Winter 12-15-2019

# Genomic Contributors to Individual Differences in Reward-Related Neural Activity

Lindsay Jane Michalski
*Washington University in St. Louis*

WASHINGTON UNIVERSITY IN ST. LOUIS

Department of Psychological & Brain Sciences

Dissertation Examination Committee:
Ryan Bogdan, Chair
Todd Braver
Emma Johnson
Thomas Oltmanns
Jonathan Peelle

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by
Lindsay Jane Michalski

A dissertation presented to
The Graduate School
of Washington University in
partial fulfillment of the
requirements for the degree
of Doctor of Philosophy

December 2019
St. Louis, Missouri

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# Acknowledgments

My interest in the field of neurogenetics began early, in a high-school course called Genetics, Bacteriology, Biotechnology, and Embryology, where I wrote an essay exploring the potential for "personalized medicine" as informed by our ever-expanding knowledge of the human genome. More than ten years later, my doctoral dissertation keeps with a similar theme, though it's more directed at contributing to our understanding of how, exactly, genomic factors contribute to the complex etiology of psychiatric diagnoses, rather than leveraging them for treatment.

I never dreamed I'd follow this thread through high school, college, my first post-baccalaureate job, and graduate school, but – largely thanks to Ryan Bogdan and the BRAIN Lab, who have made these steps possible for me – here we are. To those who have lent support along the way, I am endlessly grateful. To my partner, Andrew, for having my back when I felt defeated and lifting me up when I saw success, I couldn't have done this without you.

Lindsay Jane Michalski

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*December 2019*

ABSTRACT OF THE DISSERTATIONs

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Professor Ryan Bogdan, Chair

Aberrant reward-related behavior, including impulsive and risk-taking behaviors, is a common feature of externalizing psychopathology (e.g., attention deficit hyperactivity disorder, antisocial personality disorder, and substance-use disorders). Through imaging studies, these behaviors have been linked to dysregulated reactivity within a diffuse reward-related corticostriatal neural network, including the striatum, frontal regions (namely orbital, ventromedial, and dorsolateral cortices), the insula, and the hippocampus. Because variability in risk-taking behavior and related psychopathology is moderately-to-largely heritable (i.e., with estimates ranging from 40 – 80%), a genetically-informed approach is well-positioned to provide valuable insight into the etiology of reward-related neural and behavioral phenotypes that characterize externalizing psychopathology. Using summary statistics from a recent genome-wide association study (GWAS) of risk tolerance among 939,908 individuals, we generated polygenic risk scores (PRS) for a European-ancestry subsample (usable data ranging from n=457 to n=518; see Table 2) of the Duke Neurogenetics Study (DNS; a large community sample) and examined associations between genomic liability and risk-taking phenotypes (i.e., self-reported impulsivity and alcohol use, and behavioral delay discounting), as well as BOLD activation of the ventral striatum. Contrary to our hypotheses, GWAS-based PRS were not consistently significantly associated

with risk-related behavior or with activation of the ventral striatum. In order to increase biological informativeness, we also used PrediXcan analyses to identify genes with differential expression based on the risk-related genomic liability; however, PRS of these differentially-expressed variants were also not significantly associated with risk-related behavioral or neural-activation phenotypes in the DNS. Though these null findings may reflect a true lack of association between risk-related genetic liability and behavior/neural externalizing phenotypes, we discuss possible alternative explanations regarding imprecise phenotyping in the discovery GWAS, inadequate statistical power, and questionable reliability of task-based fMRI measurements.

# 1.0 Introduction

Externalizing psychopathologies (e.g., ADHD, antisocial personality disorder, substance use disorders) are characterized by impulse-control problems, sensation-seeking behaviors, poor interpersonal functioning, and psychopathic traits that lead to significant adverse effects on social relationships, overall health, and quality of life. Externalizing disorders are common and often diagnosed in early life, with conduct and oppositional defiant disorders affecting up to 10% of youth and ADHD affecting roughly 10-17% of youth and adolescents (Hicks, Krueger, Iacono, McGue, & Patrick, 2004; Larsson, Chang, D'Onofrio, & Lichtenstein, 2014). Furthermore, externalizing behaviors that initially manifest in childhood often persist into adulthood (e.g., impulsive behavior, risk-taking, and attention deficits; Rodgers *et al.*, 2015) and are associated with substance use disorders, mood and anxiety disorders, and other negative outcomes, including failure to complete high school, early pregnancy, and criminality (Reef *et al.*, 2011; Loth *et al.*, 2014).

Externalizing behavior and related psychopathology also have a tremendous socioeconomic impact on society. For example, in 2010, alcohol use cost the federal, state, and local governments in the United States $249 billion; this equates to $2.05 per alcoholic beverage consumed, or an annual cost of $807 per person (Sacks, Gonzales, Bouchery, Tomedi, & Brewer, 2015). These costs can be primarily attributed to lost workplace productivity, while the remainder is due to health care, law enforcement, and motor vehicle accidents. Similarly, the literature suggests that other forms of externalizing behavior also pose a significant burden: for example, ADHD is estimated to contribute $143-266 billion in annual socioeconomic costs (Doshi et al., 2012). Altogether, estimates suggest that externalizing behavior and related

psychopathology cost the US government more than $700 billion annually (Caulkins, Kasunic, & Lee, 2014; Doshi et al., 2012; Kessler et al., 2009).

The widespread prevalence and astronomical costs of externalizing psychopathology are starkly contrasted by our limited etiologic knowledge of how these disorders arise and persist. Though etiologic factors associated with externalizing psychopathology remain unidentified (with few exceptions, e.g., the role of variation in alcohol metabolism in problematic alcohol use; Köhnke, 2008; Edenberg and Foroud, 2014), recent genetic-association and neuroscience studies do offer some clues. First, externalizing behavior and psychopathology are moderately-to-largely heritable (i.e., 49-88%; Larsson *et al.*, 2014; Verhulst, Neale and Kendler, 2015), suggesting that genetic variation plays a prominent role in their expression. Consistent with high rates of comorbidity (Vollebergh et al., 2001), twin studies show significant genetic overlap *across* externalizing disorders (Krueger et al., 2002; Slutske et al., 1998), further suggesting common mechanisms that may underlie the broad spectrum of externalizing behaviors despite diagnostic distinctions that imply unique etiology. Second, neuroimaging research has repeatedly linked externalizing behavior and psychopathology to variability in reward-related brain function. However, the neural mechanisms through which genetic risk may contribute to externalizing behavior have not yet been thoroughly investigated. Understanding the neural mechanisms of genomically-conferred risk for externalizing behaviors that are common to antisocial/conduct disorders, ADHD, and substance-use disorders alike may ultimately lead to refined nosology, prevention, intervention, treatment, and public-policy considerations that honor a complex etiologic architecture.

## 1.1 The Heritability of Externalizing Behavior and Psychopathology

Twin studies show that externalizing disorders are highly heritable (49–88%; Slutske et al., 2008; Jacobson et al., 2002; Fu et al., 2002), with ADHD being among the most heritable psychiatric disorders (alongside schizophrenia and bipolar disorder, with estimates up to 88%; Larsson *et al.*, 2014). Furthermore, both twin (Hicks et al., 2004) and epidemiologically-based studies (Krueger et al., 2002) indicate high genetic overlap across related externalizing disorders, suggesting that common genetic factors largely contribute to a broad externalizing factor rather than acting independently to impart liability for specific diagnoses. In fact, a general externalizing liability factor is highly (i.e., 80%) correlated between relatives, and associations between impulse-control issues in parents and externalizing behaviors (e.g., antisocial phenotypes) in their children are largely due to shared genetic – rather than environmental – influences (Button et al., 2009; Hicks et al., 2004; Hicks, South, DiRago, Iacono, & McGue, 2009). Taken together, these insights suggest that it is crucial to better understand the mechanisms that may underpin genetic contributions to the persistence of externalizing behaviors generally defined within families and across generations.

