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The hierarchical taxonomy of psychopathology as an approach to the psychiatric genetics of substance-related and addictive disorders in Vietnam-era twins

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THE HIERARCHICAL TAXONOMY OF PSYCHOPATHOLOGY AS AN APPROACH TO THE PSYCHIATRIC GENETICS OF SUBSTANCE-RELATED AND ADDICTIVE DISORDERS IN VIETNAM-ERA TWINS

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ABSTRACT

Pathological gambling and substance use disorders are highly prevalent and comorbid among veteran populations. These disorders also share genetic influences, although the underlying constructs and magnitude of their influence remain unclear. This project utilized the Hierarchical Taxonomy of Psychopathology (HiTOP) as a framework for modeling the underlying dimensions of psychopathology as latent factors and modeled genetic and environmental influences on substance use disorders and pathological gambling.

Study 1 examined the structure of psychopathology for 15 common mental disorders in a sample of Vietnam-era veteran twins from the Harvard Drug Study (n_{MZ} = 3,748 and n_{DZ} = 2,996) to determine the appropriate location for pathological gambling within the HiTOP framework. The best fitting model included internalizing and externalizing spectra and an illicit substance use subfactor. Pathological gambling (*loading* = .30) loaded onto the externalizing spectrum with legal substance use, conduct disorder, antisocial personality disorder, and a subfactor that subsumed all six illicit substance use disorders. The best fitting model in Study 1 did not support the existence of a 'p' factor underlying all psychopathology.

In Study 2, genetic and environmental components were modeled for the 15 disorders and 3 latent factors modeled in Study 1. Additive genetics explained from 10% (generalized anxiety disorder, panic disorder) to 49% (nicotine use) of the variance in specific disorders and from 24% (internalizing) to 46% (externalizing) of the variance of latent factors. Only cocaine use and conduct disorder demonstrated significant variance attributable to shared environment, the entirety of which occurred at the disorder-specific level. Only 9% of the genetic variance associated with alcohol use was shared across disorders, whereas 100% of genetic variance in cocaine and hallucinogen use was shared with latent factors. In total, 12% of the variance in risk for pathological gambling was associated with additive genetics, and 13% of that variance was shared via the externalizing spectrum.

Findings highlight shared risk among illicit substance use disorders and among other disorders on the externalizing spectrum. These findings suggest externalizing and illicit substance use as transdiagnostic targets for treatments aimed at individuals with comorbid substance use disorders, pathological gambling, and other externalizing disorders.

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A	A component of ACE modeling (additive genetics)
AIC	Akaike Information Criteria
APA	American Psychiatric Association
C	C component of ACE modeling (shared environment)
CFI	Comparative fit index
DIS-3R	Diagnostic Interview Schedule, Version 3 Revised
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-5	DSM, fifth edition
DSM-III(-R)	DSM, third edition (revised)
DSM-IV	DSM, fourth edition
DZ	Dizygotic
E	E component of ACE modeling (non-shared environment)
HiTOP	Hierarchical Taxonomy of Psychopathology
MZ	Monozygotic
RMSEA	Root Mean Square Error of Approximation
SAMHSA	Substance Abuse and Mental Health Services Administration
SNP	Single Nucleotide Polymorphism
SRMR	Standardized Root Mean Square Residual
SUD(s)	Substance Use Disorder(s)

CHAPTER 1. General Introduction[1]

Substance Use and Pathological Gambling in Veterans and the General Population

The mental health diagnosis associated with gambling was referred to as "pathological gambling" when introduced to the 3rd edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) in 1980 (Abbott, 2017). The fifth edition of the DSM (DSM-5) utilizes the term "gambling disorder" to describe significant pathological gambling. In the latest revision to the DSM-5, gambling disorder was included in the chapter titled "Substance-Related and Addictive Disorders" (American Psychiatric Association [APA], 2013). This change reflects increasing evidence that pathological gambling[2] shares symptoms and genetic and environmental influences with substance use disorders (SUDs). Pathological gambling is highly comorbid with multiple SUDs (Bresin, 2020; Croce & D'Agati, 2016; Dash et al., 2019; Manning et al., 2017; Nicholson et al., 2019). Moreover, gambling shares genetic influences with SUDs, whether defined categorically as a diagnosis of pathological gambling or using dimensional constructs (Frascella et al., 2010; Lang et al., 2016; Slutske et al., 2000; Slutske et al., 2001; Slutske et al., 2013). A rich body of literature also connects pathological gambling to SUDs via commonly implicated brain regions, cognitive processes, and response to clinical treatments (Anselme & Robinson, 2020; Balodis & Potenza, 2020; Grant & Chamberlain, 2020; Koob & Volkow, 2010; Linnet, 2020; Mallorqui-Bague et al., 2016; Potenza, 2017;

[1] This work was supported by the American Psychological Association, Division 19 Student Research Grant

[2] Because this study utilizes diagnostic criteria from the revised third edition DSM, the term "pathological gambling" will be used throughout unless referring directly to the 5th edition diagnostic criteria.

Rash et al., 2016; Setlow et al., 2020; Vitaro et al., 2019; Werner et al., 2020; Zois et al., 2017).

The prevalence of recreational gambling has grown along with access to online gaming and relaxed regulatory measures against terrestrial (i.e., in-person) gambling (Abbott, 2020). Adult problem gambling (which is distinct from pathological gambling and is defined in most studies as a pattern of gambling behavior resulting in negative consequences that does not meet DSM criteria for a pathological gambling diagnosis) has increased, with current worldwide prevalence estimated in the range of 0.1-5.8% (Abbott, 2020). One study of 6,613 participants revealed that 22.7% of the sample reported gambling at least $10 monthly. Of those regular gamblers, 8.5% met criteria for fourth edition DSM (DSM-IV) pathological gambling (Rennert et al., 2014). The prevalence of pathological gambling in the United States and Canada is estimated between 0.4% to 0.6%, using DSM-IV criteria (Potenza et al., 2019). Both pathological gambling and subclinical problem gambling may cause significant harm to affected individuals in the form of financial impacts, damage to relationships, and psychological distress (Abbott, 2017; Abbott, 2020). Recent studies suggest that the burden of harm associated with problem gambling is similar in magnitude to alcohol dependence and major depression (Browne et al., 2016) and three times greater than drug use disorders (Browne et al., 2017).

The most recent prevalence estimates for SUDs in the United States are derived from the 2019 National Surveys on Drug Use and Health. Twelve-month prevalence for SUDs was estimated at 14.1% among adults aged 18 to 25 and 6.7% among adults 26 and older (Substance Abuse and Mental Health Services Administration [SAMHSA], 2020a).

Among individuals with any SUD diagnosis, 11.8% were diagnosed with comorbid drug use disorder(s) and alcohol use disorder. SUD diagnoses have been associated with increased risk for physical and mental health conditions (e.g., sexually transmitted disease, heart disease, bipolar disorder, cancer) as well as accidental injury (Schulte & Hser, 2013).

Rates of both SUDs and pathological gambling are higher among veterans compared to the general population (Levy & Tracy, 2018). Among veterans completing the 2019 National Surveys on Drug Use and Health, 6.2% of those 18 or older had a SUD diagnosis within the last year (SAMHSA, 2020b). In total, 3.9 million veterans had a mental illness or SUD in 2019, and veteran misuse of alcohol, prescription stimulants, methamphetamine, and cocaine have increased annually since 2016 (SAMHSA, 2020b). In a study of Veteran Affairs medical records, 472,624 veteran patients were diagnosed with at least one SUD, and of those 27% had one or more comorbid SUDs (Bhalla et al., 2017). Another study utilizing Veterans Affairs records found a 0.2% lifetime prevalence of pathological gambling among veterans, although this is likely a low estimate, as pathological gambling is not regularly screened for in Veterans Affairs medical centers (Levy & Tracy, 2018). Among veteran clinical populations already in treatment for other mental health diagnoses, prevalence estimates for pathological gambling range from 2% to 29%, with up to 35.1% of veterans engaging in recreational gambling within the past year (Levy & Tracy, 2018). Further, pathological gambling is associated with increased risk for suicide, depression, criminal behavior, and domestic violence among veterans (Levy & Tracy, 2018). Unique risk factors for pathological gambling and SUDs in veteran populations include deployment, combat exposure, and higher rates of post-traumatic stress

disorder (Teeters et al., 2017). Moreover, SUDs and pathological gambling are associated with increased suicidal ideation and suicide attempts for which military populations are already at higher risk compared to civilian populations (Drescher et al., 2003; Potenza et al., 2019).

The substantial risks conferred by SUD and pathological gambling are compounded by the fact that these diagnoses are often comorbid. In a meta-analysis of studies including clinical samples of substance users, 14% of patients met criteria for pathological gambling, and 23% engaged in subthreshold problem gambling (Cowlishaw et al., 2014). One Australian study assessed gambling and SUD symptoms in an online sample of 837 participants and found that rates of nicotine and drug dependence were significantly higher among moderate-risk and pathological gamblers compared to non-gamblers and low-risk gamblers (Manning et al., 2017). Another study utilizing the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions data found that 53.7% (using DSM-IV criteria) to 56.7% (using DSM-5 criteria) of individuals with a diagnosis of pathological gambling had at least one comorbid mental health diagnosis (Nicholson et al., 2019). In a study of veterans randomly selected from Veterans Affairs centers and community clinics in the Albuquerque and Minneapolis catchment areas of the United States, veterans with a SUD had 3.11 times the odds of having met criteria for pathological gambling during their lifetime (Westermeyer et al., 2013).

The high rates of SUDs and pathological gambling among veterans, underscore the importance of elucidating cognitive, behavioral, neurological, and genetic mechanisms underlying SUDs and pathological gambling as well as their comorbidity. The remainder

of this chapter highlights important cognitive, behavioral, neurological, and genetic mechanisms shared across SUDs and pathological gambling and outlines an approach for further studying genetic phenotypes that may be shared across the addictive disorders.

Shared and Disorder-Specific Mechanisms Underlying SUDs and Pathological Gambling

Several aspects of cognition and personality have been investigated as mechanisms of co-occurring SUDs and pathological gambling. One study of 3,298 individual twins and 487 singleton siblings from the Australian Twin Registry revealed that the presence of a SUD and/or pathological gambling diagnosis was significantly associated with high neuroticism, low agreeableness, and low conscientiousness (Dash et al., 2019). Another study of 591 Spanish participants who were grouped into healthy controls, participants with pathological gambling, and participants with SUDs found that learning profiles on the Iowa Gambling Task were impaired in the pathological gambling and SUD groups compared to healthy controls. Specifically, the clinical sample profiles reflected decreased learning from cues that tapped into reward sensitivity and incentive motivation (Mallorquí-Bagué et al., 2016). In one veteran sample of 1,129 individuals with SUD, 140 participants who had comorbid SUDs and pathological gambling displayed significant coping skill deficits compared to their peers with only a SUD diagnosis; in the comorbid sample, participants reported a heavy reliance on impulsive and avoidant coping styles (Levy & Tracy, 2018). Impulsivity has been closely linked to externalizing disorders, which are mental health diagnoses characterized by maladaptive behaviors directed outwardly (i.e., towards an individual's environment; Krueger et al., 2005). These findings suggest that veterans with

comorbid pathological gambling and SUDs might benefit from treatments focused on externalizing more broadly (Bresin, 2020).

However, research also supports the existence of disorder-specific personality profiles that underlie different addictive disorders. For example, Zilberman and colleagues (2018) administered the Big Five Inventory and the Baratt Impulsivity Scale to 216 individuals from rehabilitation centers who were diagnosed with either substance use (drug and alcohol) or behavioral (gambling and sex) addictions. The authors found that a profile of high impulsivity and neuroticism was shared across all addiction populations compared to a sample of 78 healthy controls who endorsed these traits in lesser amounts; people with drug use disorders and sex addictions both endorsed less agreeableness and conscientiousness. People with DSM-IV pathological gambling endorsed personality profiles most similar to those of healthy controls, while individuals with alcohol use disorder endorsed less extraversion, agreeableness, and openness to experience. These findings suggest the importance of both common (e.g., impulsivity, neuroticism) and disorder-specific (e.g., low agreeableness and conscientiousness) personality profiles that may contribute to substance and behavioral addictions.

Neurologically, investigations of shared and disorder-specific mechanisms underlying SUDs and pathological gambling have focused on dopamine pathways related to the brain's reward system (Croce & D'Agati, 2016). Individuals who abuse cocaine or alcohol show abnormally high levels of dopamine in the ventral striatum along with elevated craving in response to drug-related cues, whereas dopamine levels are depleted in the HPA axis of pathological gamblers (Anselme & Robinson, 2020). Yet, dopamine

neurons are hypersensitized in individuals with SUDs or pathological gambling, indicating that both populations are sensitive to dopaminergic changes in the brain (Anselme & Robinson, 2020). Similarly, a recent meta-analysis found diminished dopaminergic anticipatory reward responses in the bilateral ventral striata among both SUD and pathological gambling samples; however, the SUD group demonstrated increased ventral striatal activity compared to the pathological gambling group, who demonstrated decreased dorsal striatal activity (Balodis & Potenza, 2020).

