et al., 2019). IPTs also demonstrate variability in their genetic correlations with other traits and disorders. For instance, emotion-based IPTs (urgency) show stronger genetic correlations with internalizing psychopathology (Gustavson et al., 2020), while lack of self-control traits show stronger genetic correlations with externalizing psychopathology (Linnér et al., 2021; Sanchez-Roige et al., 2019).

Heterogeneity in genetic correlations across IPTs can be difficult to interpret in the absence of strong theoretical models. Dual-systems models provide a potential framework for interpreting such results, but there is a lack of research attempting to validate these models and corresponding measures at the genetic level by examining their hypothesized relations to distinct neuroanatomical variation. Recent advances in modeling of GWAS summary statistics allow for theory-driven examinations of the interrelations among genetic influences on psychological traits as well as their genetic relations with hypothesized neural correlates to examine support for existing theories such as dual-systems models.

The aims of the present study were two-fold. First, the study aimed to leverage extant IPT GWAS and an advanced multivariate GWAS approach (GenomicSEM; Grotzinger et al., 2019) to quantify and parse sources of unique and shared variance associated with dual-systems constructs. Separable factors of two distinct bottom-up constructs and a single top-down construct were hypothesized and empirically evaluated: (1) a reward-based bottom-up factor (sensation seeking), (2) an emotion-based bottom-up factor (urgency), and (3) a common top-down factor (lack of self-control). Second, the study aimed to distinguish between neurogenetic influences related to top-down and bottom-up constructs by examining genetic correlations with neuroimaging phenotypes. While these analyses were comparatively exploratory in nature, it was expected that dual-systems constructs would exhibit separable but overlapping genetic associations with brain regions implicated by previous phenotypic research and theory: lack of self-control with PFC regions, sensation seeking and urgency with subcortical regions involved in reward- and emotion-processing, respectively. Though previous GWAS research has examined differences in correlations between IPTs and other relevant behavioral phenotypes, including psychological disorders (Linnér et al., 2019; 2021; Sanchez-Roige et al., 2019), examinations of shared genetic architecture between IPTs and neuroanatomical features are conspicuously absent from both twin and GWAS literatures.

Methods

Table 1 contains descriptions of GWAS summary statistics for all phenotypes used. Summary statistics were restricted to individuals of European ancestry and common variants (minor allele frequency [MAF] > 0.01). See online Supplementary Methods for descriptions of genotyping, imputation, quality control, meta-analytic procedures, and additional measurement information for GWAS.

Impulsive personality trait GWAS

GWAS IPT phenotypes were primarily measured using the brief version of the UPPS-P (Cyders, Littlefield, Coffey, & Karyadi, 2014b), the BIS-11 (Patton, Stanford, & Barratt, 1995), and Cloninger's Temperament and Character Inventory (TCI; Cloninger, Przybeck, Svrakic, and Wetzel, 1994). Summary statistics were obtained from three primary sources: UK Biobank (UKB; risk-taking, Linnér et al., 2019), direct-to-consumer genetics company 23andMe, Inc. (Sunnyvale, CA; BIS-11, UPPS-P, risk-taking, and adventurousness; Linnér et al., 2019; Sanchez-Roige et al., 2019), and a meta-analytic sample comprised of four European-ancestry cohorts (TCI harm avoidance and novelty seeking; Service et al., 2012).

A priori hypotheses regarding appropriate phenotype structure for dual-systems models, given available GWAS data and prior phenotypic research, led to specification of two separate two-factor confirmatory genomic structural models. The first model, referred to as the sensation seeking-self-control (SSSC) model, consisted of a bottom-up 'sensation seeking' factor indexing genetic influences for reward-based drive, and a top-down '(lack of) self-control' factor indexing genetic influences for low self-control, lack of planning, and lack of forethought (see Fig. 1a). The second model, referred to as the urgency-self-control (UGSC) model, consisted of a bottom-up 'urgency' factor indexing genetic influences for emotion-based rash action, and the