## 1.2 Methods of Characterizing Genetic Risk

### Candidate-gene and Genome-wide Studies

Thus far, molecular genetics research on externalizing psychopathology and reward-related brain function has largely focused on single variants within candidate genes (e.g., *MAOA*; dopamine-system genes including *DRD2* and *DRD4*; Weeland *et al.*, 2015). However, mounting evidence suggests instead that complex behavior and neural phenotypes are undergirded by extensive polygenicity, with common variants conferring only small effects that require large samples to detect. As a result, use of the single-variant, candidate-gene approach has become increasingly

controversial and, consequently, has been largely abandoned in mainstream genetics. Moreover, while some candidate-gene work on externalizing phenotypes and reward-related brain function has been successfully replicated [e.g., gene-environment interaction between *MAOA* variant and childhood adversity predicting antisocial phenotypes (Byrd & Manuck, 2014); the influence of several *DRD2* variants and the Taq1A variant in *ANKK1* on striatal dopamine-receptor binding potential (Gluskin & Mickey, 2016)], the vast majority is characterized by inconsistent findings that suggest a high rate of false positives (Pasche & Yi, 2010).

In light of these issues, which limit the utility of candidate-gene studies (Duncan & Keller, 2011), as well as the realization that psychiatric phenotypes are a product of complex polygenic architecture, the past decade has seen a surge in genome-wide association studies (GWAS; Visscher *et al.*, 2012, 2017; Kendler, 2013). Made possible by recent advancements in technology, associated reductions in cost, and a field-wide push for a more collaborative approach to science, this shift has led to the acquisition of (previously-unfathomably) large datasets and, in turn, the identification of novel genetic variants linked to psychopathology and associated traits. Specific to externalizing phenotypes, GWAS of alcohol-use disorders from the past decade have consistently implicated genes within the *ADH* cluster (see: Frank et al., 2012; Gelernter et al., 2014; Walters *et al.*, 2018) and other GWAS have implicated loci across externalizing diagnoses [e.g., GABRA2 associated with both conduct phenotypes in children and substance use in adults (Dick et al., 2006); *ABCB1* linked to both substance-use disorders and antisocial traits in adulthood (Salvatore et al., 2015)].

**Polygenic Risk Scores**

The era of GWAS has provided two compelling insights. First, associations of common genetic variation with both psychiatric and neural phenotypes are characterized by small effects that

require large samples for detection. Second, and more encouraging, the additive effects of independent and commonly-occurring variants, when weighted by summary statistics from a well-powered GWAS in what is called a polygenic risk score (PRS) approach, are reliably predictive of related constructs (Bogdan, Baranger, & Agrawal, 2018). Briefly, the PRS approach is informed by large-scale GWAS of thousands of participants that serve as discovery samples; other large, healthy community samples (i.e., "target" samples) are used for both replication and extension, wherein PRS are calculated for each participant using statistics from the original discovery sample. Using odds ratios or beta-weights, depending on the nature (i.e., continuous or discrete) of the trait for which the GWAS was conducted, each genetic variant's contribution to the total polygenic score is weighted by the strength of its association with the phenotype-of-interest in the discovery sample. Then, within the target sample, these scores are used to determine the extent to which variations in genetic liability at the subject level are associated with a given phenotype (Dima & Breen 2015). For example, in a sample of adolescents and young adults, externalizing PRS reliably predicted externalizing diagnoses, subclinical externalizing behavior, and impulsiveness, indicating that externalizing behaviors likely precede psychiatric diagnosis in those at high genetic risk (Salvatore *et al.*, 2015b); further, in a sample of children aged 9-12, ADHD PRS predicted externalizing symptoms and explained nearly 1% of variance in a broad psychopathology factor (Brikell et al., 2018; Caspi, Houts, Belsky, & Goldman-Mellor, 2015). Because this innovative technique increases power to detect small effect sizes relative to single variant approaches, it bolsters the success of replication attempts and enables researchers to examine links between polygenic risk and psychiatrically-relevant phenotypes in large cohorts of healthy individuals, which avoids confounding variables inherent to patient samples (i.e., medication use, comorbidity, disease course, and symptom

severity). Furthermore, genotype – and, thus, PRS – is stable across the lifetime, which cannot be said of other neural, physical, or biological markers that may be considered "predictors" of disease. Thus, the PRS method is uniquely positioned to improve our understanding of the mechanisms that underlie externalizing behaviors across diagnostic categories.

In the last year, numerous GWAS of externalizing-related constructs have been published, the most well-powered of which was conducted by Linner *et al.* using 939,908 total participants aggregated from the UK Biobank (n=431,126) and 23andMe (n=508,782) datasets. This study, which reported 124 independent loci associated with risk-tolerance measured via responses to a single self-report item, may inform our examination of genetic associations with reward-related neural function and risk-related behavioral measures.

## 1.3 Reward-Related Neural Activity: Associations with Externalizing Behavior and Psychopathology

### Reward-related Neural Circuitry

The ventral striatum (VS), a hub of a corticostriatal circuit that is chiefly involved in reward processing, has been reliably implicated in reward-related behaviors among healthy controls and patients with psychiatric diagnoses (Hariri, 2009). Within this reward circuit, the VS may be conceptualized as a "gate," opening and closing to convey motivation toward goals and allowing us to initiate action in order to acquire or achieve it. The corticostriatal circuit also includes several nodes which engage in unilateral and reciprocal connections with the VS hub. The dorsal striatum (DS), which is divided into two subregions, the putamen and the caudate, is a downstream target of the VS. Namely, the caudate belongs to an "executive loop" that primarily projects to the frontal cortex via the thalamus, and allows for formulation of an action plan; the putamen engages in a "motor loop" that predominantly sends connections between the VS, DS,

and motor and premotor cortices and aids in the generation and activation of motor programs to physically achieve a goal (e.g., picking up a glass and taking a drink). Various frontal regions also play a significant role in this circuit. These include the orbitofrontal cortex, which is associated with the assignment of subjective value to options in order to evaluate and choose between them, and the ventromedial prefrontal cortex, which integrates signals from the aforementioned regions and modulates motivational impulses received from the VS (Rushworth, Noonan, Boorman, Walton, & Behrens, 2011). Altogether, this multifaceted circuit is responsible for our range of responses to reward signals, including anticipating eventual reward receipt, integrating external environmental and internal subjective awareness to plan actions that will satisfy our motivations, and initiating the motor actions required to carry out those goal-directed plans (Haber, 2011; Haber & Knutson, 2010).

**Associations with Externalizing Psychopathology**

The corticostriatal reward circuit is inextricably linked to impulsiveness, a key externalizing symptom that is common to ADHD, antisocial and conduct disorders, and substance-use disorders. In fact, in healthy controls, higher scores on behavioral measures of impulsivity are correlated with increased levels of VS reactivity to appetitive stimuli, suggesting that VS activation may generally track with impulsive tendencies (van der Laan, Barendse, Viergever, & Smeets, 2016; Weiland et al., 2014). Externalizing diagnoses, which may be conceptualized as the outward manifestation of disordered functioning of the corticostriatal circuit, tend to be associated with differential VS activation. For instance, impulsive traits are positively correlated with VS reactivity among antisocial patients (Buckholtz et al., 2010), indicating that antisocial behaviors may stem from aberrant behavioral control mechanisms. However, psychiatric extremes of impulsivity do not necessarily follow a stereotypic pattern of increased activation

during all stages of reward (i.e., anticipation and receipt). For example, while ADHD and polygenic risk for its expression have been linked to increased VS response to reward receipt (Carey, Knodt, Conley, Hariri, & Bogdan, 2017; Von Rhein et al., 2015), dampened VS activation among ADHD patients during reward anticipation suggests that the VS may fail to activate externally-prompted downstream motivation-dependent processes that enable focused goal pursuit (Scheres, Milham, Knutson, & Castellanos, 2007). As such, this may lead to dysregulated reward-related behavior, independent of long-term (and even short-term) goals. Meanwhile, substance use disorder – which is defined by cyclical periods of craving/seeking (i.e., disordered motivation and goal-direction), binging/compulsive use (i.e., disordered behavioral control mechanisms), and withdrawal – has been linked to increased VS reactivity to both associated conditioned stimuli (e.g., drug paraphernalia) and delivery of the preferred substance, as well as deficient top-down prefrontal modulation of the reward circuit (Kober et al., 2010). Taken together, these findings highlight a key role of the VS in externalizing behavior and psychopathology.