Other studies have highlighted common ventral frontostriatal circuity in pathological gambling and SUDs linked to reward processing and disadvantageous decision making (Frascella et al., 2010; Koob & Volkow, 2010; Setlow et al., 2020). In one unique study, individuals taking medications for Parkinson's disease (resulting in increased dopaminergic brain activity) reported developing gambling and substance use problems at higher rates than controls, again highlighting the importance of dopamine as a neurobiological mechanism underlying SUDs and pathological gambling (Grant & Chamberlain, 2020).

However, Zois and colleagues (2017) compared the neurological structures of 60 individuals with only pathological gambling to 31 individuals with pathological gambling plus alcohol use disorder and 16 with polysubstance use and pathological gambling. They found unique frontal cortex gray matter deficits in individuals with pathological gambling alone, suggesting that some structural brain alterations might be specific to gambling-related addictive behaviors. Taken as a whole, neurological studies suggest that there are

both common and disorder-specific dopaminergic processes and structural brain alterations that impact the development and course of GD and SUDs.

Genetics Influences on SUDs and Pathological Gambling

Child (Hicks et al., 2011; Iacono et al., 1999) and adult (Agrawal & Lynskey, 2014; Kendler et al., 2011; Kendler, Jacobson, et al., 2003; Kendler et al., 2007; Kendler, Prescott, et al., 2003; Palmer et al., 2012; Prom-Wormley et al., 2017; Tsuang et al., 1998) family and twin studies have identified both common cross-disorder genetic variance and disorder-specific genetic variance in SUDs. Several twin studies also support the existence of common and disorder-specific genetic and environmental influences among SUDs and pathological gambling (Slutske et al., 2000, 2001; Xian et al., 2014). Candidate genes such as GABRA2 (Agrawal et al., 2006; Dick et al., 2006; Drgon et al., 2010; Philibert et al., 2009; Yang et al., 2012) are heavily implicated in studies examining the genetics of both illicit and licit substance use, whereas other candidate gene associations to cross-disorder substance use have been identified but require replication (Buhler et al., 2015; Kreek et al., 2005; Luo et al., 2007; Sun et al., 2019). While GABRA2, DRD3, and DRD4 are all theorized to have associations with pathological gambling, no known candidate gene studies have reported significant candidate gene associations with pathological gambling (Comings et al., 2001; Mick et al., 2017; Nivard et al., 2016; Potenza, 2017). Finally, genome wide association studies have identified common genetic variants related to cell adhesion processes that are common across substance dependence cases, but no known genome wide association studies have included behavioral addictions in their analyses (Drgon et al., 2010; Johnson et al., 2008; Li et al., 2011; Liu et al., 2006). Two known

genome wide association studies examined pathological gambling, although neither study revealed significant SNPs associated with gambling behaviors (Lang et al., 2016; Nivard et al., 2016).

In the past two decades, psychiatrics genetics research has shifted from a focus on finding specific genes associated with specific categorical DSM diagnoses to finding multiple genes associated with alternative diagnostic phenotypes (Waszczuk et al., 2020). One explanation for this shift is mounting evidence to support the phenomenon of pleiotropy in psychiatric genetics, defined as genetic variation within a given locus that is associated with multiple phenotypes (Jang et al., 2020; Johnson et al., 2020). There are three theorized types of pleiotropy. Biological pleiotropy occurs when DNA variants are causally involved in the development of multiple psychological traits independently. Another theory involves mediated pleiotropy, where comorbidity occurs because DNA variants increase risks for one liability (e.g. externalizing) that in turn influences the presentation of other symptom sets (e.g. SUDs and conduct disorder). Generalized pleiotropy involves DNA variants that form a general susceptibility underlying all forms of psychopathology (e.g. the hypothesized 'p' factor; Selzam et al., 2018).

Justification for HiTOP as an Approach to the Genetics of Substance Use and Pathological Gambling

The Hierarchical Taxonomy of Psychopathology (HiTOP) is a quantitatively derived dimensional model of psychopathology proposed for use in research and clinical practice as an alternative to traditional categorical diagnoses (Kotov et al., 2017). The model was initially proposed in response to concerns with the current DSM diagnostic system. Specifically, the framework addresses heterogeneity within mental disorders (e.g.,

depression can be associated with weight loss or weight gain, hypersomnia or insomnia) by eliminating diagnostic categories and attempts to better explain comorbidity by grouping highly comorbid disorders under shared dimensions (e.g., externalizing, internalizing; Kotov et al., 2017). The HiTOP framework also takes a dimensional rather than categorical approach, such that there are no diagnostic cutoffs that suggest arbitrary boundaries between normality and psychopathology (Waszczuk et al., 2020).

The current HiTOP framework has been derived from studies that predate the consortium and continue today. As such, the HiTOP model is constantly evolving with the most up-to-date structure depicted in Figure 1 (all figures are located in Appendix A). Currently, symptoms and components make up the lowest tiers of the framework; these tiers represent the symptoms that make up disorders/syndromes, which are most similar to existing categorical diagnoses (Krueger et al., 2018). These three tiers of HiTOP are constructed from observed variables in structural equation modeling analyses. Beginning at the subfactor level, factor analyses have derived dimensions whose influences are shared across multiple mental disorders. Seven current subfactors have been proposed, including a SUD subfactor, although research at this level has resulted in disagreement about the stability of these dimensions with the HiTOP framework (Eaton et al., 2015). At the spectra level broader dimensions influence both subfactors and observed symptoms and syndromes; internalizing and externalizing are two of the most widely replicated dimensions in factor analytic research (Kotov et al., 2017). Internalizing disorders are generally characterized by anxiety, depressive, and somatic symptoms whereas externalizing disorders are characterized by impulsivity, disruptive conduct, substance use,

and other addictive behaviors (APA, 2013). With the creation of the HiTOP consortium, a bifurcation of the externalizing spectra and three additional spectra have been proposed; however, more research is required to validate these dimensions (Eaton et al., 2015). At the super spectra level is a general susceptibility underlying all psychopathology—the proposed 'p' factor (Caspi et al., 2014; Kotov et al., 2017). The 'p' factor has been observed and replicated in both child and adult samples (Caspi et al., 2014; Eaton et al., 2015; Oltmanns et al., 2018; Selzam et al., 2018). Nevertheless, whether the 'p' factor represents an underlying susceptibility, response bias, or a statistical artifact has been the subject of much debate among nosology researchers (Caspi et al., 2014; Eaton et al., 2015; Fried et al., 2021; Oltmanns et al., 2018; Selzam et al., 2018; Tackett et al., 2013).

In addition to addressing limitations to categorical diagnoses in clinical practice, adopting the HiTOP framework in research design can also address limitations to categorical diagnostic phenotypes in psychiatric genetics (Figure 2). One limitation to using yes/no diagnostic phenotypes is that categorical diagnoses often mask pleiotropy (Jang et al., 2020; Johnson et al., 2020). Research suggests that psychopathology is dimensional rather than categorical; there may be common genetic variants across regular substance use, problem use, and SUDs that are not detectable if subthreshold individuals are excluded from the analysis (Haslam et al., 2012; Haslam et al., 2020; Hicks et al., 2011; Kotov et al., 2017; Krueger et al., 2018; Krueger et al., 2007). Similarly, if there are common genetic effects that influence the whole spectrum of addictive behaviors, then dimensional phenotypes might be more well-suited to identifying genetic contributions to SUDs and pathological gambling. Modeling dimensional components of SUDs and

pathological gambling might help to unmask important pleiotropic genetic associations. A second limitation is that categorical diagnoses have the potential to limit statistical power in genetics research on SUDs. Genome wide association studies require large sample sizes to detect significant associations among single nucleotide polymorphisms (SNPs) and substance use (Dick et al., 2018; Smoller et al., 2019). Limiting the sample to individuals who meet the diagnostic cutoff decreases sample sizes considerably (Smoller et al., 2019). The use of dimensional symptoms rather than yes/no diagnoses in the HiTOP model addresses this limitation.

The current HiTOP structure proposes that SUDs are influenced by the externalizing spectrum as well as a unique SUD subfactor, while pathological gambling has not yet been added to the HiTOP model (Bailey & Finn, 2019, 2020; McDonald et al., 2019). Beginning at the super spectra level, there is a small but significant amount of research confirming the existence of a 'p' factor reflecting a generalized risk for psychopathology that contributes to both a quantitative and genetic risk for other psychiatric disorders, including SUDs (Caspi et al., 2014; Lahey et al., 2011; Selzam et al., 2018; Tackett et al., 2013). However, other research suggests that the 'p' factor represents response bias or an artifact reflecting the severity of distress and/or impairment, rendering it less useful in characterizing the spectrum of psychopathology (Fried et al., 2021; Oltmanns et al, 2018). Further research is necessary to both confirm the presence of a 'p' factor and to determine its genetic contributions to SUDs and other psychopathology.

At the spectra level, externalizing accounts for common variance among SUDs, conduct disorder, antisocial personality disorder, intermittent explosive disorder,

oppositional defiant disorder, and attention deficit hyperactivity disorder (Kotov et al., 2017). Numerous twin and family studies have identified an externalizing factor responsible for significant genetic and environmental variance across the aforementioned disorders (Hicks et al., 2004; Hicks et al., 2011; Kendler et al., 2011; Krueger et al., 2002; McDonald et al., 2019; Sellbom et al., 2020). There are also molecular genetics studies that have identified common SNPs and/or loci specific to the externalizing spectrum that also influence SUDs and antisocial behavior (Arcos-Burgos et al., 2012; Jang et al., 2020; Stallings et al., 2005).

There is little research examining the genetics of a substance use subfactor such as the one proposed in HiTOP (Figure 1); McDonald and colleagues (2019) found that all of the common genetic variance in SUDs was accounted for by externalizing rather than the SUD subfactor; a more recent genome wide association study identified 10 loci common across tobacco, cannabis, and alcohol use via a substance use subfactor in a study that also modeled internalizing and externalizing spectra (Jang et al., 2020). Follow-up studies that attempt to model the substance use subfactor and its genetic components may help to clarify these mixed findings.

Only two studies have attempted to model pathological gambling within the dimensional structure proposed by the HiTOP consortium. In one young adult sample, King and colleagues (2019) found evidence that pathological gambling loaded (.31) onto the externalizing factor. Similarly, a sample from the National Epidemiological Survey of Alcohol and Related Conditions examined the dimensional structure of pathological gambling and found evidence to suggest that pathological gambling is associated with

externalizing in men, although it was associated with both externalizing and the anxious misery (also known as fear) subfactor of internalizing in women (Oleski et al., 2011). These findings largely align with Bresin's (2020) hypothesis that pathological gambling shares variance with SUDs and other disorders common to the externalizing spectrum. However, given the significant commonalities between pathological gambling and SUDs, it is also possible that these diagnoses encompass an "addictive disorder" subfactor rather than a SUD subfactor. No known research has tested this alternative theory.

The HiTOP framework currently utilizes a level of syndromes (Level III in Figure 1) to represent and bridge current diagnostic categories with the rest of the proposed taxonomy, and this has been useful in research when symptom level data has not been available (Kotov et al., 2017); however, HiTOP consortium researchers encourage the development and use of symptom-level measures when analyzing the structure of psychopathology (Kotov et al., 2017; Krueger et al., 2002; Krueger et al., 2007). In the absence of such measures (largely due to lack of inclusion in data collection, particularly with historical data sets), researchers have utilized symptom counts as a dimensional alternative to categorical diagnoses to model genetic variance for HiTOP spectra and subfactors (Agrawal & Lynskey, 2014; Hicks et al., 2011; Kendler et al., 2011; Kendler et al., 2007; Krueger et al., 2002; Perkins et al., 2020). Thus, utilizing the HiTOP framework and existing knowledge about shared SUD and pathological gambling heritability, it is possible to: (1) examine how other addictive behaviors fit within the proposed HiTOP framework, (2) identify mediated and generalized pleiotropic processes unique to SUDs

and other addictive behaviors, and (3) model the common and substance-specific genetic variance at each level of psychopathology.