Table 1. Overview of GWAS used in study

GWAS phenotypes	GWAS sample size	Number of SNPs (MAF > 0.01)	Sample/cohort
Impulsive personality traits			
Top-Down Self-Control			
BIS-11 total score	21 505	9 021 109	23andMe[1]
UPPS-P lack of premeditation	22 774	9 010 312	23andMe[1]
TCI novelty seeking	11 612	6 172 768	NFBC + YFS + HBCS + QIMR[2]
Bottom-Up Sensation-Seeking			
Adventurousness	557 928	9 151 591	23andMe[3]
Risk-taking	490 873	9 520 439	23andMe + UKB + 10 rep. samples[3]
UPPS-P sensation seeking	22 745	9 006 418	23andMe[1]
Bottom-up urgency			
UPPS-P negative urgency	22 795	9 006 418	23andMe[1]
UPPS-P positive urgency	22 738	9 006 418	23andMe[1]
TCI harm avoidance	11 597	6 175 142	NFBC + YFS + HBCS + QIMR[2]
Neuroimaging			
Cortical volume			UKB[4]
31 right + 31 left hemisphere regions	31 968	9 279 434	
Cortical surface area and thickness			ENIGMA + UKB[5]
Surface area (34 regions)	33 992	8 376 876	
Thickness (34 regions)	33 992	8 357 547	
Sub-cortical Volume			CHARGE + ENIGMA + UKB[6]
Nucleus accumbens	28 697	7 563 415	
Amygdala	30 142	7 066 805	
Brainstem	24 945	7 049 063	
Caudate nucleus	30 153	6 778 919	
Globus pallidus	30 124	7 601 584	
Putamen	29 984	6 785 509	
Thalamus	30 175	7 609 352	

Note: MAF, minor allele frequency; BIS-11, Barratt Impulsiveness Scale; UPPS-P, UPPS-P Impulsive Behavior Scale; TCI, Temperament and Character Inventory; NFBS, Northern Finland Birth Cohort; YFS, Cardiovascular Risk in Young Finns Study; HBCS, Helsinki Birth Cohort Study; QIMR, Australian Twin Registry; UKB, UK Biobank; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; ENIGMA, Enhancing Neuro Imaging Genetics Through Meta-Analysis Consortium.
Publications: 1. Sanchez-Roige et al. (2019), 2. Service et al. (2012), 3. Linnér et al. (2019), 4. Smith et al. (2021), 5. Grasby et al. (2020), and 6. Satizabal et al. (2019).

same top-down '(lack of) self-control' factor (see Fig. 1b). Notably, a model containing all three factors (correlated three-factor model) failed to converge. GWAS indicator selection and rationale are described below for each factor.

Lack of self-control

BIS-11 total score, UPPS-P lack of premeditation, and TCI novelty seeking GWAS were specified as indicators of the top-down (lack of) self-control factor. The first two indicators were selected given prior research suggesting that BIS-11 subscales demonstrate inadequate psychometric properties (Morean et al., 2014; Reise, Moore, Sabb, Brown, & London, 2013) and that BIS-11 total scores and UPPS-P lack of premeditation scores exhibit substantial genetic and phenotypic overlap related to lack of self-control and planning prior to action (Gustavson et al., 2020; Sanchez-Roige et al., 2019). Though some reviews have clustered novelty seeking with sensation seeking measures (Fischer, Smith, & Cyders, 2008; Stautz & Cooper, 2013), TCI novelty seeking was selected as an indicator of lack of self-control given empirical evidence across a number of samples, including the UPPS development sample (Whiteside & Lynam, 2001), suggesting this scale is more strongly associated with lack of premeditation than with sensation seeking (Evren, Durkaya, Evren, Dalbudak, & Cetin, 2012; Savvidou et al., 2017; Vonmoos et al., 2013). Relatedly, prior research suggests that TCI novelty seeking may not reflect a single construct but rather two: one reflecting characteristics more closely associated with sensation seeking and the other lack of self-control (Evren et al., 2012; Herbst, Zonderman, McCrae, & Costa, 2000; Jaksic et al., 2015; Vonmoos et al., 2013). A series of sensitivity analyses examining models including novelty seeking as (1) an indicator of lack of self-control, (2) an indicator of sensation seeking, and (3) omitting novelty seeking from either factor further supported our proposed model (see online Supplementary Methods and Supplementary Tables S3–S5 and S14).

Urgency

UPPS-P negative and positive urgency and TCI harm avoidance GWAS were specified as indicators of the bottom-up urgency factor. Empirical studies have suggested that negative and positive urgency are highly correlated and together may represent a common transdiagnostic risk factor for psychopathology (Billieux et al., 2021). This notion is substantiated by high phenotypic and genetic correlations between negative and positive urgency ($r = 0.59$; $r_g = 0.74$) in the 23andMe sample (Sanchez-Roige et al., 2019). TCI harm avoidance is thought to reflect a tendency to respond intensely to aversive stimuli and negative affect with loss of control of behavioral responses (Cloninger, 1987) and has been shown to be moderately correlated with negative urgency in clinical samples ($r = 0.28$–0.55; Jiménez-Murcia et al., 2020; Savvidou et al., 2017).