## 1.4 The Current Study

Given evidence that common genetic factors contribute to a continuum of externalizing-related constructs (Dick et al., 2008), rather than to singular diagnostic categories specifically, the current study examines whether genetic variants linked to risk-taking behavior predict 1) reward-related brain function and 2) behavioral markers of risk-taking and impulsiveness.[1] In light of the limited utility of single-variant analyses – as they do not capture the polygenic architecture of complex behavior and often explain only a small proportion of variance of complex traits (Dima & Breen, 2015; Ferreira et al., 2008; Sullivan, 2010) – a polygenic risk score (PRS) approach is employed here to leverage genetic risk across the genome, which can account for much larger proportions of phenotypic variance (Lee, Wray, Goddard, & Visscher, 2011). The PRS method is well-positioned to detect neuroimaging phenotypes associated with psychiatric disorders at small effect sizes, which is key to expanding our understanding of the etiology of complex disease. Further, as discovery sample sizes continue to increase, so does the utility and predictive power of PRS (Dima & Breen 2015); thus, a potential strength of the Linner et al. risk-taking GWAS is its sample size of more than 900,000 participants, though we must also consider the possible implications of a single-item phenotype used to delineate risk-taking behavior. Importantly, in isolation, the PRS approach does not provide insight into the mechanisms underlying any emerging associations between genotype and externalizing phenotypes, and its predictive capacity for brain-based phenotypes may be limited by the inclusion of other contributors (e.g., variants affecting peripheral arousal).

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**1** Given null findings (see Results), as well as recent literature pointing to questionable reliability of task-related fMRI (Elliot *et al.*, 2019; see Discussion), we further probed whether risk-taking PRS are associated with variability in brain structure phenotypes. As these analyses were not planned in the original dissertation, they are presented in **Supplemental Tables 2 and 3** and discussed only briefly.

Variability in brain-based gene expression may be another key mechanistic contributor to both the etiology and heritability of psychiatric diagnoses and related phenotypes (Nicolae et al., 2010; Gusev et al., 2014). Given this, we also examined whether genomically-associated differences in gene expression are correlated with risk taking, and, if so, whether polygenic variation within these differentially-expressed genes is correlated with reward-related brain function and behavior (Gamazon et al., 2015). To do so, we used PrediXcan software: this program imputes static-DNA-related differences in brain-based gene expression using post-mortem gene expression and DNA genotyping; as such, it allows us to test whether such differences in gene expression are correlated with genomic liability for risk-tolerance based on the Linner *et al*. GWAS (2019). Following these imputation-based analyses, we then computed a PRS based on PrediXcan-identified gene to investigate whether integrating gene expression data may improve the predictive utility of PRS for neural phenotypes.

Together, the PRS and PrediXcan methods allow us to better characterize the temporal contribution of genetic influences on phenotypic outcomes: that is, whether psychiatric neural phenotypes arise due to predisposing genomic factors or, rather, as a consequence of behavioral expression or its correlates. The current study uniquely leverages a large community sample (the Duke Neurogenetics Study) to contribute to this etiological understanding while working within the multifaceted genetic and phenotypic architecture of externalizing psychopathology. It is important to keep in mind, however, that the nature of phenotypic assessment required to attain large sample sizes – as in the Linner *et al*. GWAS upon which we are drawing – is necessarily broad, and therefore may sacrifice specificity. In light of this, the current study also attempts to disentangle potential strengths and limitations by comparing the predictive power of GWAS-derived PRS to a more biologically-informed gene-expression-based PRS. We hypothesized that

PRS based on the Linner *et al*. risk-tolerance GWAS will be associated with differential VS activation, as well as risk-related behavior (i.e., increased self-reported impulsivity, delay discounting, and problematic alcohol use) in our community sample. We also hypothesized that PrediXcan analyses will identify genetic variants that impart differential gene expression based on genomic liability for risk-tolerance. Further, because of its improved biological relevance, we hypothesize that PrediXcan-based PRS will outperform GWAS-based PRS and be more strongly associated with both brain activation and behavioral measures of risk-taking.

# 2.0 Methods

## 2.1 Sample: The Duke Neurogenetics Study

The Duke Neurogenetics Study (DNS) assesses a wide range of behavioral, experiential, and biological phenotypes among young-adult (18–22-year-old) college students. Self-report, neuroimaging, and genomic data are available from 526 non-Hispanic participants of European ancestry. Ancestry was determined via self-report and confirmed using ancestrally informative principal components derived from genomic data (no individuals were ±6 SDs from the mean on the top 10 components; Purcell et al., 2007) Following quality control, 34 individuals were excluded from fMRI analyses (see **Table 1** for specific exclusions), leaving a final sample of 492 (mean age=19.80±1.23; 234 males) participants of European ancestry for functional analyses (see **Table 2** for further information on this sample). Each participant provided written informed consent to a protocol approved by the Duke University Medical Center Institutional Review Board prior to participation and received $120 remuneration. All participants were in general good health and free of exclusion criteria specific to this study, including: (1) medical diagnosis of cancer, stroke, diabetes requiring insulin treatment, chronic kidney or liver disease, or lifetime psychotic symptoms; (2) use of psychotropic, glucocorticoid, or hypolipidemic medication; (3) conditions affecting cerebral blood flow and metabolism (e.g., hypertension); and (4) contraindications to MRI scanning. DSM-IV Axis I and select Axis II (i.e., borderline and antisocial personality disorder) psychiatric disorders were assessed with the electronic Mini International Neuropsychiatric Interview (Sheehan et al., 1998) and Structured Clinical Interview for the DSM-IV Axis II (SCID-II; see **Supplemental Table 1**; First et al., 1996).

**Table 1. DNS Exclusion Criteria**

| Exclusion Reason | Number of Participants (% of n=492) |
|---|---|
| Scanner related artifacts in fMRI data | 4 (0.01%) |
| Movement outliers | 9 (0.02%) |
| Inadequate signal in regions of interest | 10 (0.02%) |
| Poor behavioral performance | 5 (0.01%) |
| Incomplete data collected from task | 4 (0.01%) |
| Incidental structural brain abnormalities | 2 (0.02%) |

**Table 2. DNS Sample Data**

| Variable | Number of Participants (% of n=492) |
|---|---|
| Sex | 234 males (47.5%) |
| Presence of any psychiatric diagnosis* | 131 participants (26.6%) |
| | **Mean ± SD** |
| Age | 19.80 ± 1.23 |
| Left VS reactivity (n=457) | 0.0522 ± 0.0522 |
| Right VS reactivity (n=457) | 0.0514 ± 0.1621 |
| BIS score (n=496) | 60.7527 ± 8.7766 |
| DDT score (n=496) | -2.7022 ± 0.7972 |
| AUDIT score (n=494) | 6.0084 ± 4.3791 |

*Breakdown of specific diagnostic categories is supplied in **Supplemental Table 1**

## 2.2 Self-Report and Behavioral Measures of Risk-Taking

### Delay Discounting

Delay discounting tasks assess preferences for varying amounts of money contingent upon whether they are delivered immediately or after a specified amount of time. Both the amount of money and the delay before receipt are varied such that we can calculate participant "indifference points," i.e., the likelihood of choosing a smaller reward delivered immediately versus a larger reward delivered after a delay. A consistent preference for a smaller reward received sooner is associated with impulsivity (Green, Myerson, & Vanderveldt, 2014). In the DNS, delay discounting is assessed as follows: immediate reward amounts are varied from $0.10

to $105. The waiting period for delayed reward (valued at a constant $100) is varied from 0 days to 5 years (in intervals of 0, 7, 30, 90, 180, 365, or 1825 days; Nikolova *et al.*, 2016). Then, as a summary measure, we computed area-under-the-curve measurements of discounting for each participant (Myerson, Green, & Warusawitharana, 2001). This method is both reliable and flexible, as it does not assume any specific form of the discounting function.