Outline of Dissertation

There are five primary studies that have utilized data from the Harvard Drug Study to model the common and disorder-specific genetic components of SUDs and pathological gambling. This body of research provides the foundation for the current study. One study examined common and disorder-specific genetic variance for illicit substances only (marijuana, sedatives, stimulants, heroin/opiates, and psychedelics; Tsuang et al., 1998). A second study examined shared and disorder-specific variance across alcohol, nicotine, and cannabis phenotypes only (due to low rates of other illicit substance use; Xian et al., 2008). Three other studies examined relationships across SUDs and pathological gambling. Two of those studies analyzed genetic variance common across pathological gambling and alcohol dependence (Slutske et al., 2000) and pathological gambling and antisocial personality disorder (Slutske et al., 2001). A third study modeled genetic variance among pathological gambling, cannabis dependence, nicotine dependence, and stimulant dependence (Xian et al., 2014). The current study will expand upon these original studies by 1) modeling the structure of common mental disorders using symptom counts rather than diagnostic yes/no categories, 2) integrating all of the licit and illicit SUDs as well as pathological gambling into one model, and 3) using the HiTOP structure to inform the proposed model, including the addition of the ‘p’ factor into models for this population. This study has the potential to identify the dimensional nature of pathological gambling

within HiTOP, which no known research has confirmed, and to provide an explanation for some of the shared genetic variance across pathological gambling and SUDs.

The purpose of this investigation is two-fold: 1) This study will examine the structure of psychopathology and the placement of pathological gambling within that taxonomy using dimensional phenotypes; 2) This study will utilize the best fitting structure to derive genetic and environmental variance that is both common to SUDs and pathological gambling as well as variance unique to each phenotype. Findings can help to elucidate the mechanisms through which substance use and pathological gambling are highly comorbid, particularly in a veteran sample of Vietnam-era twins. This study requires access to a large sample of twin pairs to facilitate biometrical modeling and to provide enough power to detect significant effects. Therefore, this study utilized secondary diagnostic data collected by phone interview during the Harvard Drug Study (described in Chapter 3 methods). As a result, this study builds upon previous studies that utilized data from the Harvard Drug Study to identify common and disorder-specific genetic variance across SUDs and across SUDs and pathological gambling using structural equation modeling. Chapter 2 provides an overview of the existing literature describing the use of structural equation models in twin studies and in studies modeling the dimensional nature of psychopathology and clarifies how these two approaches can be combined to address limitations in psychiatric genetics and dimensional psychopathology research. Study 1 (described in Chapter 3) reports findings examining the structure of SUDs and pathological gambling using the HiTOP framework. Study 2 (described in Chapter 4) builds upon Study 1 by modeling the common and disorder-specific psychiatric genetics of SUDs and

pathological gambling in the best fitting structure derived from Study 1. Chapter 5 integrates these findings, suggests implications for future research, and discusses the clinical implications of the research, particularly regarding treatment options for veterans.

CHAPTER 2. Structural Equation Modeling as an Approach to Understanding the Genetics of Comorbid Substance Use and Pathological Gambling

High rates of comorbid and untreated SUDs and pathological gambling among veteran populations suggest the need to understand common mechanisms underlying these disorders to better address the needs of this population (Golub et al., 2013; Teeters et al., 2017; Vazan et al., 2013; Westermeyer et al., 2013). A large body of research has elucidated cognitive, behavioral, neurological, and genetic mechanisms shared between SUDs and pathological gambling. Notably, several recent reviews highlight cognitive and neurological connections, particularly in the dopaminergic reward pathways of the brain, that contribute to both SUDs and pathological gambling (e.g., Anselme & Robinson, 2020; Balodis & Potenza, 2020; Croce & D'Agati, 2016; Grant & Chamberlain, 2020). Similarly, reviews have examined molecular genetics studies and how cell adhesion processes might represent one common mechanism underlying different SUDs (Agrawal & Lynskey, 2014; Johnson et al., 2020; Kreek et al., 2005; Liu et al., 2006). The purpose of this review is to highlight key research that has leveraged structural equation modeling to investigate the dimensional nature of SUDs and pathological gambling. Structural equation modeling provides a statistical means of modeling the dimensional structure of psychopathology, and it allows for the modeling of genetic and environmental variance attributable to both common dimensions and disorder-specific variance for mental health symptoms. This review will highlight previous structural equation modeling research in behavioral genetics and in modeling the dimensional nature of psychopathology, particularly via the HiTOP framework. Finally, this review will discuss opportunities for future research by

combining structural equation modeling approaches from these two separate fields of research.

SUDs and Pathological Gambling within the HiTOP framework

Introduction to the HiTOP Framework

The debate over the utility of categorical mental health diagnoses in clinical and research settings has resulted in efforts to rewrite the nosology of psychopathology over the years. Perhaps the most prominent issue, comorbidity across mental disorders is the rule rather than the exception. This stands true for addiction-related disorders; according to data from the 2019 National Survey on Drug Use and Health, 9.5 million of adults surveyed had a SUD and any other mental illness compared to 9.7 million who had a SUD and no other mental illness (SAMHSA, 2020a). Another concern with categorical diagnostic systems is the heterogeneity of presentation across different cases. Heterogeneity in SUDs is particularly prominent, given that differing dimensions can include the substance used, the number of substances used, severity, and the depth and breadth of problems that occur because of substance use (e.g., legal problems for some substance use, financial concerns for behavioral addictions such as pathological gambling; Carroll, 2021). Categorical diagnoses also set thresholds for psychopathology, suggesting that there is a line past which symptom sets should be considered relevant to research (Kotov et al., 2017).

In 2015, the HiTOP consortium was formed to advance a new, quantitative nosology that is both dimensional and capable of classifying mental illness in a way that is valuable in research and useful to patients and clinicians (Ruggero et al., 2019). The

HiTOP model, introduced in Chapter 1, accounts for the dimensionality of subthreshold symptoms to more severe presentations by measuring mental health concerns at the symptom level (Level V, Figure 1). The model also proposes that comorbidity results from the influence of latent dimensional factors (e.g., super spectra, spectra) that underlie commonly comorbid mental disorders. HiTOP addresses heterogeneity by allowing for symptom-level measurement and an effort to exclude diagnostic categories over time in favor of quantitatively derived diagnostic boundaries that operate on a spectrum rather than using cutoff if a certain number of symptom criteria are met.

The quantitative nosology that represents the strength of the HiTOP framework rests on the use of structural equation modeling and is born from a rich history of techniques, including cluster analysis, modeling the structure of affect, factor analytic studies of child symptomatology, and more recently, modeling the structure of normal personality (defined using traditional personality models such as the Big Five; Kotov et al., 2017). The current HiTOP structure is based largely on factor analyses that followed the road map of these earlier studies. As such, it assumes that psychopathology is dimensional in nature rather than categorical (Kotov et al., 2017). This aligns with research that finds little support for discrete categories of mental disorders (Haslam et al., 2012, 2020).

A recent meta-analysis examined factors representing the psychopathology dimensions at the subfactor, spectra, and super spectra level of HiTOP and selected a best fitting model that included the five spectra and a ‘p’ factor; however, they did not have enough indicators to model the proposed subfactors, including the SUD subfactor (Ringwald et al., 2021). Consistent with previous studies, the authors found strong

evidence to support internalizing and externalizing spectra as well as a ‘p’ factor underlying all psychopathology (Eaton et al., 2015; Ringwald et al., 2021).

Dimensional Structural Equation Modeling Studies of SUDs and Pathological Gambling

While spectra and super spectra are well-supported by data from recent HiTOP studies, there are still some questions about the existence of a SUD subfactor, and it is unclear where pathological gambling fits into the framework. Two published studies have attempted to place pathological gambling into the proposed HiTOP framework. One nationally representative sample of 43,093 individuals completing the National Epidemiological Survey on Alcohol and Related Conditions provided information about symptoms of major depressive disorder, dysthymia, generalized anxiety disorder, simple (or specific) phobia, social phobia, panic disorder, agoraphobia, antisocial personality disorder, pathological gambling, and alcohol and drug dependence to explore the location of pathological gambling within the dimensional structure of psychopathology. The best fitting model included internalizing and externalizing spectra as well as internalizing subfactors of anxious misery and distress, and pathological gambling loaded (.49 overall) onto the externalizing spectrum (Oleski et al., 2011). A sample of 1,329 young adult twins from the Minnesota Family Twin Study were assessed for major depressive disorder, generalized anxiety disorder, simple (or specific) phobia, social phobia, post-traumatic stress disorder, panic disorder, adult antisocial behavior, problem gambling, and for alcohol, cannabis, and nicotine dependence (King et al., 2019). Symptom counts were used in confirmatory factor analysis, and the best fitting model suggested that problem gambling

loaded (.30) onto the externalizing factor along with all substance dependence diagnoses and adult antisocial behavior; all other diagnoses loaded onto the internalizing factor (King et al., 2019). Neither study described here attempted to model a SUD subfactor.

Findings regarding the existence of a subfactor underlying susceptibility to SUDs have been mixed among adolescent and youth samples. One study examined more than 9,000 adolescents from the nationally representative National Comorbidity Survey Adolescent Supplement and found evidence for a SUD subfactor with a strong loading (.83) onto an externalizing factor (Blanco et al., 2015). Similarly, 2,232 participants across eight European research sites reported on externalizing symptoms at ages 14 and 16, and factor analyses again supported the existence of a SUD subfactor, although only drinking behaviors were analyzed in this study (Castellanos-Ryan et al., 2014). However, a third study included 223 youths aged 10 to 17 years assessed for externalizing disorders, including marijuana and alcohol use behaviors, and the best fitting model for the study found evidence for a SUD factor at the spectra level rather than as a subfactor of externalizing (Verona et al., 2011). Another study analyzed a representative sample of 3,021 adolescents and found that models including a SUD subfactor were a poor fit to the data compared to models with no externalizing subfactors (Beesdo-Baum et al., 2009).

There is little research in adult samples investigating the existence of a SUD subfactor within the HiTOP framework. Bailey and Finn (2019) examined a sample of 837 young adults assessed for antisocial personality disorder, conduct disorder, and marijuana, alcohol, and drug dependence symptoms and found evidence for a SUD subfactor that loaded strongly (.88 females, .84 males) onto an externalizing factor. In a separate study,

the same authors examined a large sample size of 2,482 young adults from the same sample as their 2019 study (Bailey & Finn, 2020). In this study, the authors used multiple SUD symptoms as indicators to create latent variables for each substance (i.e., alcohol, cannabis, stimulants, sedatives, opiates, and polysubstance use), all of which loaded onto a general SUD factor. Loadings ranged from .53 (alcohol desire) to .95 (opioid withdrawal), with the lowest loadings from alcohol use indicators. However, McDonald and colleagues (2019) analyzed a sample of 497 adults with a history of SUD or criminal behavior to model an externalizing factor and a SUD subfactor; they found that these two factors were highly correlated (r = .96), and the SUD subfactor was dropped from the model.

To date, the adolescent literature provides more evidence for the existence of a SUD subfactor, and only one known study has attempted to place pathological gambling within the externalizing spectrum. This review has cited evidence to support the existence of internalizing and externalizing spectra as well as a 'p' factor super spectra. However, more research is needed to understand the structure of externalizing psychopathology, particularly the existence of a SUD subfactor and the placement of pathological gambling within the framework.

Twin Studies of SUDs and Pathological Gambling

Pleiotropy in Genetics

As Smoller and colleagues (2019) noted in a recent review of genetics and nosology, "Our genes don't seem to have read the DSM." Smoller was referring to the fact that late 20th century candidate gene studies have not carved nature at the joints outlined within DSM diagnostic criteria; instead, one candidate gene was often found to be

associated with multiple mental health diagnoses, or it accounted for a very small proportion of the total genetic variance that would be expected based on previous twin studies (Dick et al., 2018). As a result, researchers shifted to large, population-based studies that leverage the collection of data on hundreds of thousands of SNPs in genome wide association studies to understand the contribution of many gene variants to the occurrence of mental health diagnoses (Agrawal & Lynskey, 2014). Theories of genetic pleiotropy (described in Chapter 1) are one explanation for this shift.

Most research to date has examined biological pleiotropy, largely because the studies have used interviews and self-report measures that assess DSM diagnoses; as a result, many of these studies do not account for symptoms that overlap across mental health disorders, subthreshold symptoms, and high rates of comorbidity among DSM diagnoses (Waszczuk et al., 2020). However, twin studies are uniquely suited to address these issues, because this line of research makes use of structural equation modeling that can be expanded to model theorized dimensions of psychopathology as well as additive genetic, shared environmental, and non-shared environmental contributions to the variance in these dimensions.

Twin Studies

Twin studies provide a method of statistically modeling the contributions of additive genetics (A), the shared family environment (C), and the non-shared family environment (E) to variance in observed phenotypes, known as biometrical or ACE models. One advantage of these structural equation models is that they can include higher-order factors that may explain common genetic variance and disorder-specific variance

across multiple disorders. This is typically done via independent pathway or common pathway models (Figure 3). In independent pathway models, the common genetic and environmental factors influence observed variables directly, whereas in common pathway models, common genetic and environmental factors influence all observed variables via a singly underlying latent liability (e.g., a spectrum or subfactor). Using these modeling approaches, twin studies have pioneered much of the existing research on mediated pleiotropy in behavioral genetics.