Sensation seeking

A risk-taking GWAS meta-analysis including both UKB and 23andMe samples (see online Supplementary Methods for description and online Supplementary Fig. S1 for quantile–quantile [Q–Q] plot) was specified along with adventurousness and UPPS-P sensation seeking GWAS as indicators of the bottom-up sensation seeking factor.
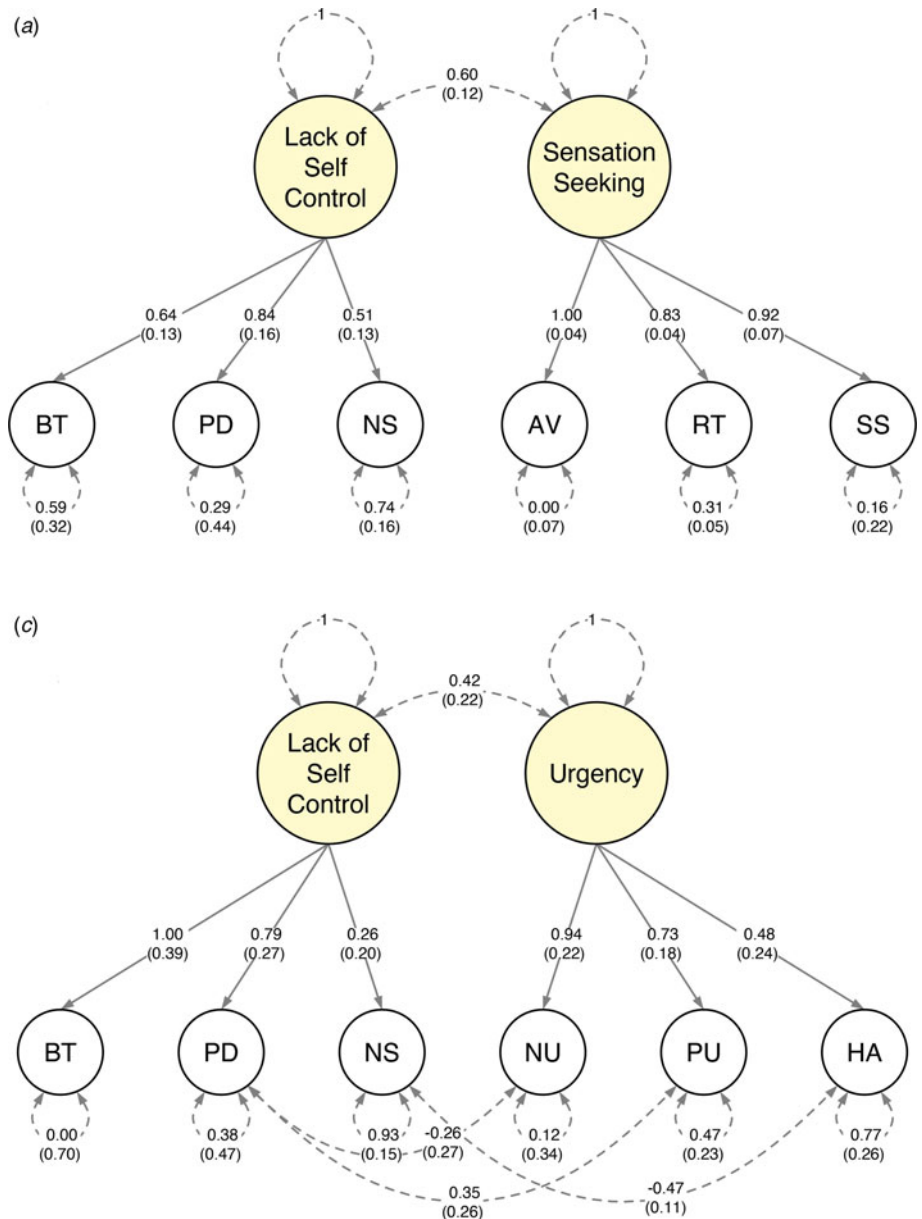
Figure 1. Final path diagrams of the SSSC (A) and UGSC (B) dual-systems models estimated using GenomicSEM. Presented parameters are standardized and SE are shown in parentheses. Variances and covariances are shown as dashed lines and factor loadings are shown as solid lines. See online Supplementary Tables S3 and S4 for model fit indices. BT, BIS-11 total score; PD, UPPS-P lack of premeditation; NS, TCI novelty seeking; AV, adventurousness; RT, risk-taking; SS, UPPS-P sensation seeking; NU, UPPS-P negative urgency; PU, UPPS-P positive urgency; HA, TCI harm avoidance.

Neuroimaging GWAS

Three sets of neuroimaging GWAS were utilized for genetic correlation analyses (see Table 1 and online Supplementary Methods). The first set included UKB GWAS of 62 (31 left/right hemisphere) cortical parcellation volumetric phenotypes obtained from the Oxford Brain Imaging Genetics web server (Smith et al., 2021). The second set included GWAS of 34 cortical surface area and thickness parcellation phenotypes (Grasby et al., 2020). The third set included volumetric GWAS of seven subcortical structures (Satizabal et al., 2019).