**Impulsivity**

To examine trait impulsivity, the DNS uses the Barratt Impulsiveness Scale (BIS), a self-report measure that assesses impulsivity as a behavioral construct / personality trait with good internal consistency ($\alpha$=0.84; M=61.78; SD=9.41; range: 37-113; Barratt and Patton, 1995).

**Substance Use**

The DNS examines potentially-problematic alcohol use using the Alcohol Use Disorders Identification Test (AUDIT), a 10-item self-report questionnaire that gathers information on consumption and behavioral tendencies (Saunders *et al.*, 1993).

Scores range from 0-40, with scores >7 indicating hazardous drinking and >20 indicating alcohol dependence. This measure has been reported to have good internal consistency across diverse samples and settings (median reliability coefficient of 0.83; Reinert & Allen, 2007).

## 2.3 Functional Magnetic Resonance Imaging Protocols

**Reward-Related Behavior Paradigm**

A number-guessing paradigm was used to elicit ventral striatum reactivity. This block-design paradigm consists of three blocks of predominantly positive feedback (80% correct guess; gain feedback), three blocks of predominantly negative feedback (80% incorrect guess; loss feedback)

and three control blocks (displaying a yellow circle after each response; Delgado et al. 2000, Hariri et al. 2006). Blocks are presented in pseudo-random order and are composed of five trials each. During each trial of the positive and negative feedback blocks, participants are given 3 s to guess via button press whether the value (between 1–4 or 6–9) of a card presented face-down is higher or lower than 5. The numerical value of the card is then presented for 500 ms, followed by an arrow indicating positive (green upward-facing arrow) or negative (red downward-facing arrow) feedback for 500 ms. Finally, a neutral crosshair is presented for 3 s, such that the total trial length is 7 s. One incongruent trial (e.g. a negative-feedback trial within a predominantly positive block) was included within each block to maintain task engagement and motivation and prevent participants from anticipating trial feedback. Three control blocks are interleaved between the six experimental card-guessing blocks, during which participants are instructed to make button presses during the 3-s presentation of an 'x,' which is then followed by an asterisk and a yellow circle (presented for 500 ms each). Participants were unaware of the fixed outcome probabilities and were led to believe that their performance would determine their net monetary gain. All subjects received $10 upon completion of the task.

**BOLD fMRI Data Acquisition**

Participants were scanned at the Duke-UNC Brain Imaging and Analysis Center using a research-dedicated GE MR750 3T scanner equipped with high-power high-duty-cycle 50-mT/m gradients at 200 T/m/s slew rate, and an eight-channel head coil for parallel imaging at high bandwidth up to 1 MHz. BOLD fMRI were acquired using a semi-automated high-order shimming program in order to ensure global field homogeneity. A series of 34 interleaved axial functional slices aligned with the anterior commissure-posterior commissure (AC-PC) plane were acquired for full-brain coverage using an inverse-spiral pulse sequence to reduce

susceptibility artifact [TR/TE/flip angle = 2000 ms/30 ms/60; FOV=240 mm; 3.75×3.75×4 mm voxels; interslice skip=0]. Four initial RF excitations were performed (and discarded) to achieve steady-state equilibrium. High-resolution three-dimensional structural images were acquired in 34 axial slices co-planar with the functional scans (TR/TE/flip angle=7.7 s/3.0ms/12; voxel size=0.9×0.9×4 mm; FOV=240 mm, interslice skip=0) to allow for spatial registration of each participant's data to a standard coordinate system.

**BOLD fMRI Data Preprocessing**

Individual subject data were realigned to the first volume in the time series to correct for head motion before being spatially normalized into the standard stereotactic space (Montreal Neurological Institute (MNI)) template using a 12-parameter affine model (final resolution of functional images=2 mm isotropic voxels). Next, data were smoothed to minimize noise and residual difference in gyral anatomy with a Gaussian filter, set at 6-mm full-width at half-maximum. Voxel-wise signal intensities were ratio normalized to the whole-brain global mean. To determine movement, the ARTifact Detection Toolbox (http://www.nitrc.org/projects/artifact_detect; (Mazaika et al., 2007) was used to generate regressors accounting for images due to large motion (i.e. >0.6mm relative to the previous time frame) or spikes (i.e., global mean intensity 2.5 standard deviations from the entire time series). Individual whole-brain BOLD fMRI volumes meeting at least two criteria were flagged and regressed out when determining task-specific effects: 1) significant mean-volume signal intensity variation (i.e., within volume mean signal greater or less than 4 standard deviations of mean signal of all volumes in time series), and 2) individual volumes where scan-to-scan movement exceeded 2 mm translation or 2º rotation in any direction. Participants with 5% or more

acquisition flagged volumes per task run were removed from analysis. An ROI mask (AAL template) from WFU pickatlas (Maldjian, Laurienti, Kraft, & Burdette, 2003) was used to ensure adequate BOLD signal. Participants who had less than 90% coverage were excluded from analyses.

## 2.4 Genotype and Gene Expression Data

### DNA Collection and Genotyping

DNA was isolated from saliva derived from Oragene DNA self-collection kits (DNA Genotek) customized for 23andMe (www.23andme.com). DNA extraction and genotyping were performed through 23andMe by the National Genetics Institute (NGI), a CLIA-certified clinical laboratory and subsidiary of Laboratory Corporation of America. One of two different Illumina arrays with custom content was used to provide genome-wide SNP data, the HumanOmniExpress or HumanOmniExpress-24 (Hu et al., 2016). Relatedness was assessed using pairwise identity by descent estimation in Plink 1.07; pairs with a PI_Hat greater than 0.20 had one member excluded from analyses (n=2). Genotype imputation was performed on all DNS participants with genome-wide chip data using the prephasing/imputation stepwise approach implemented in SHAPEIT/IMPUTE2 (Delaneau, Marchini, & Zagury, 2011; Howie, Fuchsberger, Stephens, Marchini, & Abecasis, 2012). Imputation was run separately for participants genotyped on the Illumina HumanOmniExpress and the Illumina HumanOmniExpress-24 arrays using biallelic SNPs only, the default value for effective size of the population (20,000), and chunk sizes of 3 Mb and 5 Mb for the respective arrays. Within each array batch, genotyped SNPs used for imputation were required to have missingness <.02, Hardy-Weinberg equilibrium p > 10-6, and minor allele frequency >.01. The imputation reference set consisted of 2504 phased haplotypes from the full 1000 Genomes Project Phase 3 data set (May 2013, >70 million variants, release

"v5a"). Imputed SNPs were retained if they had high imputation quality (Info >.9), low missingness (<5%), and minor allele frequency (MAF) >.01.