Only a handful of known twin studies have examined heritability estimates for pathological gambling and/or subthreshold problem gambling. Most recently, in a study using participants from the Australian Twin Registry, common genetic factors accounted for 45.6% of the variance in gambling behaviors among men, and 58.2% among women (Davis et al., 2019). These estimates did not significantly differ across genders, and heritability estimates remained relatively stable even when lowering the threshold for categorical designation as a problem gambler.

Four studies from the Minnesota Twin and Family Study have investigated genetic associations between substance use and externalizing behaviors in adolescents. The cohort includes approximately 2,700 adolescent twins and their parents who completed a battery of self-report measures and diagnostic interviews assessing personality, substance use, and mental health diagnoses to include conduct disorder and antisocial personality disorder (Iacono et al., 1999). The earliest study utilized a common pathway model, in which single genetic and environmental factors load on to observed traits via a defined phenotypic latent

variable and found that liability for tobacco (36%), alcohol (35%), and drug use[2] (23%) were all substantially heritable, and genetics accounted for 23% of the variance in a latent phenotypic factor for substance use liability (Iacono et al., 1999). Three additional studies took a different approach to the common pathway model, examining symptom counts and alternative phenotypes as observed variables (e.g., alcohol consumption, constraint) (Hicks et al., 2004; Hicks et al., 2011; Krueger et al., 2002). Across all three studies, approximately 80% of the variance in externalizing was heritable in models using the alternative phenotypes. In two of the three studies, disorder-specific genetic and non-shared environmental contributions were also observed (Hicks et al., 2004; Hicks et al., 2011), whereas in another study only constraint was associated with disorder-specific genetic risk, with all other variance being accounted for by common factors (Krueger et al., 2002). These four consistent studies show the utility of latent constructs such as externalizing and substance use liability in modeling mediated pleiotropic relationships.

In the Tennessee Twin Study, 2,646 families including twins, parents and children were interviewed to assess psychopathology in young adults ages 17 to 29, and three independent pathways (internalizing, externalizing, and a general factor) were modeled to examine genetic influences on young adult psychopathology (Lahey et al., 2011). Lahey found evidence for a "generalist genes, specialist environment model", in which most disorders shared common genetic influences via internalizing, externalizing, and/or the general factor, whereas nonshared environment contributed to disorder-specific variance

[2] This study examined substance use rather than abuse, because the population consisted primarily of adolescents and young adults.

in the model. Of the 11 symptom dimensions analyzed in the model, 8 shared at least 68% of their genetic variance with higher order factors (Lahey et al, 2011).

Kendler and colleagues have examined both independent and common pathway models across multiple twin cohorts in the past two decades. One study examined independent pathway models for lifetime substance use and for abuse/dependence of illicit drugs in a sample of 1,196 white, male twin pairs (Kendler, Jacobson et al, 2003). The best fitting abuse/dependence model revealed one common genetic factor that contributed from 23% (opiates) to 74% (cannabis) of the total variance across six substances. The model also suggested significant common shared and non-shared environmental influences and disorder-specific non-shared environmental influences on drug use/dependence.

A second study utilizing the Virginia Twin Registry cohort examined genetic associations across internalizing and externalizing diagnoses among 2,027 complete twin pairs and 811 singletons (Kendler, Prescott et al., 2003). This study modeled two sets of A, C, and E factors to represent variance specific to internalizing and externalizing disorders. The results mirrored previous studies that have detected associations across internalizing (e.g., depression, generalized anxiety, and specific phobias) and externalizing (alcohol dependence, drug dependence, adult antisocial behavior, and conduct disorder) diagnoses; heritability estimates of a common genetic (presumed externalizing) liability ranged from 14% (conduct disorder) to 42% (drug dependence; Kendler, Prescott, et al., 2003). Notably, these findings were not significantly different across gender-specific models.

Another study utilizing the Virginia Twin Registry examined both independent and common pathway models for cannabis, cocaine, alcohol, caffeine, and nicotine dependence symptoms (Kendler et al., 2007). The exploratory, independent pathway model revealed two common additive genetic factors and one common non-shared environmental factor. The common pathway model theorized separate genetic factors contributing to licit and illicit substance use and did not allow for cross-loadings of the two factors. Results revealed that the licit and illicit substance use factors were highly correlated (r = .82), although modeling one substance use factor resulted in poorer model fit (Kendler et al, 2007). Heritability estimates attributable to the common genetic licit substance use factor ranged from 2% (caffeine) to 46% (alcohol). Heritability estimates attributable to the common illicit drug use factor were 59% (cocaine) and 67% (cannabis) (Kendler et al., 2007). Similar to the findings of Lahey and colleagues (2011), there was no evidence to suggest shared environmental factors contributed significantly to the variance of SUDs at the common or disorder-specific level (Kendler et al., 2007).

In a similar study, Palmer and colleagues (2012) examined independent and common pathway models for substance dependence vulnerability in a sample of 2,484 twins from the Colorado Community Twin Study and Longitudinal Twin Study at University of Colorado. A common pathway model confirming a substance use liability factor provided the most parsimonious fit to the data and revealed that 41% of the variance in substance dependence vulnerability was attributable to common additive genetic factors across alcohol, tobacco, and cannabis use (Palmer et al., 2012).

Two twin studies have examined common genetic associations among SUDs in a sample of 3,372 male veteran twin pairs from the Vietnam-era Twin Registry. One study estimated a common pathway model to examine common and disorder-specific genetic variance for illicit substances only (marijuana, sedatives, stimulants, heroin/opiates, and hallucinogens); they found evidence for common additive genetic effects ranging from 30% (opioids) to 100% (hallucinogens) as well as common shared environment, and non-shared environmental effects across the disorders (Tsuang et al., 1998). A second study examined shared and disorder-specific variance across alcohol, nicotine, and cannabis phenotypes (Xian et al., 2008). This study also estimated a common pathway model and found that 77% of the variance in a latent factor for substance use was attributable to a common genetic liability, although disorder-specific genetic and non-shared environmental effects were also observed (Xian et al., 2008).

Three other studies utilizing the Vietnam-era Twin Registry cohort examined relationships across SUDs and pathological gambling. They are the only known twin studies to examine pathological gambling and its common relationship to SUDs and other externalizing behaviors. One such study analyzed genetic variance common across pathological gambling, subthreshold problem gambling, and alcohol dependence (Slutske et al., 2000). In this study, common genetic factors accounted for 64% of the overlap between pathological gambling and alcohol dependence and 75% of the overlap between problem gambling and alcohol dependence (Slutske et al., 2000). Using a similar study design, Slutske and colleagues (2001) examined relationships between antisocial personality disorder, conduct disorder, and pathological gambling. They found that the risk

for antisocial behavior disorder accounted for 16% to 22% of the genetic variation in pathological gambling risk; however, most of the risk for pathological gambling was not explained by this shared vulnerability (Slutske et al., 2001). Given that common genetic variance differed across dimensional problem gambling and categorical pathological gambling phenotypes, these findings suggest the importance of considering a dimensional range of symptoms rather than a categorical diagnosis alone in genetics research to better characterize genetic relationships across disorders. These findings also highlight the utility of the common pathway model as a method of explaining mediated pleiotropic variation across disorders.

A third study modeled genetic variance among pathological gambling, cannabis dependence, nicotine dependence, and stimulant dependence (Xian et al, 2014). However, genetic variance for pathological gambling and each of the substances were modeled separately using a correlated factors model rather than an independent or common pathway model. Thus, genetic risk for pathological gambling was correlated with genetic risk for each of the substances, but common underlying factors contributing to that relationship were not identified. The models revealed genetic correlations of moderate (nicotine dependence $r = .22$; cannabis dependence $r = .32$) to large effect size (stimulant dependence $r = .58$) with pathological gambling as well as significant correlations between non-shared environmental effects for pathological gambling and nicotine dependence and pathological gambling and cannabis dependence (Xian et al., 2014).

Of note, most twin studies have modeled relationships between SUDs, conduct disorder, antisocial personality disorder, and externalizing or SUD factors. Few studies

have examined where pathological gambling best fits into this structure. Moreover, while there is evidence to support a latent factor of SUD vulnerability (Palmer et al, 2012), studies have yet to examine the possibility that both externalizing and SUD vulnerability represent latent factors that contribute to additive genetic, shared environmental, and non-shared environmental variation across SUDs, pathological gambling, and other externalizing disorders. This underscores the need for further research using more complex models.

There are two recent studies that have combined advanced structural equation modeling techniques to model dimensional facets of psychopathology as well as their genetic and environmental variance. One study examined temporal genetic relationships in a sample of 373 twin pairs who reported on gambling and substance use behaviors at ages 17 and 19. The study modeled correlated genetic factors at each age and found that common genetic factors largely accounted for the concurrent associations between pathological gambling and SUDs at both ages as well as for a unidirectional longitudinal association between substance use and future participation in gambling (Vitaro et al., 2019). Another study modeled DSM-IV Axis I and II disorders in a sample of 2,801 twins from the Norwegian Institute of Public Health Twin Panel and found evidence to suggest genetic contributions to 11 disorders via internalizing, externalizing, and 'p' factors (Rosenström et al., 2019).

These findings suggest that there are some promising avenues for future research, including modeling mediated and/or generalized pleiotropy to better understand underlying genetic mechanisms that contribute to comorbid SUDs and pathological gambling. Indeed, many researchers have suggested the need for improved SUD phenotypes in behavioral

genetics research to improve our understanding of common genetic influences and to decrease the power needed to detect significant effects through the use of more accurate dimensional measurement models of psychopathology (Agrawal & Lynskey, 2014; Prom-Wormley et al., 2017).

Combining Structural Equation Modeling Approaches to Understand the Genetics of SUDs and Pathological Gambling

This review has provided evidence to support a dimensional structure of psychopathology that is quantitatively defined and that includes a 'p' factor super spectra as well as internalizing and externalizing spectra. However, more research is needed to confirm the existence of a SUD subfactor within the externalizing spectra, and there is a need to replicate early findings that pathological gambling is associated with the externalizing spectrum. This review also provided evidence that a substantial portion of genetic risk for SUDs and pathological gambling comes from the spectra-level externalizing dimension rather than the diagnosis-specific level. However, while twin studies have attempted to model factors influencing SUDs and pathological gambling, most estimate only one factor, such as externalizing, or a SUD liability factor, and few attempt to simultaneously model these components as spectra and subfactors, as observed in the current proposed dimensional structure of HiTOP (Kotov et al, 2017).

The two main goals of HiTOP are to use quantitative methods to understand the dimensional structure of psychopathology and to use that new system to improve research into common underlying mechanisms that are not well understood when examined through the lens of categorical diagnoses (Kotov et al., 2017). Moreover, recent reviews have

provided road maps for how to apply HiTOP to clinical applications (Ruggero et al., 2019; Hopwood et al., 2020) as well as to neuroscience (Latzman et al., 2020) and genetics research (Waszczuk et al., 2020). These reviews and lessons learned from previous research in behavioral genetics suggest that combining the structural equation modeling approaches of factor analysis and biometrical modeling can provide new insights into how dimensions of psychopathology influence genetic and environmental risks for SUDs and pathological gambling.

One lesson learned is that it may be time to move away from the diagnostic thresholds and skip logic that have defined DSM-driven research variables (Kotov et al., 2017). Future studies can implement this recommendation easily by changing data collection methods. While it is less ideal, existing data can be adapted by using symptom counts to capture a range of severity across different syndromes (Kotov et al., 2017; Waszczuk et al., 2020). Indeed, several behavioral genetics studies highlighted in this review used symptom counts rather than categorical diagnoses in their biometrical models (e.g., Kendler et al., 2007; Krueger et al., 2002; Slutske et al., 2000; Slutske et al., 2001 Palmer et al., 2012), and some of the research included alternative SUD phenotypes (e.g., constraint; see Krueger et al., 2002). Both nosological and behavioral genetics research would benefit from a continued move towards operationalizing mental health symptoms in ways that are amenable to dimensional approaches.

Another lesson learned is that combining structural equation modeling techniques can provide traditional biometrical twin models with a theoretical foundation for examining genetic and environmental influences on psychopathology. As two studies have shown, it

is possible to combine longitudinal structural equation modeling approaches as well as more traditional factor analytic approaches to explain dimensional and temporal genetic relationships between SUDs and pathological gambling (Rosenström et al., 2019; Vitaro et al., 2019). Future studies can focus on first replicating early findings that pathological gambling may be associated with the externalizing spectrum (King et al., 2019) and then modeling the proposed externalizing structure to examine common and disorder-specific genetic and environmental contributions to these highly co-occurring disorders.