Data analysis

Genomic factor models

GenomicSEM (version 0.0.5; Grotzinger et al., 2019) was employed using diagonally weighted least-squares estimation and unit variance identification to conduct genomic confirmatory factor analyses. Two primary models were tested: (1) the SSSC

model reflecting shared genetic architecture between top-down lack of self-control and bottom-up sensation seeking, and (2) the UGSC model reflecting shared genetic architecture between top-down lack of self-control and bottom-up urgency. Model fit was assessed using χ^2 tests, the comparative fit index (CFI), the standardized root mean square residual (SRMR), and the Akaike information criterion (AIC). Given that dual-systems models contained indicator GWAS from the same measures (UPPS-P, TCI) across correlated latent factors, follow-up models allowing within-measure cross-factor residuals to covary were fit with changes in model fit assessed using χ^2 difference tests ($\Delta\chi^2$).

Single latent factor models were specified for each of the three dual-systems constructs in multivariate GWAS to: (1) minimize the effect of uneven sample sizes between traits as described in online Supplementary Methods, (2) increase the number of variants tested for each construct as variants are excluded using listwise deletion across indicators, and (3) limit any potential estimation bias introduced by residual covariance structures described above. Because these single latent factor models each

had three indicator GWAS (fully saturated just-identified models, $df = 0$), model fit indices were unavailable, and fit was instead assessed by examining the significance of factor loadings and residual variances.

Multivariate GWAS

Multivariate GWAS of SNPs available across all indicator GWAS and present in the 1000 Genomes Project Phase 3 v5 reference panel with MAF⩾0.5% (The 1000 Genomes Project Consortium, 2015) were conducted in GenomicSEM to estimate SNP associations with each latent dual-systems genetic factor. Effective sample sizes for each latent factor ($\widehat{N}$) were estimated (Mallard et al., 2022a). SNP-based heritability estimates (h_g^2) of latent genetic factors derived using $\widehat{N}$ are more accurately referred to as genetic variances (Mallard et al., 2022a) and are subsequently denoted by ζ_g. To identify SNP effects not fully mediated by the specified latent factor (common pathway model), follow-up multivariate GWAS including unique pathways were conducted to calculate Q_{SNP} tests of heterogeneity. SNPs with genome-wide significant (GWS; $p < 5 \times 10^{-8}$) Q_{SNP} statistics exert effects on genetic indicators independent of the latent factor (Grotzinger et al., 2019). Thus, these SNPs were removed from model-derived GWAS summary statistics to reduce heterogeneity in the latent genetic factors for downstream analyses.

Neuroimaging genetic correlation analyses

Linkage disequilibrium score regression (LDSC; Bulik-Sullivan et al., 2015) genetic correlation analyses were conducted to examine whether dual-systems constructs differed with respect to their genetic overlap with regional cortical volume, surface area, and thickness and subcortical structural volume. GenomicSEM was used to calculate genetic correlations between each genetic factor and each neuroimaging phenotype with a 5% FDR correction used to account for multiple testing within each imaging phenotype set for each latent construct separately. To determine whether correlations with each neuroimaging phenotype differed between paired top-down and bottom-up constructs, χ^2 tests were used to evaluate the null hypothesis that each pair of genetic correlations could be constrained to equality (Demange et al., 2021).

Results

Genomic factor models

Preliminary univariate and bivariate LDSC estimates for all indicator GWAS are shown in online Supplementary Tables S1, S2 and Fig. S2. SNP-based heritability estimates were all significant at $p < 0.05$ ($h_g^2 = 0.040$–0.362). Ratio values (LDSC intercept − 1)/(mean $\chi^2 - 1$) were not significantly different from zero for most traits, suggesting negligible inflation of test statistics from sources other than true genetic effects (e.g. uncontrolled population stratification). Of note, the novelty seeking and harm avoidance GWAS were likely underpowered, as evidenced by λ_{GC}, mean χ^2, and LDSC intercept values below 1, suggesting h_g^2 estimates (0.305–0.362) are likely inflated. Nevertheless, genetic correlations between these traits and other constituent indicator GWAS demonstrated appreciable clustering among indicator GWAS for each dual-systems latent genetic factor (online Supplementary Fig. S2). Further, these GWAS contributed to the polygenic signal and ζ_g of subsequent latent genetic factors as described in the Multivariate GWAS section below.