**Polygenic Risk Score Calculations**

Polygenic risk scores (PRS) were derived using PLINK (Purcell, 2017), across ten p-value significance thresholds (PT; i.e., 0.0001, 0.001, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, and 1.0) from the Linner *et al.* 2019 GWAS of risk tolerance. SNPs were required to have a MAF of >0.02, genotyping rates of >0.98, and HWE p-values $>10^{-6}$ to be included in the PRS. SNPs within the major histocompatibility complex (MHC; present on chromosome 6) were excluded, due to complex linkage structure within this region. All remaining SNPs were pruned based on linkage disequilibrium (LD; i.e., genetic correlation) using a p-value-informed method, called "clumping," which groups correlated SNPs together and preferentially prunes markers that are less-significantly associated with the phenotype at hand; this process is implemented in PLINK to preserve the predictive accuracy of PRS. At all 10 p-value thresholds, each participant had a single PRS score that reflects genome-wide liability for risk-taking, calculated using beta weight for risk-taking for each component SNP (i.e., those in the original meta-analysis with p-values below the cutoff threshold), multiplied by the number of reference alleles for that SNP, then aggregated and divided by the total number of contributing SNPs.

**Discovery GWAS Risk Taking Phenotyping**

The Linner *et al*., 2019 GWAS assessed risk tolerance via a single-item, self-report measure. The measure was unique to each of the two studies from which the 939,908 participants were drawn. Participants acquired from the UK BioBank (n=431,126) answered the following: "Would you describe yourself as someone who takes risks? Yes/No," where "yes" was coded as a 1 and "no"

coded as a 0 (mean response ± SD: 0.26 ± 0.44). Participants acquired from 23andMe (n=508,782) self-rated overall comfort with taking risks on a scale with the following options: [1] Very uncomfortable / [2] Somewhat uncomfortable / [3] Neither comfortable nor uncomfortable / [4] Somewhat comfortable / [5] Very comfortable (mean rating ± SD: 3.16 ± 1.15; Karlsson Linnér et al., 2019).

**PrediXcan Analyses**

We used PrediXcan to examine whether genomic risk for risk taking is correlated with brain-based gene expression. This approach uses postmortem gene expression and static-DNA-sequence data from the Genotype-Tissue Expression (GTEx) Project (Lonsdale et al., 2013) to estimate genomic influence on gene expression and examine whether such genetically-related differences in gene expression are correlated with a trait of interest based upon GWAS summary statistics (Gamazon et al., 2015). PrediXcan provides tissue-specific models of 44 tissues from GTEx, as well as a whole-blood model from the Depression Genes and Networks (DGN) cohort (Battle et al., 2014), and may help prioritize GWAS-identified loci (Li et al., 2018). Here, we applied PrediXcan to postmortem brain data to identify specific genes that have differential expression based on the risk tolerance GWAS (Linner *et al*., 2019); in effect, the PrediXcan approach detects significant correlations between imputed gene expression and risk tolerance in order to identify genes that may play an etiological role in risk-taking behavior. Then, we created a PRS for each participant that contained variants from these PrediXcan-implicated genes. PrediXcan-based PRS were computed using the same standards (i.e., MAF, genotyping rates, HWE, and LD-pruning) and computational methods described above and were weighted based upon association with the risk-tolerance phenotype (see Polygenic Risk Score Calculations).

## 2.5 Statistical Analyses

We performed linear regression analyses using R to test for associations between risk-taking PRS (at each of ten significance thresholds, i.e., 0.0001 through 1.0) and self-reported risk-taking measures, as well as activation in the ventral striatum. For these analyses, covariates included biological sex, age, and the top-three ancestry-informative scaling components to account for potential effects of population stratification.[2]

[2] For structural analyses, which were performed in light of null functional findings (see Results), we applied this same linear regression approach with all listed covariates plus average cortical thickness.

# 3.0 Results

## 3.1 Self-Reported Risk-Taking

We observed no significant associations between risk-taking PRS and delay discounting, BIS, and AUDIT scores [i.e., the only nominally-significant associations arose between PRS at the 0.30 threshold and delay discounting (b=0.7822; p = 0.0172) and between PRS at the 0.0001 and 1.0 thresholds and BIS score (b=0.0961; p = 0.0284 and b=-0.7586; p = 0.0423); all other ps > 0.1129; see **Table 3**].

**Table 3. Main Effects of Risk-Taking PRS on Behavioral Measures**

| | **DDT SCORE** | | **BIS SCORE** | | **AUDIT SCORE** | |
|---|---|---|---|---|---|---|
| **PRS p-threshold** | ***β*** | ***p*** | ***β*** | ***p*** | ***β*** | ***p*** |
| **0.0001** | -0.0215 | 0.6288 | **0.0961** | **0.0284** | 0.0667 | 0.1333 |
| **0.001** | -0.0594 | 0.4341 | -0.0503 | 0.4997 | 0.0819 | 0.2797 |
| **0.01** | -0.0432 | 0.6042 | 0.0659 | 0.4220 | -0.3474 | 0.6769 |
| **0.05** | 0.0281 | 0.8181 | 0.0894 | 0.4580 | 0.0834 | 0.4954 |
| **0.1** | 0.0347 | 0.8243 | -0.2073 | 0.1791 | 0.0459 | 0.7709 |
| **0.2** | -0.3421 | 0.1129 | -0.0311 | 0.8838 | -0.0230 | 0.9153 |
| **0.3** | **0.7822** | **0.0172** | 0.1891 | 0.5575 | -0.4230 | 0.1967 |
| **0.4** | 0.1624 | 0.7178 | 0.2264 | 0.6075 | 0.5589 | 0.2122 |
| **0.5** | -0.5826 | 0.2751 | 0.4372 | 0.4047 | 0.1316 | 0.8048 |
| **1** | -0.0772 | 0.8384 | **-0.7586** | **0.0423** | -0.3408 | 0.3682 |

## 3.2 Regional Neural Activation

Consistent with prior work (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000), the card-guessing task yielded robust bilateral ventral striatal activation (i.e., positive-activation > negative-activation contrast) that was roughly normally-distributed across participants (see **Supplemental Figure 1**). However, while there were sporadic nominal significant associations between PRS at

individual thresholds (PRS associated with left VS activity at the 0.01 threshold, p = 0.0438; PRS associated with right VS activity at the 0.01 threshold, p = 0.0222; see **Table 4**), there were no consistent significant associations between risk-taking PRS and ventral striatal reactivity across PRS thresholds (all other ps > 0.110). Of note, Pearson product-moment correlations computed between bilateral VS activation values and self-reported risk-taking scales show that only left VS activation and AUDIT score were significantly correlated (r = 0.114, p = 0.007; see **Figure 1**); all other correlations were non-significant (all r's < 0.081, p's > 0.1065; see **Table 5**).

**Table 4. Main Effects of Risk-Tolerance PRS and Ventral Striatum Activation**

| | VS ACTIVATION | | | |
|---|---|---|---|---|
| **PRS** | **Left** | | **Right** | |
| **p-threshold** | ***β*** | ***p*** | ***β*** | ***p*** |
| **0.0001** | -0.0181 | 0.6972 | -0.0369 | 0.4285 |
| **0.001** | -0.0269 | 0.7327 | -0.0532 | 0.4991 |
| **0.01** | **-0.1751** | **0.0438** | **0.1986** | **0.0222** |
| **0.05** | -0.0582 | 0.6585 | -0.0191 | 0.8845 |
| **0.1** | -0.0369 | 0.8232 | -0.0914 | 0.5798 |
| **0.2** | 0.0263 | 0.9061 | 0.1020 | 0.6467 |
| **0.3** | 0.2555 | 0.4555 | 0.1472 | 0.6668 |
| **0.4** | -0.3788 | 0.4139 | -0.1587 | 0.7318 |
| **0.5** | -0.5892 | 0.2947 | -0.5581 | 0.3205 |
| **1** | 0.6413 | 0.1065 | 0.4411 | 0.2661 |