CHAPTER 3. The Structure of Substance Use and Pathological Gambling in a Sample of Vietnam-Era Twins

As reviewed in Chapters 1 and 2, there is a need for research to better characterize the shared dimensions underlying liability to SUDs and pathological gambling. The HiTOP model was developed as a quantitatively derived dimensional nosology to address ongoing issues with traditional diagnostic frameworks, including questionable diagnostic reliability and high rates of comorbidity (Conway et al., 2019). More than a decade of research has resulted in a hypothesized hierarchical structure of psychopathology, and it may be possible to better explain the relationship between SUDs and pathological gambling using this structure (Kotov et al., 2017)

The currently proposed HiTOP structure includes super spectra (a generalized susceptibility to all mental health diagnoses also known as a 'p' factor), spectra (e.g., internalizing and externalizing dimensions), and subfactors (e.g., liability to SUDs as a subfactor of externalizing; Kotov et al., 2017). A full description of the model is provided in Chapter 1 and depicted in Figure 1. There is substantial evidence in both child and adult populations to support the existence of an externalizing spectrum that influences behaviors such as substance use, child conduct disorder, and adult antisocial behaviors (Eaton et al., 2015). Evidence also suggests that disorders on the internalizing spectrum include panic disorder, agoraphobia, generalized anxiety disorder, post-traumatic stress disorder, and depression (Kotov et al., 2017). In addition, several studies have found evidence to support a 'p' factor underlying all psychopathology in adults and children, although this has not

been replicated across all HiTOP studies (Caspi et al., 2014; Lahey et al., 2011; Selzam et al., 2018; Tackett et al., 2013).

Findings to support dimensions of psychopathology at the subfactor level are mixed (Eaton et al., 2015). In two studies using the same sample, Bailey and Finn examined the location of borderline personality disorder within the HiTOP structure (2019) and examined the existence of a SUD subfactor that encompasses both licit and illicit substances (2020). In both studies, the authors found evidence to support the existence of a SUD subfactor. However, McDonald and colleagues (2019) modeled an externalizing factor and a SUD subfactor using data from a sample of 497 adults with a history of SUD or criminal behavior to model; the SUD subfactor demonstrated substantial overlap with the externalizing factor (r = .96), and the SUD subfactor was dropped from the model.

In a recent review of common mechanisms underlying dysregulated behaviors, Bresin (2020) suggested that pathological gambling might best fit into the proposed dimensional structure of psychopathology as a syndrome of the externalizing spectrum. However, only two known studies have tested this theory. One study modeled internalizing and externalizing spectra as well as anxious misery (also known as fear) and distress internalizing subfactors in a large community sample derived from the National Epidemiological Survey of Alcohol and Related Conditions (Oleski et al., 2011). Oleski and colleagues (2011) found that pathological gambling was associated with the externalizing spectrum in men (loading =.41), but problem gambling cross-loaded onto the externalizing spectrum and onto the anxious misery subfactor of internalizing. In a sample of young adults (mean age 24) King and colleagues (2019) found evidence to suggest that

pathological gambling shares variance with SUDs via the externalizing spectrum. However, no known research has tested whether these diagnoses encompass an "addictive disorder" subfactor rather than a SUD subfactor encompassed by the externalizing spectrum.

The purpose of this study was to examine the structure of psychopathology in a sample of Vietnam-era veteran twins and to determine the placement of pathological gambling within that structure. This study attempted to replicate and expand on existing research by including six, separate illicit substances in the model rather than one combined drug dependence variable and by attempting to model a SUD subfactor. Our hypotheses were as follows: 1) the best fitting model will include a 'p' factor at the super spectra level, internalizing and externalizing spectra, and a SUD subfactor, and 2) pathological gambling will load most strongly on a SUD subfactor of the externalizing spectrum, which most likely represents a susceptibility to addictive behaviors rather than a substance-specific liability.

Methods

Participants

The Vietnam Era Twin Registry consists of male monozygotic (MZ) and dizygotic (DZ) twin pairs born between 1939 and 1955 in which both were on active military duty during the Vietnam War era (1965–1975). A computerized database of veterans discharged after 1967 was utilized as the source for identifying veteran twins, because it included approximately 50% of the total Vietnam era population and provided a simple method of identifying twins (Eisen et al., 1987). Veterans from the registry were recruited to

participate in a telephone interview as a part of the Harvard Drug Study. To be eligible for interview in 1992, twins must have had a Department of Defense military record and identifying and locating information had to be available. Of 10,300 eligible individuals (5,150 twin pairs) from the Vietnam Era Twin Registry, 8,169 (79.3%) were interviewed successfully (pairwise response rate 66.1%, 3372 pairs; Xian et al., 2008). For the present paper, completed interview data were available for 3,372 twin pairs (1,874 MZ pairs, 1,498 DZ pairs).

Measures

Subjects responded to a computer-assisted telephone interview version of the Diagnostic Interview Schedule, Version 3 Revised (DIS-3R; Robins et al., 1989). Participants were assessed for lifetime diagnoses of DSM-III-R nicotine, alcohol, hallucinogen, amphetamine, stimulant, heroin/opioid, sedative, and cannabis abuse/dependence as well as for panic disorder, generalized anxiety disorder, agoraphobia, post-traumatic stress disorder, depression, bipolar disorder, antisocial behaviors (childhood conduct disorder and adult antisocial personality disorder), and pathological gambling. Trained staff from the Institute for Survey Research, Temple University, interviewed twins after verbal informed consent was obtained, a method approved by the Institutional Review Boards at all participating institutions.

Interviews were conducted using skip logic with the specifics defined in Table 1. Of note, greater than 99% of data were available for all of the disorders for which participants answered questions. The exception was pathological gambling, for which only 62.29% of participants answered the symptom-related questions. This is likely because if

participants endorsed ever having used any of six illicit substances, they were screened for symptoms of substance use across all categories. Greater than 99% of participants endorsed trying at least one illicit substance to get high and were thus screened for abuse and dependence symptoms across all illicit substances. However, if an individual denied ever gambling or if they gambled less than five times in their lifetime, their symptom responses are missing from the final dataset.

Table 1. Skip Logic Used in DIS-3R Interview

Diagnostic Category	Section Skipped If Participant…
Nicotine (cigars, pipes, cigarettes, chewing tobacco)	Denied a period of one or more per day
Illicit Use (cannabis, amphetamines, sedatives, cocaine, opioids, hallucinogens)	Denied using ***any*** illicit substance to for a mental effect, or other than as prescribed
Alcohol	Never had a drink
Gambling	Never gambled, bet, bought a lottery ticket, or used a slot machine > 5 times
Other Mental Health Concerns	According to DSM-III-R criteria

Notably, panic disorder and agoraphobia are often highly correlated and in prior studies have been combined into one variable representing panic and/or agoraphobia (Krueger et al., 2018). In the Harvard Drug Study DIS-3R interview, participants answered the same set of questions for panic and agoraphobia, and diagnoses were differentiated by participant responses to two questions regarding panic symptoms in specific situations. Thus, we collapsed these two categories into one symptom count variable. Furthermore, when examining phenotypic correlations, we found that major depressive disorder and

dysthymia were highly correlated (r = .91), suggesting multicollinearity. We chose to exclude dysthymia from further analyses. When modeling the externalizing spectrum, we included all six illicit substance abuse/dependence symptom counts, adult antisocial personality disorder, childhood conduct disorder, and pathological gambling in the model. While bipolar disorder is theorized to have its own latent spectra, our sample had a low prevalence of both bipolar I and bipolar II disorder (total n = 46), which did not provide sufficient information to model a bipolar disorder spectrum.

While the HiTOP consortium does suggest using alternative phenotypes (e.g., alcohol consumption, age of initiation, symptom-specific self-report measures) to better model the dimensional structure of psychopathology (Kotov et al., 2017), this historical dataset used skip logic and only asked questions related to substance use if individuals endorsed any period of regular use (five or more times) for a substance. We did attempt to model latent factors for each substance similar to those derived in Bailey and Finn's study (2020) of a substance use factor and based on endorsement of regular versus continuous use and age of initiation. However, due to the missing data patterns resulting from skip logic, we lost significant power to detect effects and thus discarded these phenotypes in final analyses. Thus, this study operationalized each disorder using symptom counts to better capture the range of severity and to avoid using diagnostic yes/no thresholds, which algins with HiTOP recommendations and with prior research (Kotov et al., 2017).

Analyses

Data cleaning and the calculation of descriptive statistics were completed using SPSS Statistics version 27.0.1.0. All structural equation modeling procedures were

completed using Mplus version 8.6. All factor analyses utilized a robust max likelihood estimator, which provides maximum likelihood parameters estimates with standard errors and chi-square test statistics (when applicable) that are robust to non-normality, particularly skewness and kurtosis (Muthén & Muthén, 2017). We also accounted for clustering of twin data using the Mplus CLUSTER function and the COMPLEX model type. For all models, we requested standardized estimates as well as 95% confidence intervals and modification indices greater than 3.84 to examine any issues with model fit. We set thresholds of .30 or greater to define "salient" factor loadings and less than .85 to define factor loadings with sufficient discriminant validity (Brown, 2015). Parameter estimates were considered statistically significant if they met the p-value threshold of .05 or less. We confirmed these values by examining 95% confidence intervals to confirm that no interval overlapped with zero.

We tested models using a two-step process to 1) determine whether a 'p' factor or correlated factors model including externalizing and internalizing best fit the data and 2) to determine how a SUD subfactor fit onto the best fitting model from step 1. We tested models consistent with existing HiTOP literature and theory, and as such used confirmatory factor analysis. In the event that proposed models did not satisfy model fit criteria as defined below, we planned to use an exploratory factor analysis to identify alternative models that might better fit the data. We fit the following models:

M1: A single-factor model in which the 'p' factor explains all covariation among phenotypes (used for model comparisons (*Figure 4*).

M2: A correlated factors model including the correlated internalizing and externalizing spectra with pathological gambling loading onto externalizing (*Figure 5*).

M3: A higher-order factor model including internalizing, externalizing spectra and a 'p' factor, pathological gambling loading onto externalizing (*Figure 6*).

M4a: Best fitting Model (M1-M3) plus an addictive disorder subfactor that includes pathological gambling (*Figure 7*).

M4b: Best fitting Model (M1-M3) including a SUD subfactor and pathological gambling, which loads onto the externalizing spectrum but not the SUD subfactor (*Figure 8*).

Models were examined for goodness of fit to the data using a Comparative Fit Index (CFI) > .90, Root Mean Square Error of Approximation (RMSEA) < 0.08, and Standardized Root Mean Square Residual (SRMR) < .08 (Kline, 2016). While chi-square statistics were available, in studies with sample sizes greater than 200 the chi-square tends to be significant even in models with very good fit and is not recommended when comparing models with different degrees of freedom (Brown, 2015). Therefore, we examined the Akaike Information Criteria (AIC), a fit statistic that is robust to large sample sizes and valid for comparing non-nested models (Brown, 2015). However, when all other fit statistics are adequate, models with similar AIC values should both be considered a good fit to the data (Cavanaugh & Neath, 2019). In the event that more than one model was an adequate fit to the data, we relied on the principle of parsimony to determine a final model. We defined a more parsimonious model as having more degrees of freedom and fewer freely estimated parameters. Full information max likelihood was used to account for

missing data. However, greater than 99% of data were available for all variables except pathological gambling (see Table 1).

Power Analyses

The determination of adequate sample size for factor analytic and structural equation modeling methods depends upon a number of factors that both increase (e.g., non-normality, model complexity, model saturation, covariance of indicators, etc.) and decrease (e.g., high reliability, continuous variables, simple models, no missing data) the required sample to detect significant effects (Brown, 2015; Kyriazos, 2018). Brown (2015) noted that fit indices such as RMSEA and CFI are also sensitive to smaller sample sizes in that they are prone to false model rejections. Because the factors influencing adequate power for structural equation modeling and confirmatory factor analyses are complex, we chose to follow the most stringent rules of thumb laid out by statistical experts in determining the power in our sample. Some authors recommend a ratio of cases to free model parameters (N:q) that ranges from 10:1 to 20:1 (Kline, 2016; Kyriazos, 2018). With our sample of 3,372 twin pairs and our most complex model estimating 46 free parameters, our N:q ratio is 135:1, which far exceeds the more conservative recommendations for sufficient power in structural equation modeling and factor analyses.

Results

Sample Characteristics

At the time of the 1992 survey the mean age of respondents was 42 years (SD = 2.8, range 33–55 years). The sample was 93.3% non-Hispanic/Caucasian, 6.3% African-American, and 0.4% identified as ‘other’. In terms of education, 8% of respondents had

not graduated from high school, 96% were high school graduates, and 23% college graduates. Most participants (95.6%) were employed, 75.9% were married, 16.4% widowed, separated or divorced and 7.7% had never been married.