GenomicSEM analyses showed that the correlated factors dual-systems models provided good fit to genetic covariance matrices. The SSSC model exhibited good fit ($\chi^2 = 10.67$, $df = 8$, $p = 0.22$, AIC = 36.67, CFI = 1.00, SRMR = 0.09) and was not improved with the inclusion of within-measure cross-factor residual covariation between UPPS-P sensation seeking and lack of premeditation ($\chi^2 = 10.69$, $df = 7$, $p = 0.15$, AIC = 38.69, CFI = 1.00, SRMR = 0.08; $\Delta\chi^2 = -0.02$, $df = 1$, $p = 0.887$). The bottom-up sensation seeking factor and the top-down (lack of) self-control factor in the SSSC model were significantly correlated ($r_g = 0.60$, S.E. = 0.12, $p = 2.15 \times 10^{-7}$; Fig. 1a; online Supplementary Table S3).

The initial UGSC model exhibited poor fit ($\chi^2 = 56.15$, $df = 8$, $p = 2.63 \times 10^{-9}$, AIC = 82.15, CFI = 0.56, SRMR = 0.16), but fit was drastically improved with the inclusion of within-measure cross-factor residual covariances between UPPS-P negative and positive urgency and lack of premeditation and between TCI harm avoidance and novelty seeking ($\chi^2 = 10.67$, $df = 5$, $p = 0.058$, AIC = 42.67, CFI = 0.95, SRMR = 0.09; $\Delta\chi^2 = -45.49$, $df = 3$, $p = 7.29 \times 10^{-10}$). The bottom-up urgency factor and the top-down (lack of) self-control factor in the UGSC model exhibited a moderate, but non-significant, correlation ($r_g = 0.42$, S.E. = 0.23, $p = 0.063$; Figure 1B; online Supplementary Table S4).

For the single factor models, loadings were acceptable to large ($\lambda = 0.38$–1.00) and significant at $p < 0.05$ apart from novelty seeking ($\lambda = 0.38$, S.E. = 0.22, $p = 0.083$). Residual variances were generally small and non-significant apart from novelty seeking, harm avoidance, and risk-taking ($\varepsilon_{NS} = 0.86$, S.E. = 0.19, $p = 6.83 \times 10^{-5}$; $\varepsilon_{HA} = 0.78$, S.E. = 0.24, $p = 0.001$; $\varepsilon_{RT} = 0.32$, S.E. = 0.05, $p = 1.52 \times 10^{-9}$, respectively). See online Supplementary Table S5 and Fig. S3, respectively, for model parameters and path diagrams.

Multivariate GWAS

The multivariate sensation seeking GWAS ($\widehat{N} = 710\,971$) identified 1092 independent GWS variants (online Supplementary Table S6). LDSC analysis indicated that results reflect the extensive polygenicity of this trait ($\zeta_{g=}0.087$, S.E. = 0.003; mean $\chi^2 = 2.26$; online Supplementary Table S7 and Fig. S4 for Q-Q plot), and were not due to uncontrolled inflation, bias, or stratification (ratio value = 0.01, S.E. = 0.01). For a more detailed description of these results see Miller and Gizer (2023).

In contrast, no variants in the (lack of) self-control ($\widehat{N} = 27\,656$) or urgency GWAS ($\widehat{N} = 28\,316$) reached GWS (online Supplementary Tables S8, S9). LDSC analyses suggested these traits displayed significant genetic variance ([lack of] self-control $\zeta_g = 0.072$, S.E. = 0.019; urgency $\zeta_g = 0.093$, S.E. = 0.022; online Supplementary Table S7), but examination of Q–Q plots (online Supplementary Figs S5, S6) and mean χ^2 values (1.03–1.06) implied that sample sizes for these traits lack the power necessary to identify meaningful variant-level associations.

Q_{SNP} analyses identified no significant heterogeneity in individual SNP effects for the sensation seeking factor or the (lack of) self-control factor, but 323 GWS Q_{SNP}s were identified for the urgency factor. These were removed from urgency summary statistics prior to $\widehat{N}$ calculation and downstream analyses.

Genetic correlations with neuroimaging phenotypes

Key findings from neuroimaging genetic correlation analyses included the following significant associations ($p_{FDR} < 0.05$): (1) sensation seeking exhibited small positive correlations with

cortical surface area across several regions ($0.07 < |r_g| < 0.10$); (2) (lack of) self-control exhibited moderate negative correlations with cortical thickness across the majority of tested regions ($0.22 < |r_g| < 0.43$); and (3) urgency exhibited a negative correlation with cortical thickness in the rostral middle frontal gyrus ($r_g = -0.39$, $p_{FDR} = 0.031$). Dual-systems factors were not associated with regional cortical brain volumes nor subcortical structural volumes following FDR correction (online Supplementary Tables S10, S11).