**Figure 1. Correlation between Left VS and AUDIT Scores**

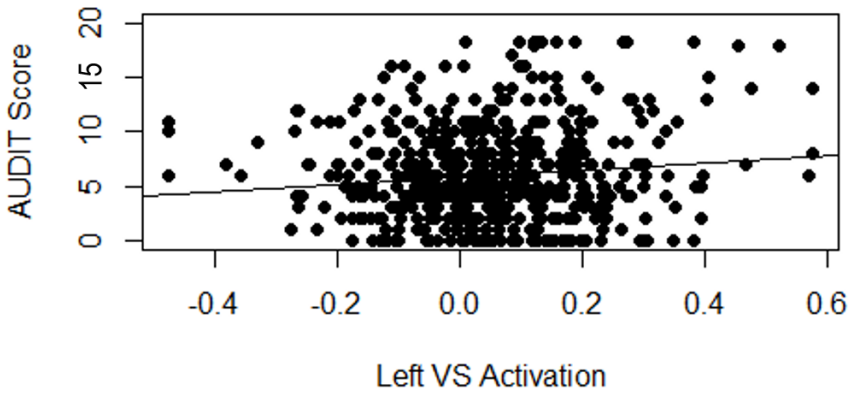

**Table 5. Pearson Correlations between Ventral Striatum Activation and Self-Report Scales**

| | BIS | DDT | AUDIT |
|---|---|---|---|
| **LEFT VS** | -0.0203 | -0.0178 | 0.1140* |
| **RIGHT VS** | -0.0570 | -0.0037 | 0.0807 |

*denotes significant correlation at $p<0.01$

## 3.3 PrediXcan

Our analyses identified 15 genes that showed differential expression across various tissue types: CENPV, ZSCAN23, SDCCAG8, AL022393.7, ZSCAN31, XRCC3, BTN3A2, RP5-874C20.3, FAM184A, ADORA2B, C10orf32, DPYSL5, RP11-62H7.2, ZKSCAN3, THEM6 (all ps < .0000113; see Table 6). However, PRS computed using SNPs from these 15 genes were not significantly associated with VS reactivity or behavioral risk-related phenotypes (all ps > 0.0978). GWAS-computed PRS and PrediXcan-computed PRS for each participant were not significantly correlated (Spearman's rho = -0.011, p = 0.812).

**Table 6. PrediXcan-Identified Genes with Differential Expression based on Risk-Tolerance GWAS**

| GENE | TISSUE TYPE(S) WITH HIGHEST EXPRESSION | β | P |
|---|---|---|---|
| CENPV | Cerebellum | -0.0152 | $4.81e^{-08}$ |
| ZSCAN23 | Cerebellum | -0.0153 | $3.36e^{-07}$ |
| SDCCAG8 | Diffuse across brain; thyroid | -0.0379 | $5.63e^{-07}$ |
| AL022393.7 | Diffuse across brain | -0.0098 | $6.51e^{-07}$ |
| ZSCAN31 | Diffuse across brain | -0.0104 | $1.16e^{-06}$ |
| XRCC3 | Cerebellum | 0.0244 | $3.69e^{-06}$ |
| BTN3A2 | Spleen and lymphocytes | 0.0127 | $4.47e^{-06}$ |
| RP5-874C20.3 | Cerebellum | 0.0167 | $5.75e^{-06}$ |
| FAM184A | Diffuse across brain | 0.0152 | $6.01e^{-06}$ |
| ADORA2B | Frontal regions; nucleus accumbens; vagina | -0.0398 | $6.84e^{-06}$ |
| C10orf32 | Diffuse across brain; adrenal cortex | -0.0109 | $7.38e^{-06}$ |
| DPYSL5 | Spinal cord | 0.0161 | $9.62e^{-06}$ |
| RP11-62H7.2 | Thyroid, kidney, lungs | 0.0110 | $9.88e^{-06}$ |
| ZKSCAN3 | Diffuse across peripheral regions | 0.0165 | $1.03e^{-05}$ |
| THEM6 | Cerebellum, frontal cortex, bladder | 0.0245 | $1.13e^{-05}$ |

# 4.0 Discussion

Externalizing diagnoses, including ADHD, substance-use disorders, and antisocial and conduct disorders, are moderately-to-largely heritable and characterized by both increased risk-taking behaviors (i.e., impulsivity, delay discounting, and alcohol use) and differences in neural activation in key reward-related regions (e.g., ventral striatum). In light of mounting evidence of a complex polygenic architecture underlying complex behavior and the limited utility of single SNP and candidate-gene approaches for examining genetic contributions to heritable psychiatric phenotypes, the current study used a polygenic risk score (PRS) method to assess associations between risk-related phenotypes and genome-wide liability for risk-taking behavior. Contrary to our hypotheses, we did not find any consistent significant associations between PRS and neural activation in the ventral striatum, or between PRS and impulsivity, delay discounting, or AUDIT scores. Further, though PrediXcan analyses of post-mortem gene-expression data pointed to 15 genes with differential expression related to genomic risk-taking liability, none were significantly associated with the behavioral or neural phenotypes in question, nor was a PRS calculated using variants from these genes.

Our null findings run counter to several recent publications showing significant associations between increased genomic risk for psychopathology and differential neural and behavioral phenotypes. For example, Erk and colleagues have reported that schizophrenia-based PRS predicts increased cingulate activation during episodic memory and social-cognition tasks (Erk et al., 2017), and a systematic review published just this year indicates that, across multiple studies, genetic liability for bipolar disorder and schizophrenia predicts aberrant activation of frontal regions (Dezhina, Ranlund, Kyriakopoulos, Williams, & Dima, 2019); together, these findings putatively link genomic risk to cortical inefficiency during task performance.

Furthermore, PRS based on cross-diagnostic liability has been linked to increased generalized risk for substance use, suggesting shared mechanisms between psychopathology and substance involvement (Carey et al., 2017). PRS computed using genes derived from PrediXcan analyses showed similar null associations to the GWAS-generated PRS, which suggests that, here, a biologically-informed approach to PRS did not yield increased predictive power. Notably, no studies have been published to date utilizing PrediXcan-generated PRS that may reflect etiological contributions via gene-expression differences, nor have studies been published comparing predictive power GWAS-generated PRS to that of PrediXcan-informed PRS, rendering the current study particularly novel. It is possible that predictive power of the PrediXcan-informed PRS in our study may be limited by potential regulatory factors at play; as such, it may be useful for future studies to conduct more comprehensive analyses by integrating further with mRNA-expression databases (e.g., GTEx) to find expression quantitative trait loci (eQTLs) that are associated with PrediXcan-identified genes (but may be located outside of them).

Our lack of significant findings may indeed reflect truly null associations; that is, that genomic liability for risk-taking does not predispose individuals to differences in related neural or behavioral measures, regardless of whether liability is based upon on statistically- or biologically-informed associations. However, our null findings may also be attributable to alternative explanations, which are detailed below.

## 4.1 GWAS Phenotyping

As noted previously, the Linner *et al.* GWAS assesses general risk tolerance via a one-item, self-report measure. Participants acquired from the UK BioBank (n=431,126) answered the

following: “Would you describe yourself as someone who takes risks? Yes/No,” where “yes” was coded as a 1 and “no” coded as a 0 (mean response ± SD: 0.26 ± 0.44). Participants acquired from 23andMe (n=508,782) self-rated overall comfort with taking risks on a scale with the following options: [1] Very uncomfortable / [2] Somewhat uncomfortable / [3] Neither comfortable nor uncomfortable / [4] Somewhat comfortable / [5] Very comfortable (mean rating ± SD: 3.16 ± 1.15; Karlsson Linnér *et al.*, 2019). This broad phenotyping has allowed for consequently high response rates, enabling Linner and colleagues to concatenate data from over 900,000 participants. However, this phenotype is questionably ecologically relevant, and relatively low endorsement of extreme risk-taking behaviors and attitudes (as surmised from mean scores on both scales) may indicate that this group is not particularly well-populated with risk-tolerant individuals. As well, the two datasets that comprise Linner and colleagues’ sample (i.e., the UK BioBank and 23andMe) used different assessments of risk tolerance, which may have affected phenotypic continuity across the sample at large. In all, a lack of precision in phenotypic assessment may have compromised the study’s ability to assess externalizing in a way that would meaningfully and/or practically correlate with neural or behavioral markers.