Table 2 characterizes mean symptom counts for MZ and DZ twin pairs as well as for the entire sample. Of note, greater than 99% of the sample answered questions for each of the 16 disorders with the exception of pathological gambling, for which 62.29% of respondents answered questions about symptoms. In the total sample, symptom counts were lowest for illicit substance use and pathological gambling. Average symptom counts were highest for post-traumatic stress disorder, alcohol use, and nicotine use. Table 3 depicts the phenotypic correlations among disorders within the total sample. All correlations were significant at the level of $p < .001$, except for pathological gambling and opioid use ($p < .01$). Notably, pathological gambling demonstrated small phenotypic correlations with all illicit substances ($r = .03$, opioids to $r = .13$, cannabis).

Table 2. Harvard Drug Study Symptom Count Statistics

	MZ (n = 3,748)	DZ (n = 2,996)	Total (n = 6,744)
Variable	Mean (SD)	Mean (SD)	Mean (SD)
CAN	0.45 (1.26)	0.48 (1.27)	0.46 (1.26)
AMP	0.19 (0.92)	0.17 (0.81)	0.18 (0.87)
SED	0.10 (0.67)	0.09 (0.62)	0.10 (0.65)
COC	0.17 (0.97)	0.14 (0.86)	0.16 (0.92)
OPI	0.06 (0.55)	0.08 (0.69)	0.07 (0.61)
PCP	0.07 (0.48)	0.07 (0.49)	0.07 (0.49)
ALC	2.24 (2.34)	2.34 (2.36)	2.29 (2.35)
NIC	2.29 (2.03)	2.44 (2.02)	2.36 (2.03)
PG	0.28 (1.02)	0.27 (0.94)	0.28 (0.99)
CON	0.75 (1.13)	0.81 (1.18)	0.78 (1.15)
ASP	1.70 (2.01)	1.77 (2.12)	1.73 (2.06)
DEP	1.96 (2.35)	2.03 (2.40)	1.99 (2.37)
GAD	1.41 (3.45)	1.47 (3.46)	1.43 (3.45)
PTS	2.44 (4.04)	2.52 (4.13)	2.47 (4.08)
PAN	0.55 (2.24)	0.53 (2.17)	0.54 (2.21)

CAN = cannabis use disorder; AMP = amphetamine use disorder; SED = sedative use disorder; COC= cocaine use disorder; OPI = opioid use disorder; PCP = hallucinogen use disorder; ALC = alcohol use disorder; NIC = nicotine use disorder; PG = pathological gambling; CON = conduct disorder, ASP = antisocial personality disorder; DEP = major depressive disorder, GAD = generalized anxiety disorder, PTS = post-traumatic stress disorder, PAN = panic/agoraphobia

Table 3. Phenotypic Correlations by Diagnostic Symptom Counts

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1 CAN	--													
2 AMP	0.48	--												
3 SED	0.35	0.45	--											
4 COC	0.30	0.38	0.23	--										
5 OPI	0.22	0.28	0.33	0.22	--									
6 PCP	0.40	0.53	0.41	0.30	0.17	--								
7 ALC	0.33	0.27	0.20	0.17	0.13	0.19	--							
8 NIC	0.24	0.18	0.11	0.12	0.09	0.11	0.42	--						
9 PG	0.13	0.10	0.08	0.09	0.03	0.06	0.18	0.12	--					
10 CON	0.23	0.20	0.17	0.13	0.09	0.16	0.27	0.23	0.18	--				
11 ASP	0.40	0.39	0.30	0.32	0.21	0.33	0.49	0.30	0.27	0.44	--			
12 DEP	0.28	0.23	0.19	0.15	0.11	0.17	0.35	0.29	0.17	0.27	0.39	--		
13 GAD	0.18	0.15	0.15	0.09	0.06	0.13	0.24	0.18	0.12	0.17	0.26	0.53	--	
14 PTS	0.20	0.18	0.12	0.12	0.11	0.10	0.29	0.25	0.12	0.23	0.31	0.47	0.37	--
15 PAN	0.17	0.18	0.12	0.11	0.05	0.11	0.21	0.15	0.13	0.15	0.22	0.32	0.34	0.26

CAN = cannabis use disorder; AMP = amphetamine use disorder; SED = sedative use disorder; COC= cocaine use disorder; OPI = opioid use disorder; PCP = hallucinogen use disorder; ALC = alcohol use disorder; NIC = nicotine use disorder; PG = pathological gambling; CON = conduct disorder, ASP = antisocial personality disorder; DEP = major depressive disorder, GAD = generalized anxiety disorder, PTS = post-traumatic stress disorder, PAN = panic/agoraphobia

Structure of Psychopathology

In step 1, we examined a basic, one-factor model (M1), a model of correlated spectra (M2), and a model including theorized spectra and super spectra (M3) from the HiTOP framework (Table 4a). Both models M1 and M2 were a poor fit to the data, although M2 was slightly better. In M3, the estimated factor loading for externalizing onto the 'p' factor exceeded the maximum value of 1, suggesting poor fit for a super spectra in this sample. AIC values suggested a substantial fit improvement from M1 to M2. Thus, model testing continued by fitting a correlated factors model (M2) with an addictive disorder subfactor including pathological gambling (M4a) and with a SUD subfactor with pathological gambling loading onto the externalizing spectra (M4b). We again found that both M4a and M4b did not meet the model fit criteria of CFI > .90, and both models showed poorer fit compared to M2 based on increased AIC values (Table 4b). Upon further examination, we observed that several indicators loading onto the SUD (or addictive behavior) subfactor resulted in large modification indices. Thus, none of the proposed models were a good fit to the data.

Table 4a. Model Fit for Models M1 vs. M2-M3

Model	RMSEA (<.08)	CFI (>.90)	SRMR (<.08)	AIC [a]
M1	.056	.72	.075	331500.37
M2	.043	.83	.060	328831.13
M3[b]	NA	NA	NA	NA

RMSEA = Root mean square error of approximation; CFI = Comparative fit index; SRMR = Standardized root mean square residual; AIC = Akaike Information Criteria

[a] Lower AIC indicates better model fit compared to M1.

[b] Externalizing loaded onto the 'p' factor with a value greater than 1, and this model was discarded from further analyses.

Table 4b. Model fit for M2 vs. all M4 Models

Model	RMSEA (<.08)	CFI (>.90)	SRMR (<.08)	AIC [a]
M2	.043	.83	.060	328821.13
M4a	.047	.81	.074	329328.88
M4b	.046	.81	.075	329278.63
M4c	.034	.90	.063	327344.20
M4d	.026	.94	.035	326979.49

RMSEA = Root mean square error of approximation; CFI = Comparative fit index; SRMR = Standardized root mean square residual; AIC = Akaike Information Criteria
[a] Lower AIC indicates better model fit compared to M2.

Table 5. Model Fit for Exploratory Factor Analysis

Model	RMSEA (<.08)	CFI (>.90)	SRMR (<.08)	AIC [a]
2 Factor	0.065	0.91	0.036	327132.29
3 Factor	0.045	0.96	0.021	325811.66
4 Factor	0.036	0.98	0.016	325409.28

RMSEA = Root mean square error of approximation; CFI = Comparative fit index; SRMR = Standardized root mean square residual; AIC = Akaike Information Criteria
[a] Lower AIC indicates better model fit compared to other models.

To determine what model would best capture the structure of psychopathology in our sample, we ran exploratory factor analyses for 2- to 4-factor solutions using a maximum likelihood estimator and GEOMIN OBLIQUE rotation. We found that all three solutions met model fit criteria. However, factor loadings within the 4-factor solution exceeded values of 1, and the 3-factor solution showed substantial improvements across all fit indices compared to the 2-factor solution. Model fit indices suggested the superiority of a 3-factor solution that included internalizing and externalizing spectra as well as an illicit substance use factor (Table 5). However, it was unclear whether this factor was a

subfactor of externalizing (M4c; Figure 9) or represented a spectrum correlated with internalizing and externalizing (M4d; Figure 10). We tested both models using confirmatory factor analysis and found that they both met fit criteria and thresholds for salient factor loadings and discriminatory validity (Table 4b). Model 4d had marginally better fit statistics, including CFI and RMSEA. Model 4d also had a marginally higher AIC. However, neither Model 4c nor model 4d could be rejected based on fit statistics alone, so we relied on the principle of parsimony to select our final model. Model 4c estimated less parameters, resulting in more degrees of freedom and was thus selected as the best fitting and most parsimonious model.

Standardized factor loadings are presented in Figure 11 for the final model. Loadings on the internalizing spectrum ranged from .44 (panic/agoraphobia) to .80 (depression). Loadings on the externalizing spectrum ranged from .30 (pathological gambling) to .81 (antisocial personality disorder). Loadings on the illicit substance use subfactor ranged from .39 (opioids) to.77 (amphetamines). None of the 95% confidence intervals included a zero-value, suggesting that all loadings were significant.

Discussion

In this study, we found evidence to partially support our hypothesis that the best fitting model would associate pathological gambling with the externalizing spectrum. However, pathological gambling symptom counts were not strongly correlated with illicit substance use symptom counts, and in the final model illicit substance use constituted a unique subfactor of the externalizing spectrum. Accordingly, there was no evidence to support the existence of a broad liability to all addictive disorders; rather, there was a

distinct dimensional vulnerability to illicit substance use that was also associated with the externalizing spectrum. Nevertheless, alcohol, nicotine, and pathological gambling all were associated with illicit substance use, conduct disorder, and antisocial personality disorder via the externalizing spectrum.

Our study did not find evidence to support the existence of a 'p' factor, which adds to the mixed findings on whether there is a broad susceptibility to psychopathology that underlies all mental health diagnoses. In our data specifically, factor loadings for internalizing and externalizing onto the 'p' factor exceeded the acceptable value of 1, resulting in an invalid model. One body of research has suggested that 'p' is a re-expression of the sum total of all diagnoses that a person experiences, and as such it represents comorbidity rather than reliability (Fried et al., 2021). Given the problematically high loadings for externalizing onto the 'p' factor, our findings may reflect the severity of externalizing compared to internalizing in our population, or it may simply reflect that there is not a 'p' factor underlying all psychopathology. Most of the variance across the 15 mental disorders in this study was attributable to the internalizing and externalizing spectra as well as the illicit substance use subfactor, adding more support to a large body of research confirming the existence of internalizing and externalizing mechanisms that underlie highly comorbid mental health diagnoses.

There is some evidence to suggest that common mechanisms underlying substance use might be differentiated by the classification of substances as licit or illicit. Kendler and colleagues (2007) found evidence for unique genetic and non-shared environmental contributions to licit and illicit substance use via separate mechanisms (i.e., two separate

factors). In Kendler and colleagues' (2007) study, they modeled cannabis and cocaine as illicit substances and caffeine, nicotine, and alcohol as licit substances. The findings reported here provide additional evidence to suggest that the use of illicit substances may share common underlying mechanisms of action unique from those of licit substances such as alcohol or nicotine. Likewise, problematic engagement in legalized gambling may be related more strongly to traits on the externalizing spectrum than to mechanisms underlying illicit substance use. However, it is important to note that this study modeled all illicit substances separately rather than combining them into one "drug dependence" variable. Many studies have utilized only a handful of specific illicit substances in structural models, most often cannabis, cocaine, or opioid use disorders (e.g., Bailey & Finn, 2019; McDonald et al., 2019). Other studies have collapsed illicit substance use into one drug dependence variable, taking the largest symptom count amongst the substances assessed as the value for each participant (Hicks et al., 2004; Hicks et al., 2011; Kendler et al., 2011; Kendler, Prescott, et al., 2003; Krueger et al., 2002).

These findings raise questions about what aspects of illicit SUDs differentiate them from licit SUDs and pathological gambling. While one explanation is that unique neurobiological mechanisms influence illicit substance use, there is more evidence to suggest that unique personality and/or behavioral traits may differentiate an individual's willingness to experiment with illegal substances (Bresin, 2020; Kendler et al., 2007). For example, there is some evidence that facets of disinhibition and risk taking that relate to externalizing first influence the decision to initiate illicit substance use, and the high reward sensitivity associated with SUDs increases the susceptibility to addiction (Carlson et al.,

2013). Perhaps it is this interaction of risk factors that differentiates illicit substance use from other externalizing disorders, but more research is needed to better understand the current findings.