Differences in genetic correlations with cortical surface area and thickness were generally robust across factors (Fig. 2; Supplementary Tables S12, S13). Broadly, genetic correlations between dual-systems factors and cortical surface area were in the positive direction while genetic correlations with cortical thickness were negative. However, (lack of) self-control and

urgency were only nominally associated with cortical surface area in two and one regions, respectively ($p = 0.012$–0.025). Sensation seeking, in contrast, was associated with cortical surface area following FDR correction across more than 25% of regions tested ($p_{FDR} < 0.05$) with equal representation in the frontal, parietal, and temporal lobes. Notably, χ^2 tests constraining the magnitude of these correlations to equality across traits were generally non-significant ($p_{diff} > 0.05$), suggesting that these weaker associations were less specific to sensation seeking. Conversely, (lack of) self-control was negatively correlated with cortical thickness across more than 60% of regions tested ($p_{FDR} < 0.05$) with the greatest representation in the PFC (max-$r_g = -0.41$, pars orbitalis) and parietal lobe (max-$r_g = -0.38$, precuneus), where correlations were significantly larger than those between sensation seeking and cortical thickness ($p_{diff} < 0.05$) which were not significant.
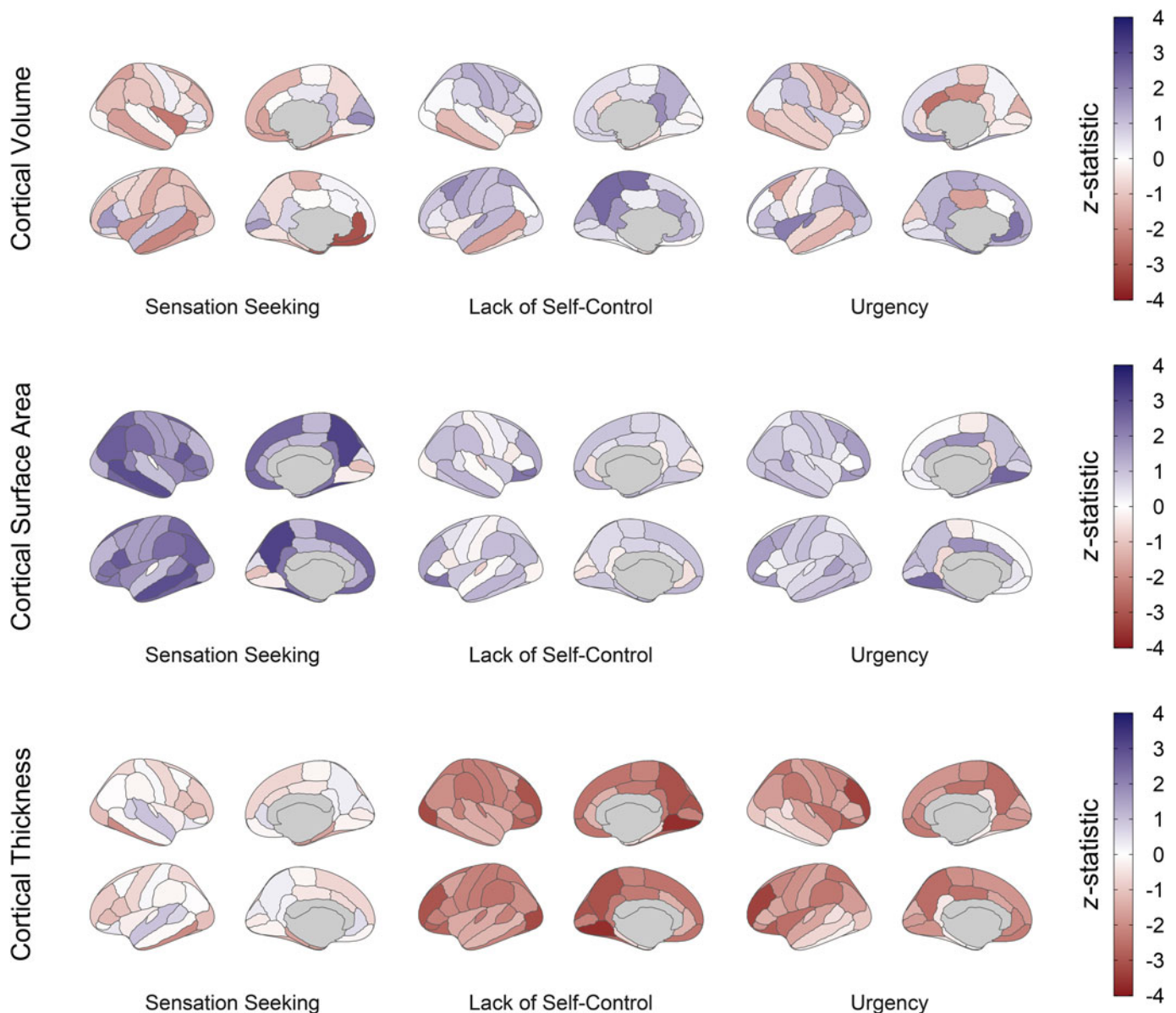

Figure 2. Genetic correlations between dual-systems factors and regional cortical brain volume, cortical surface area, and cortical thickness. Cortical patterning of genetic correlations plotted as *z* statistics (blue = positive correlation, red = negative correlation) across IPT dual-systems factors for cortical regional volume (top) according to the Desikan–Killiany–Tourville atlas (Klein & Tourville, 2012), and cortical regional surface area (middle) and thickness (bottom) according to the Desikan–Killiany atlas (Desikan et al., 2006). Plots were constructed using the *ggseg* package in R (Mowinckel & Vidal-Piñeiro, 2020).