Indeed, evidence suggests that phenotyping and sample size may both impact the power and utility of discovery GWAS (Bogdan et al., 2018). GWAS based on low-pass phenotypic measurements (i.e., measurements that allow for data to be easily acquired from large samples, but, in turn, may sacrifice quality or specificity) have successfully identified significant loci: for example, a GWAS of AUDIT scores, a self-report measure assessing alcohol use in the past 12 months, identifies similar genetic loci and produces results that are genetically correlated with ($r_g$: 0.33-0.63) with alcohol dependence (Sanchez-Roige et al., 2019). Should we see similar results for other complex psychiatric phenotypes, it would suggest that low-pass phenotypes,

such as the metric used by the risk-tolerance GWAS referenced in the current study, may allow us to quickly amass findings that lend insight into the role of genetic variation in psychopathology. On the other hand, it is possible that low-pass phenotypes are not positioned to detect the most mechanistically-informative loci. In fact, some evidence supports the idea that low-pass phenotyping is not sufficient to uncover the genetic architecture of complex psychopathology: for instance, in contrast to an initial larger GWAS of major depressive disorder (Ripke et al., 2012), a smaller GWAS of severe, primarily melancholic, depression characterized by anhedonia was notably more successful at identifying genomic loci associated with depression risk, including a previously-reported candidate gene, *SIRT1* (Cai et al., 2015). Meanwhile, other studies using a meta-analytic approach to examine GWAS of heterogenous depressive phenotypes have identified many variants (Howard et al., 2019; Wray et al., 2018), e.g., upwards of 100 in a single meta-analysis (see Howard *et al.*, 2019). Going forward, it will be important for intermediate-phenotype research, such as neuroimaging, to evaluate whether genomic risk for low-pass phenotypes (e.g., Linner *et al*., 2019) is differentially predictive than formal psychiatric diagnoses.

## 4.2 Reliability of Task-Related fMRI

Our null results may stem from constraints on the precision of our neuroimaging methodology. In the DNS, VS activation is measured via a canonical card-guessing task: in the scanner, participants are instructed to guess whether a face-down card will be greater or smaller than a target number, earning a positive monetary reward for correct guesses and incurring a loss for incorrect guesses. This task has been shown to reliably elicit robust increases in VS activation to positive feedback as compared to negative feedback. Notably, task-based fMRI was initially

developed to measure average regional activation at the group level, in order to identify specific neural regions associated with phenotypes. Examining whether individual differences in the extent or variability of activation are associated with complex behavior and psychiatric phenotypes was intuitively appealing following reliable map-based activation patterns. However, emerging evidence from meta-analyses and independent studies suggests that the magnitude of task-related activation as typically studied in individual differences research has poor reliability as measured via intraclass correlation (ICC; mean ICC=0.39; see: Elliot *et al.,* 2019). This is based on two converging empirical findings: 1) Across a host of tasks designed to elicit activation in specific brain regions (included the card-guessing task), target-region reliability failed to surpass non-target-region reliability, and 2) Using a meta-analytic approach to examine published task-fMRI findings, test-retest reliability was relatively low (ICC=0.397; Elliot *et al.*, 2019). Because low reliability necessarily reduces statistical power, this sobering estimate of task-fMRI reliability for individual-differences research may suggest that previously-published findings have questionable replicability and validity. Here, it might suggest that task-fMRI is not the right vehicle with which to identify neural markers of genomic risk or externalizing disorders, and our null VS-reactivity findings may be the result of employing a method that is unfit to establish putative links between brain activation and externalizing. Structural MRI may be better-suited to the individual-differences nature of the current study, as even in between-subjects research, structural measures yield encouragingly-high test-retest reliability [ICC>0.90; specifically, cortical thickness and surface area are able to be measured with much greater reliability than task activation; (Elliot et al., 2019; Han et al., 2006; Jovicich et al., 2006)]. In light of this, we examined PRS associations with cortical thickness calculated using FreeSurfer. While estimates were not available for the VS, we examined frontal and sub-cortical regions that

have been implicated in reward-related processes. These investigations yielded null results as well (see **Supplemental Tables 2** and **3**), which may be a product of power and phenotyping limitations. Of note, we did not use these regions as ROIs for follow-up analyses of task activation, in part to limit multiple testing, and in part because the ventral striatum is the single ROI that is most robustly activated during the card-guessing task, while other frontal and sub-cortical reward-related regions are not activated to nearly the same extent.

## 4.3 Predictive Power

Critiques of the PRS method have noted that studies are often underpowered to detect small effects on complex phenotypes (Bogdan et al., 2018). Among PRS computed for psychiatric diagnoses, those with the greatest predictive power typically predict less than 1% of variance in psychiatrically-relevant traits. One well-powered schizophrenia PRS (SCZ2-PRS, created by the Schizophrenia Working Group of the Psychiatric Genomics Consortium, based on a sample of 36,989 cases and 113,075 controls) has been reported to predict 0.7% of variance in negative symptoms (Jones et al., 2016) and 0.3% of variance in cognition (Riglin et al., 2017) among the general population. These effect sizes are not particularly encouraging, and the PRS method's mixed predictive success is compounded by its reliance on multiple factors, including the PRS itself (as calculated using summary statistics from a discovery GWAS), the size of the target sample (i.e., here, the DNS), the nature of the trait it is used to predict, and the true strength of the association between genomic liability and behavioral or neural phenotypes across diagnoses.

The GWAS on which we based our PRS calculations had an impressive sample of over 900,000 individuals amassed from two large datasets (Karlsson Linnér et al., 2019), which is more than many previous studies of its kind. However, power calculations (using G*Power

software) indicate that a target sample size of at least 800 is required to account for a benchmark 1% of variance. Because our target sample, the DNS, has a sample size smaller than this estimate, it is arguably underpowered to detect effects that may truly exist in the population at large, which may have led to the null effects we have reported. Further, PRS have been reported to yield much larger effect sizes when they are used to predict the exact trait on which a discovery GWAS was based. For instance, estimates suggest that a GWAS for a phenotype with n = 1,000,000 may generate PRS that explain up to 15% of variance *in that same phenotype* in an independent target sample (Rietveld et al., 2013). However, when PRS are used to predict more distal, related traits – as we have done here to predict neural and behavioral risk-related phenotypes – they tend to generate smaller effect sizes, which may have also contributed to our null results.

## 4.4 Limitations and Future Directions

In all, our results should be considered in the context of several important limitations. Above, we explored several possible explanations for the null results we report. These included potential limitations on predictive power, which in the current study stem largely from the relatively-small sample size of the DNS, despite a quite-large discovery GWAS. In the future, studies with larger target samples may be better poised to detect small differences in complex externalizing phenotypes (Bogdan et al., 2018). Further, we discussed the use of task-based fMRI in between-subjects research, which yields lower reliability than would be needed to detect disorder-related biomarkers (Elliot et al., 2019). Importantly, the literature recommends a few key actions to remedy this, including using tailored analyses techniques with existing data (e.g., latent variable models, machine learning); encouraging open reporting of reliability for all task-fMRI measures

used to assess individual differences, which will bolster replication attempts; creating new tasks that prioritize reliable measurement and increase validity; and exposing subjects to complex stimuli during imaging (i.e., "naturalistic fMRI"), which may maximize ecological validity (for a more detailed explanation of these points, see: Elliot *et al.,* 2019). Finally, we discussed imprecise phenotyping in the discovery GWAS that may have limited our study's practical applicability. Of note, the discovery GWAS employed a case-control dichotomy of "risk tolerant" versus "non-risk tolerant" individuals based on a single self-report item. Self-report measures are especially prone to bias, which may be related to social desirability and experimenter-expectancy effects, among other factors. Thus. this measurement may have introduced error to the summary statistics we used to compute PRS. Future genome-wide explorations of externalizing should consider more robust measures of risk-related phenotypes that assess various facets of both behavior (e.g., substance consumption, impulsive behaviors) and attitudes (e.g., assessment of risk tolerance in both self and other).