Similar to previous studies, factor loadings for pathological gambling were relatively low; the factor loading was .30 in the current study compared to .31 in a young adult sample (King et al, 2019) and .41 in a male sample (Oleski et al., 2011), both of which were from previous studies that attempted to model the placement of pathological gambling within the structure of psychopathology. These studies all suggest that pathological gambling does have some relationship to externalizing; however, it may be worthwhile to consider prior research on the pathways model of gambling. Blaszczynski and Nower's (2002) model posits that there are three different pathways to developing problematic gambling behaviors. In the first pathway, gamblers have no predisposition to underlying mental health concerns and simply lose control over the behavior. Gamblers within the second pathway are susceptible to internalizing disorders, such as anxiety and depression, which can result in gambling to relieve pain. Gamblers on the third pathway display similar characteristics to the second pathway, but they also demonstrate impulsivity (Blaszczynski & Nower, 2002; Croce & D'Agati, 2016). The pathways model suggests that for some individuals pathological gambling may be influenced by both externalizing and internalizing traits. There is evidence to support this theory in a sample of females; Oleski and colleagues (2011) found that pathological gambling for females loaded onto both the internalizing and externalizing spectra. However, in the male sample and the total sample of the same study, pathological gambling was associated only with the externalizing

spectrum. Nevertheless, future research might consider how the structure of psychopathology, and in particular pathological gambling, is influenced by different risk pathways.

While the use of a veteran sample is warranted in this study, our findings are also generalizable. Previous studies utilizing participants from the Vietnam-era Twin Registry have demonstrated that this sample's demographic and lifestyle characteristics are comparable to that of similarly-aged males in the general U.S. population (Schoenborn & Heyman, 2009). Moreover, our large sample size gave our study substantial power to detect effects, and by using symptom counts we were able to capture the structure of psychopathology for veterans with a wide range of symptom severity. The use of symptom counts is particularly important for studies of pathological gambling, as most harm from gambling actually occurs to non-problem gamblers (Abbott, 2020).

There are also some limitations to our research worth consideration. First, while our sample does share many characteristics with the general population, the individuals who responded to initial requests to participate in the Vietnam-era Twin Registry were majority white (93.3%), had higher educational attainment, and were older at enlistment than non-respondents (Henderson et al., 1990). Further, the sample consisted of all male twin pairs. There is evidence to suggest that racial/ethnic minority veterans have significant rates of SUD and that those needs largely go untreated (Vazan et al., 2013). Further, while male active-duty service members and veterans demonstrate more severe levels of problem gambling overall, the interaction between military service and problem gambling severity is stronger for women (van der Maas & Nower, 2021). Thus, it is important to design future

studies that are inclusive of diverse populations who may be inordinately impacted by SUDs and pathological gambling.

This study contributes to the existing literature supporting a quantitatively-derived nosology that clarifies the dimensional nature of pathological gambling and SUDs. These findings are novel in that they contribute to a small body of literature supporting links between SUDs and pathological gambling via an externalizing spectrum. This is one of few studies to suggest the existence of an illicit substance use subfactor that uniquely influences the liability to engage in illegal drug use. Furthermore, the findings here provide insight into the high rates of comorbidity and shared symptoms between SUDs and pathological gambling and their co-occurrence in veterans. HiTOP consortium and gambling researchers have argued for the use of transdiagnostic treatment approaches targeting common mechanisms among SUDs and pathological gambling (Potenza et al., 2019; Ruggero et al., 2019). The current study supports the potential utility of such approaches, particularly for veterans with high rates of SUDs and pathological gambling and limited access to treatment (Vazan et al., 2013).

CHAPTER 4. The Genetics of Substance Use and Pathological Gambling in a Sample of Vietnam-Era Twins

In the previous chapter, we identified the dimensional structure of SUDs and pathological gambling along an externalizing spectrum, including a substance use subfactor that specifically influences liability for illicit substance use (Figure 11). This chapter builds upon those findings by modeling the additive genetic, shared environmental, and non-shared environmental influences that are common to SUDs and pathological gambling via externalizing and illicit substance use dimensions as well as the genetic and environmental variance specific to each disorder.

Decades of genetics research have established that both licit and illicit SUDs share common genetic influences (Agrawal & Lynskey, 2014). To a lesser extent, there is also evidence to suggest that pathological gambling shares genetic influences with SUDs (Rash et al., 2016). This relationship is particularly important to veteran populations, who are at greater risk for SUDs and pathological gambling, and who often have difficulty accessing adequate care (SAMHSA 2020a, 2020b). In addition, Veteran Affairs Medical Centers do not regularly screen for pathological gambling despite high rates of SUDs among patients that would suggest problem gambling may be prevalent among the veteran population as well (Levy & Tracy, 2018). Indeed, one review observed that among veteran populations already in clinical treatment for mental health diagnoses, prevalence estimates for pathological gambling ranged from 2% and 29% with up to 35% of the population engaging in some form of gambling within the last year (Levy & Tracy, 2018). It is important to explore underlying mechanisms that link SUDs and pathological gambling to

further support veteran populations who are disproportionately at risk for these mental health concerns.

Historically, psychiatric genetics research has focused on biological pleiotropy (defined in Chapter 1), largely because DSM diagnostic criteria are not easily adapted for research that allows for the modeling of commonly co-occurring disorders, overlapping symptoms, or diagnostic heterogeneity (Waszczuk et al., 2020). However, several studies have recently focused on mediated pleiotropy through the combined use of structural equation modeling, particularly confirmatory factor analysis, in conjunction with other statistical methods for analyzing genetic influences common across SUDs. These studies suggest that combining research on psychopathology structure and genetics can result in a greater understanding of both the nosology and biological underpinnings of commonly co-occurring disorders. The following sections review existing research in the areas of twin and family, candidate gene, and genome wide association studies that link SUDs and pathological gambling via shared genetic mechanisms.

Twin Studies

Research from the Minnesota Twin and Family Study provided evidence for the existence of an externalizing spectrum, a substance use subfactor; SUDs loaded onto the subfactor, and antisocial personality disorder and conduct disorder loaded onto the externalizing spectrum (Hicks et al., 2004; Hicks et al., 2011; Iacono et al., 1999; Krueger et al., 2002). Moreover, each of these four studies revealed that latent externalizing (80%) and substance use liabilities (23%) were substantially heritable. A study of young adult twins in Tennessee revealed that, upon analysis of 11 symptom domains, 8 of them shared

at least 68% of their genetic variance with higher order factors (Lahey et al., 2011). Another study using the common pathway model confirmed the existence of separate latent genetic factors influencing liability to licit and illicit substance use, although this study was limited by the inclusion of only cocaine and marijuana as illicit substances, with alcohol, tobacco, and caffeine as licit drugs (Kendler et al., 2007). While they found evidence to support the licit and illicit latent genetic factors, they were highly correlated (r =.82), so further research is needed to clarify the existence of distinct genetic pathways for licit and illicit substance use. In a separate study, a common pathway model confirming a substance use liability factor provided the most parsimonious fit to the data and revealed that 41% of the variance in substance dependence vulnerability was attributable to common additive genetic factors across alcohol, tobacco, and cannabis use (Palmer et al., 2012).

Most twin studies involving veterans utilized data from the Harvard Drug Study and the Vietnam-era Twin Registry, which includes 3,372 male MZ and DZ twin pairs. One such study examined ACE models for six illicit substances and found that each substance shared from 30% (opioids) to 100% (hallucinogens) of their genetic variance with the other substances in the model (Tsuang et al, 1998). In the same sample, a common pathway model provided evidence for a latent substance use factor influencing alcohol, cannabis, and nicotine dependence (Xian et al., 2008). Notably, both of these studies also found evidence for disorder specific genetic and environmental influences as well.

Three studies utilizing the Vietnam-era Twin Registry cohort examined genetic associations between SUDs, pathological gambling, and externalizing disorders. Slutske and colleagues (2000) found that 75% of the overlap between problem gambling (defined

using thresholds rather than yes/no diagnostic criteria) was accounted for by common genetic factors. In another study, Slutske and colleagues (2001) examined relations between antisocial personality disorder, conduct disorder, and pathological gambling. According to their findings, risk for pathological gambling shared 16% to 22% of its genetic variation with antisocial personality disorder and conduct disorder. In a third study, the genetic risk for pathological gambling was correlated with genetic risk for cannabis, nicotine, and stimulant dependence, but the common factors underlying these relationships were not modeled (Xian et al., 2014).

Candidate Gene Studies

Candidate gene studies have revealed complex relationships between select genes and multiple SUDs and externalizing disorders with mixed replicability (Agrawal & Lynskey, 2014). Most candidate genes significantly associated with multiple externalizing disorders and substance use are related to dopamine, serotonin, GABA, or other neurotransmission processes (Dick et al., 2018; Li et al., 2011). Among the most widely studied candidate genes are those related to GABA-A receptors. In one study utilizing a sample from the Collaborative Study on the Genetics of Alcoholism, an initial sample of 987 and a replication sample of 1,295 participants were included in an examination of 69 SNPs in the GABA-A receptor gene cluster (Agrawal et al., 2006). The authors of this study examined relationships among alcohol, illicit drug, and marijuana dependence and found significant associations between marijuana and illicit drug dependence and the GABRA2 gene. Another study, also from the Collaborative Study on the Genetics of Alcoholism, examined associations between marijuana, cocaine, stimulants, sedatives,

opioids, ‘other’ substances, conduct disorder, and antisocial personality disorder (Dick et al., 2006). The authors found that GABRA2 was associated with risk of conduct disorder in childhood as well as risk of alcohol dependence and drug dependence throughout different phases of the lifespan. More recent research has examined how GABRA2 and aggregate polygenic risk scores (a score that represents one’s estimated predisposition for a trait based on genome wide association data) might influence alcohol dependence via changes in reward systems or via personality traits such as impulsivity (Dick et al., 2018). A linkage study utilizing a mixed sample of African-American and White participants found evidence for linkage peaks in the area of chromosome 4 associated with GABRA4 and GABRB1, both of which are associated with receptor-encoding functions (Yang et al., 2012).

While there is evidence to suggest that problem gamblers demonstrate increased GABAergic receptor availability in brain regions associated with reward systems, the only known study to examine GABRA2 and other GABA-related candidate genes in pathological gambling did not reveal significant associations (Comings et al., 2001; Mick et al., 2017). These findings suggest that the GABRA2 gene might predispose individuals to disinhibition and/or externalizing symptoms that manifest as SUDs or other externalizing disorders, although there is no evidence to suggest a relationship between GABRA2 and pathological gambling.

Another gene of interest is CHRNA5. According to one meta-analysis of SNPs relating to different phenotypes for substance use, CHRNA5 was significantly associated with nicotine, cocaine, and alcohol phenotypes, potentially via how these substances

interact with nicotinic acetylcholine receptors (Buhler et al., 2015). However, another study utilized factor analysis to derive a structure of psychopathology including internalizing, externalizing, psychosis, and SUDs and examined genetic relationships using SNPs from a genome wide association study (Jang et al., 2020). The authors found 10 genetic loci of interest that were shared across smoking, cannabis, and alcohol use; however, nicotinic receptor genes, including CHRNA4 and CHRNA5 did not belong to these shared loci.

Arcos-Burgos and colleagues (2012) combined findings from prior candidate gene studies and utilized the data to build a network analysis of how common candidate genes were related to externalizing disorders, including polysubstance use and attention-deficit hyperactivity disorder. They found that common genetic variants harbored in multiple genes, including ANKK1, predispose to both ADHD, disruptive behavior disorders (e.g., conduct disorder), and polysubstance use. Other research has suggested that pathological gambling and alcohol use might also be associated with ANKK1 gene variants (Kreek et al., 2005; Potenza, 2017). Among other suspected candidate genes, the Met allele of the COMT gene has been linked to both problem gambling and problem drinking severities as well as to impulsivity, stress responsivity, and heroin/opioid use across a wide range of studies (Kreek et al., 2005; Potenza, 2017). DRD2 receptor encoding genes have been implicated among genes that predispose to ADHD, disruptive behaviors, smoking, cannabis use, alcohol use, and pathological gambling (Arcos-Burgos et al., 2012; Jang et al., 2020; Potenza, 2017), while DRD4 receptor encoding genes have been theorized to underlie novelty seeking processes in the brain and are associated with alcohol, cocaine, stimulant, opioid, and heroin use (Kreek et al., 2005).

There are multiple other genes that have been suggested as common mechanisms underlying substance use and other externalizing behaviors, although the genes implicated in other studies have been less replicated (Agrawal & Lynskey; Kreek et al., 2005; Potenza, 2017). However, it is important to note that even among the candidate genes listed here there are mixed findings to consistently support their roles in polysubstance use and/or externalizing behaviors, and there is very little research that has explored shared candidate genes across pathological gambling and SUDs. Even among studies examining candidate genes specific to gambling, few have yielded consistent results, with the DRD3 and DRD4 receptor genes yielding the most promising associations to date (Nivard et al., 2016; Potenza, 2017).