Discussion

The current study represents the first investigation of the latent genetic structure of dual-systems models of IPTs and their neuro-anatomical correlates using GWAS data. Genomic factor analyses supported the distinct but related hypothesized genetic components of the tested dual-systems models. The SSSC model was strongly supported with fit indices demonstrating that the putative bottom-up sensation seeking and top-down (lack of) self-control factors represented separable, though correlated ($r_g =$ 0.60), constructs. These results are consistent with prior twin studies, which reported similar support for these constructs and a similar genetic correlation between them (Ellingson et al., 2013; Hur & Bouchard, 1997). The UGSC model was also supported, showing satisfactory model fit with a modest, non-significant correlation between the putative bottom-up urgency and top-down (lack of) self-control factors ($r_g = 0.42$). Though non-significant, this correlation was within the range of previous estimates for similar traits (e.g. $r_g = 0.26$–0.64; Gustavson et al., 2019, 2020).

To further evaluate the validity of the modeled dual-systems factors, hypotheses regarding the neural underpinnings of top-down and bottom-up constructs driven by dual-systems model theory and prior research (Shulman et al., 2016b) were tested by estimating genetic correlations between the dual-systems factors and relevant neuroimaging phenotypes. Consistent with prior research and theory, cortical thickness of PFC regions was negatively correlated in the present study with (lack of) self-control reflecting overlap in genetic variation associated with thinner PFC regions and diminished self-control (max-$r_g =$ −0.41). This finding mirrors results from previous neuroimaging studies suggesting negative associations between frontocortical thickness and lack of self-control IPTs (Holmes, Hollinshead, Roffman, Smoller, & Buckner, 2016; Kaag et al., 2014; Kubera et al., 2018; Schilling et al., 2012) and complements prior research reporting a positive correlation between cortical thickness in the precentral gyrus and general cognitive functioning using these GWAS data (Grasby et al., 2020). Together, these lines of evidence imply that associations between reduced frontocortical thickness and diminished self-control may be partially explained by a common underlying genetic basis, thus lending further support to the interpretation of the modeled latent (lack of) self-control factor as a top-down construct.

However, negative correlations between the (lack of) self-control factor and cortical thickness extended to other cortical regions not hypothesized by the dual-systems model (e.g. occipital lobe), and other findings also ran contrary to the hypothesized neurobiology of the dual-systems model. For example, the observed positive genetic correlations between sensation seeking and cortical surface area across a number of regions were unexpected as dual-systems theory contends that sensation seeking, as a bottom-up construct, is primarily localized to subcortical reward structures (Steinberg et al., 2008). Similarly, previous research would partially situate urgency in the morphology of subcortical structures involved in emotion-processing (amygdala, basal ganglia; Chester et al., 2016; Cyders et al., 2015; Halcomb, Argyriou, & Cyders, 2019). Contrarily, urgency was significantly associated with a single neuroimaging phenotype following FDR correction: rostral middle frontal cortical thickness ($r_g = -0.39$), though this replicates prior phenotypic studies of neuroimaging correlates of urgency (Cyders et al., 2014a; Cyders et al., 2015; Muhlert & Lawrence,

2015). In the current study, all dual-systems constructs were uncorrelated with subcortical structural volume.

The reported results have two primary implications. First, they provide support at the genetic level for our modeled constructs ([lack of] self-control, urgency, and sensation seeking) as an organizational framework for understanding IPTs as putative endophenotypes for psychopathology but suggest that some further refinement of the hypothesized neurobiological underpinnings of these constructs as suggested by dual-systems models may be needed. As described, the top-down self-control factor was partially supported, demonstrating significant genetic correlations with its hypothesized neural correlates, but also with reduced thickness more broadly across the cortex. In contrast, neurogenetic evidence supporting sensation seeking and urgency as bottom-up constructs was more limited. While findings generally support the latent genetic structure of each, there was a lack of evidence relating these traits genetically to their hypothesized subcortical neural correlates, though previously described relations to cortical regions (rostral middle frontal gyrus) were replicated.