In addition to such methodological limitations, the generalizability of our findings may also be limited by the composition of our target sample. The DNS is comprised of largely-healthy college students and community members and is not purposefully enriched for externalizing features. This allows us to obtain a wide range of scores on behavioral measures of impulsivity, delay discounting, and alcohol use that are comparable to the population at large, but it does not allow us to use risk-taking PRS to predict current or future diagnosis of externalizing disorders. Future investigations of the link between genomic liability for risk-taking and the development of externalizing disorders in patient populations would better inform downstream consequences. Additionally, for the current study, we performed all analyses in a European-ancestry subset of the DNS, in order to match the ethnic composition of the discovery

GWAS. While the majority of GWAS studies thus far have been conducted in European-ancestry populations to control for potential confounding effects of population stratification on genetic factors (Morales et al., 2018), it will be crucial for the field to improve its knowledge of how genetic research applies across ethnicities and ancestries, as well as for future studies to recruit diverse samples.

## 4.5 Conclusions

Externalizing disorders, characterized by sensation-seeking, impulse-control issues, and risk-taking behavior, are common and have an immense socioeconomic and personal impact. Though the literature suggests that they are highly-heritable, we know surprisingly little about the etiologic mechanisms that underlie externalizing psychopathology, and, in turn, treatment and prevention methods are limited. The current study investigated whether genomic liability for externalizing, based upon a large-scale GWAS of risk tolerance, was associated with risk-related behavioral and neural phenotypes in a community sample. Further, we explored differential gene expression related to genomic liability and compared the predictive power of GWAS-based PRS to that of gene-expression-based PRS. Here, we report null results with both approaches; as such, future studies are needed to better understand how various factors that may have impacted our results – including the reliability of task-fMRI, low-pass vs. deep phenotyping in genome-wide studies, sample size, and statistical power – influence the utility of individual-differences neuroscience and genetics research to inform our mechanistic understanding of complex disorders.

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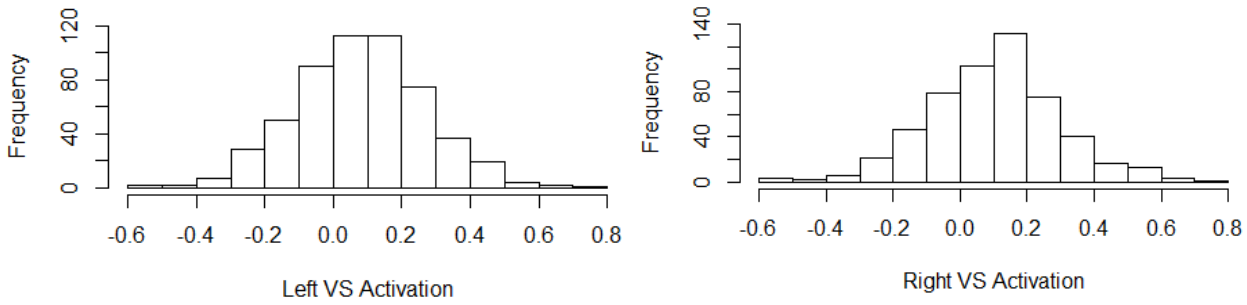
# Supplemental Materials

**Supplemental Table 1. DNS Psychiatric Diagnosis Data**

| Diagnosis | Number of Participants |
|---|---|
| Major Depressive Disorder | 28 (5.32%) |
| Bipolar Disorder | 16 (0.03%) |
| Panic Disorder (no Agoraphobia) | 14 (0.03%) |
| Panic Disorder (with Agoraphobia) | 12 (0.02%) |
| Social Anxiety Disorder | 5 (0.01%) |
| Obsessive Compulsive Disorder | 6 (0.01%) |
| Alcohol Abuse/Dependence Disorder | 67 (12.7%) |
| Post-Traumatic Stress Disorder | 0 (0.0%) |

**Supplemental Figure 1. Distribution of Ventral Striatal Activation to Card-Guessing Task**



**Supplemental Table 2. Main Effects of Risk-Tolerance PRS on Structure of Risk-Related Cortical Regions**

| | ROSTRAL ACC | | CAUDAL ACC | | LATERAL OFC | | MEDIAL OFC | |
|---|---|---|---|---|---|---|---|---|
| **PRS p-threshold** | ***β*** | ***P*** | ***β*** | ***p*** | ***β*** | ***p*** | ***β*** | ***p*** |
| **0.0001** | -0.0175 | 0.6840 | -0.0501 | 0.2341 | **-0.0871** | **0.0198** | -0.0162 | 0.6940 |
| **0.001** | **-0.1665** | **0.0203** | -0.0842 | 0.2422 | -0.0269 | 0.6729 | 0.0066 | 0.9250 |
| **0.01** | 0.1225 | 0.1186 | 0.1061 | 0.1788 | 0.1158 | 0.0976 | -0.0277 | 0.7200 |
| **0.05** | **-0.2854** | **0.0138** | -0.1944 | 0.0947 | -0.1228 | 0.2369 | -0.0245 | 0.8291 |
| **0.1** | 0.1067 | 0.4684 | 0.1562 | 0.2913 | 0.0748 | 0.5678 | 0.1533 | 0.2902 |
| **0.2** | -0.0282 | 0.8898 | 0.0711 | 0.7279 | -0.0425 | 0.8141 | -0.1393 | 0.4860 |
| **0.3** | 0.3265 | 0.2895 | 0.2695 | 0.3844 | **0.5805** | **0.0347** | 0.2320 | 0.4450 |
| **0.4** | -0.0562 | 0.8938 | 0.1091 | 0.7964 | -0.0620 | 0.8686 | -0.1376 | 0.7400 |
| **0.5** | -0.0728 | 0.8849 | -0.1626 | 0.7477 | -0.7476 | 0.0954 | 0.2061 | 0.6770 |
| **1** | -0.0450 | 0.8996 | -0.2685 | 0.4537 | 0.2352 | 0.4585 | -0.3074 | 0.3810 |

**Supplemental Table 3. Main Effects of Risk-Tolerance PRS on Structure of Risk-Related Subcortical Regions**

| | PARA-HIPPOCAMPUS | | ENTORHINAL CORTEX | | INSULA | |
|---|---|---|---|---|---|---|
| **PRS p-threshold** | ***β*** | ***p*** | ***β*** | ***p*** | ***β*** | ***p*** |
| **0.0001** | -0.0254 | 0.5676 | 0.0210 | 0.6368 | 0.0257 | 0.5180 |
| **0.001** | **-0.1700** | **0.0254** | -0.0110 | 0.8855 | 0.0766 | 0.2596 |
| **0.01** | 0.0212 | 0.7900 | -0.0405 | 0.6270 | 0.0202 | 0.7858 |
| **0.05** | 0.0494 | 0.6862 | 0.1390 | 0.2571 | -0.1281 | 0.2432 |
| **0.1** | 0.1431 | 0.3586 | -0.0214 | 0.8911 | -0.1297 | 0.3532 |
| **0.2** | -0.1966 | 0.3613 | -0.1605 | 0.4570 | 0.2034 | 0.2921 |
| **0.3** | -0.0870 | 0.7898 | -0.0534 | 0.8703 | 0.3777 | 0.1696 |
| **0.4** | 0.5817 | 0.1922 | 0.2315 | 0.6043 | 0.2073 | 0.6039 |
| **0.5** | **-1.0564** | **0.0478** | -0.2753 | 0.6060 | -0.8849 | 0.0642 |
| **1** | 0.6716 | 0.0757 | 0.2587 | 0.4941 | 0.3199 | 0.3444 |