Criticisms of the dual-systems model as overly simplified have noted that, while dual-systems constructs are theoretically and empirically separable (Duckworth & Steinberg, 2015; Shulman et al., 2016a), the underlying neurobiology is likely dynamic and multifaceted (Casey, Galván, & Somerville, 2016; Pfeifer & Allen, 2012). Moreover, given that these constructs tend to be highly correlated (Steinberg et al., 2008) and were strongly genetically correlated in the case of lack of self-control and sensation seeking in the current study, investigations of genetic correlations between one of these constructs and any neuroimaging analogue in isolation will be contaminated by the contribution of the unmeasured construct (Shulman et al., 2016b). As such, the present study provides further evidence supporting this criticism consistent with structural neuroimaging studies demonstrating that relations between bottom-up constructs and subcortical structural volume have been mixed and of generally small effect (Holmes et al., 2016; Owens et al., 2020; 2023). Notably, functional neuroimaging studies of bottom-up constructs have reported unique patterns of connectivity across frontostriatal pathways (Burnette et al., 2019; Demidenko, Huntley, Weigard, Keating, & Beltz, 2022; Hawes et al., 2017; Um, Hummer, & Cyders, 2020; Zhu, Cortes, Mathur, Tomasi, & Momenan, 2017), suggesting that assessment of coordinated cortical-subcortical activity may help with further refinement of dual-systems models and their measurement. In aggregate, study findings suggest that further refinement and validation of dual-systems constructs from neuroimaging and genetic perspectives is needed, though the consistency of some findings reported here with prior research highlight the promise of this approach.

Second, the current study provides an important demonstration of how post-GWAS approaches can complement studies using other methodologies to refine our models of psychopathology and endophenotypic measures based on these models. As noted, the present study is the first to investigate the latent genetic architecture of dual-systems models using GWAS data, and the first of any type to investigate the genetic architecture of an urgency and (lack of) self-control dual-systems model. While prior studies have examined genetic correlations amongst IPTs using GWAS approaches (Sanchez-Roige et al., 2019, 2023), focal investigations of the latent genetic architecture underlying dual-systems models are limited to a small number of twin studies (Ellingson et al., 2013, 2018; Harden et al., 2017). As a result, findings from the present study demonstrate how post-GWAS

approaches can be used to critically evaluate theoretical models of psychological traits across multiple levels of analysis from the genetic level to that of a manifest disorder, representing an important and novel extension of this prior work. Despite deviations from dual-systems theory regarding neurobiological bases of these constructs, findings here emphasize unique neurogenetic components of putative top-down and bottom-up constructs which may have distinct etiological influences on psychopathology development. Therefore, the present study may serve as a benchmark for future studies assessing evidence for neurogenetic influences underlying dual-systems models and shared associations with related psychopathology.

Limitations

The current study is not without limitations. First, smaller sample sizes likely hindered analyses of the (lack of) self-control and urgency traits, demonstrating the need for larger IPT GWAS (Sanchez-Roige et al., 2023). Second, and equally important, is the exclusion of non-European ancestry samples from the present study. Our European ancestry-specific findings may only generalize to European ancestry populations and thus contribute to the disparity in applicability of research findings to non-European populations (Martin et al., 2019). As non-European ancestry groups are extremely underrepresented in extant GWAS studies (Mills & Rahal, 2019, 2020), addressing this limitation is of dire importance for leveling health disparities across groups. Third, IPT GWAS were available only at scale-level, rather than item-level, resulting in a small number of appropriate indicators for each genomic factor. Relatedly, all GWAS included sex and age as covariates obviating examination of sex- or age-specific associations relevant to both dual-systems models and brain development (Casey, Getz, & Galvan, 2008; Shulman, Harden, Chein, & Steinberg, 2015). Future investigations using item-level data (Mallard et al., 2022b) in combination with sex-specific (Silveira, Pokhvisneva, Howard, & Meaney, 2023) and developmentally relevant (Couto Alves et al., 2019) analytic approaches will continue to improve our understanding of these complex pathways.

Conclusion

Results of the current study suggest dual-systems models of the genetic architecture of IPTs are generally well-validated through genomic structural equation modeling, though factors derived from this model were not consistently associated with theoretically relevant neuroimaging phenotypes. As such, this study serves as an important first step in defining the shared and unique genomic and neurobiological correlates of dual-systems constructs and underscores the importance of using imaging genetics to further elucidate neurobiological substrates underlying genetic overlap between complex traits (Bogdan et al., 2017).

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723003367

Data availability. The full GWAS summary statistics for the 23andMe discovery data set will be made available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. Please visit https://research.23andme.com/collaborate/#dataset-access/ for more information and to apply to access the data.

Acknowledgments. This study made use of summary statistics data from a number of sources which we wish to acknowledge. First, we thank Susan

Competing interests. None.

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