Genome Wide Association Studies

Because of the difficulties associated with pleiotropy, candidate genes studies have given way to genome wide association studies that analyze large swaths of the genome to identify significant SNPs associated with different mental health concerns (Dick et al., 2018). This body of research has advanced in recent years, although pleiotropy may still play a role in masking important associations (Prom-Wormley et al., 2017).

Early genome wide association studies focused on traditional phenotypes such as mental health diagnoses. For example, in one sample of 1,620 equally sampled European and African Americans, substance dependent individuals were compared to healthy controls to identify SNPs associated with substance dependence (Drgon et al., 2010). The findings implicated NrCAM and NRXN3, both of which are implicated in more traditional studies of substance use and relate broadly to cell adhesion processes. Similarly, a sample

of 662 respondents including those who had a history of substance use and those who were screened to rule out any significant history of substance use were compared to identify SNPs associated with substance use, and the study identified 126 different SNPs that were also related to cell adhesion processes (Johnson et al., 2008). A more recent genome wide association study combined European and African American (N = 7,291) samples to examine significant genetic associations with "any dependence" (Wetherill et al., 2019). In African-Americans, there were significant associations between substance dependence and SNPs in regions implicated in reward-related activation, particularly in the ventral striatum.

None of these studies included pathological gambling in their analyses, and no genome wide association studies have revealed SNPs of interest to the development of pathological gambling (Lang et al., 2016; Nivard et al., 2016). However, there is an extensive body of research detailing the role that the ventral striatum plays in pathological gambling and substance use (Koob & Volkow, 2010; Linnet, 2020; Potenza, 2017). Expanding genome wide association studies to include addictive behaviors other than substance use may better elucidate the absence or presence of underlying genetic associations with pathological gambling.

More recent studies have started to shift from the use of substance dependence criteria to broader phenotypes of substance use to better elucidate underlying genetic associations. Chang and colleagues (2019) measured multiple substance use phenotypes in a sample of 2,463 Australian twins who participated in the Brisbane Longitudinal Twin Study. In this study, polygenic risk scores were calculated for phenotypes representing the initiation and consumption of cocaine, amphetamine, ecstasy, cigarettes, and alcohol; there

was a significant association between polygenic risk for smoking initiation and alcohol consumption, and the polygenic risk score for smoking initiation explained a significant amount of the variance in risk for cocaine, amphetamine, hallucinogen, ecstasy, and cannabis initiation as well as risk for alcohol use disorder.

Another study combined samples from the Maternal Adversity, Vulnerability, and Neurodevelopment Cohort as well as the Study of Addiction Genetics and Environment repository (total N = 4,502) to examine the relationship between the degree to which a child acts immediately (impulsivity) or considers a range of alternatives before acting (reflectivity) and addiction risk (Hari Dass et al., 2019). Building on the theory that the activation of brain insulin receptors modulates reward sensitivity and inhibitory control, the authors generated a list of genes co-expressed with the insulin receptor in the brain's reward circuitry to compile a biologically informed polygenic risk score representing a gene network. They found this risk score to be associated with impulsivity in children, while conventional polygenic risk scores for addiction and attention-deficit hyperactivity disorder were not associated with impulsivity.

Next Steps in Twin Studies

The research reviewed here suggests that, regardless of the approach, there has been a shift in psychiatric genetics research towards examining shared associations across SUDs and other externalizing disorders using phenotypes that fall outside the boundaries of categorical DSM diagnoses. Some researchers argue that twin studies are obsolete given the new advances in molecular genetics and genome wide association studies, even to the point of suggesting the onset of a "post-behavioral-genetics era" (Joseph, 2014). However,

others argue that traditional behavioral genetics studies (i.e. twin and family studies) are complementary to genome wide association studies; twin studies provide the opportunity to examine well-defined phenotypes and longitudinal assessments of change in genetic risk throughout the lifespan (Friedman et al., 2021). Moreover, Friedman and colleagues argue that twin studies can estimate all genetic variance, as opposed to genome wide association studies, which are limited by what variants are tagged on the array (known as missing heritability). Finally, Friedman and colleagues note that twin studies are well suited to characterize genetic heterogeneity through their flexible modeling techniques.

Given that genetic heterogeneity, and particularly pleiotropy, continue to muddle psychiatric genetics research, it appears that twin studies can be helpful tools for investigating new phenotypes that can then be included in larger scale genome wide association studies. One method of better understanding genetic heterogeneity is by combining structural equation modeling approaches such as biometrical twin models and confirmatory factor analyses to model the dimensional nature of psychopathology as well as its genetic and environmental variance. Given the high rates of comorbidity across SUDs and pathological gambling and the existing research linking them via genetic, neurological, and behavioral mechanisms, it would be worthwhile to leverage the twin study approach to better understand genetic and environmental contributions to the dimensional phenotypes underlying these co-occurring disorders. As noted in this review, twin studies have modeled the genetic and environmental variance of latent factors influencing SUDs and pathological gambling, but most only attempt to model one latent factor or two correlated factors (e.g., Hicks et al., 2011; Kendler et al., 2007). The existing research

suggests that more comprehensive models combining confirmatory factor analysis and biometrical twin modeling might provide insights into sources of common genetic influence among SUDs and pathological gambling.

The HiTOP consortium is a group of researchers committed to developing a dimensional nosology for psychopathology based on quantitative analyses (Conway et al., 2019).The dimensional structure proposed in HiTOP (described fully in Chapter 3) was largely derived from confirmatory factor analysis, which is complementary to the classical twin study. By first modeling the dimensional nature of psychopathology in a sample of twins and then applying the biometrical model to that structure, we can better elucidate genetic and environmental influences on psychopathology at the common and disorder-specific levels. As such, this study will build upon the findings in Study 1 (Chapter 3) by applying a biometrical model to the internalizing and externalizing spectra as well as to the illicit substance use subfactor to discern how each of these factors contribute genetic and environmental variance to 15 common mental disorders, including misuse of six illicit substances, pathological gambling, and nicotine and alcohol use. We hypothesized that the additive genetic and non-shared environmental influences on internalizing and externalizing spectra would account for additive genetic and non-shared environmental variance across all 15 mental disorders; however, we posited that each mental disorder would have disorder-specific genetic and non-shared environmental variance as well. In line with Lahey and colleague's (2011) discussion of the "generalist genes, specialist environment model" and consistent with much of the prior literature, we did not anticipate that shared environment would have an impact on variance at the common

spectra/subfactor or disorder-specific level (Slutske et al., 2000; Slutske et al., 2001; Tsuang et al., 1998; Xian et al., 2014; Xian et al., 2008).

Methods

Participants

The Vietnam Era Twin Registry was created using an electronic database of veterans who were discharged from the military after serving in the Vietnam War era (1965-1975). The registry consists of male twin pairs, both MZ and DZ, who were born between 1939 and 1955 and who served on active duty (Eisen et al., 1987). There were 10,300 eligible individuals in the registry, and 8,169 (79%) agreed to participate in the Harvard Drug Study (Xian et al., 2008). The current study utilized data from the 3,372 complete MZ (n = 1,874) and DZ (n = 1,498) twin pairs who participated in Harvard Drug Study.

Measures

Participants completed a computer-assisted telephone interview version of the Diagnostic Interview Schedule, Version 3 Revised (Robins et al., 1989). Participants were assessed for lifetime diagnoses of DSM-III-R nicotine, alcohol, hallucinogen, amphetamine, stimulant, heroin/opioid, sedative, and cannabis abuse/dependence as well as for panic disorder, generalized anxiety disorder, agoraphobia, post-traumatic stress disorder, depression, bipolar disorder, antisocial behaviors (childhood conduct disorder and adult antisocial personality disorder), and pathological gambling. Of these diagnoses, agoraphobia and panic disorder were collapsed into one panic/agoraphobia variable, and dysthymia and bipolar disorder were not included in the model (see chapter 3 for rationale

behind exclusions). Trained staff from the Institute for Survey Research, Temple University, interviewed twins after verbal informed consent was obtained, a method approved by the Institutional Review Boards at all participating institutions. To determine zygosity, participants completed a 20-question survey and completed blood typing for ABO and rH factor (87.6% of twin pairs); the data were analyzed using logistic regression to determine the ideal method of identifying zygosity (full procedures reported in Eisen et al., 1989).

This study operationalized each disorder using symptom counts to better capture the range of severity and to avoid using diagnostic yes/no thresholds, which aligns with the HiTOP recommendations and with prior research (Kotov et al., 2017). The results of Study 1 (Chapter 3) revealed the latent dimensional structure of psychopathology in this sample. Symptoms of panic disorder/agoraphobia, depression, generalized anxiety disorder, and post-traumatic stress disorder were found to load onto the internalizing spectrum. Symptoms of illicit substance use (including opioids, hallucinogens, cocaine, cannabis, amphetamines, and sedatives) loaded onto an illicit substance use subfactor. The illicit substance use subfactor and symptoms of alcohol use, nicotine use, pathological gambling, conduct disorder, and antisocial personality disorder loaded onto the externalizing spectrum. We applied biometrical modeling to this best-fitting model derived from Study 1.

Analyses

Data cleaning and the calculation of descriptive statistics were completed using SPSS Statistics version 27.0.1.0. All structural equation modeling procedures were

completed using Mplus version 8.6. Detailed descriptions of all factor analyses and final model selection are detailed in Chapter 3. The best fitting model from Study 1 is represented in Figure 10, including standardized factor loadings.

In the last chapter, we characterized the correlations between internalizing and externalizing disorders using factor analysis; in this follow-up study, we used multivariate genetic analyses to identify the causes of those relationships among variables. While the goal of univariate genetic analysis is to decompose the variance of a single trait (e.g., alcohol dependence) into its genetic and environmental components, in multivariate genetic analysis, we can decompose sources of covariance between traits using latent factors (Kendler et al., 2000). We determined the genetic and environmental contributions to the internalizing and externalizing spectra as well as the illicit substance use subfactor in addition to disorder-specific genetic and environmental contributions to the 15 disorders included in our study. Phenotypic variance, in this case from symptom counts, was decomposed into causal latent factors representing additive genetic effects, shared environmental effects, and non-shared environmental effects.

ACE twin models operate on the following assumptions:

1) MZ and DZ twin pairs share their environments to the same extent.
2) Twins are no different from the general population in terms of the trait.
3) There is no selective mating in the population for the variables of interest (Rijsdijk & Sham, 2002).

Because all twins in this study were reared together, MZ twins were assumed to share 100% of their genetic material and 100% of their shared environment. For DZ

twins, only 50% of genetic material is shared, although they were still assumed to have in common 100% of their shared environment. Non-shared environmental influences include experiences unique to an individual as well as random error and were thus assumed to be uncorrelated in both MZ and DZ twins. For this sample, we found no evidence to suggest that twins differed from the general population across any traits, and we had no reason to consider selective mating as a confound for this set of variables.

When testing genetic and environmental influences using ACE models, it is common to test both independent and common pathway models (Figure 3). Common pathway models are theoretical in nature and often based in prior psychometrical research. These models decompose latent factor variances (in this case internalizing spectra, externalizing spectra, and illicit substance use subfactors) and residual indicator variances from the 15 disorders into additive genetic (A), shared environment (C), and non-shared environmental contributions (E). The HiTOP framework defines a quantitatively theorized framework that takes the form of a common pathway model when applied in multivariate genetic analysis, which aligns with the aims of this study. In addition, previous twin studies utilizing the same sample as the current study found the common pathway model to provide comparable fit to an independent pathway model (Tsuang et al., 1998; Slutske et al., 2000; Slutske et al., 2001). As such, this study tested only the common pathway model derived from the factor analysis results of Study 1.

We analyzed within-twin, within-trait and within-twin, across trait correlation tables for MZ and DZ twins across all 15 disorders of interest. Next, we fit the following models:

ACE Model: The ACE model estimates additive genetic, shared environmental, and non-shared environmental contributions to the variance in each latent and observed variable (Figure 12).

AE Model: The AE model aligns with Lahey and colleague's (2011) "generalist genes, specialist environments model", which suggests that twins share general genetic susceptibilities but that the expression of a trait is influenced by non-shared environmental contributions unique to each twin. This theory aligns with much of the existing research on SUDs and pathological gambling (e.g., Kendler et al., 2007; Kendler, Prescott, et al., 2003; Krueger et al., 2002; Slutske et al., 2000; Slutske et al., 2001).

CE Model: The CE model suggests that the entirety of variance in the expression of a trait is determined by shared genetics and shared environment.

E Model: The non-shared environment model implicates only unique experiences for each twin (as well as measurement errors) to be contributors to the variance in a given trait.

Modified ACE Model: The modified ACE model is derived by excluding non-significant factor loadings on A, C, and E components for each latent factor and observed variable based on findings from the original ACE model; because this model makes no broad assumptions about genetic and environmental contributions to any trait, it allows for unique configurations and often provides the best fitting model.

To determine model fit, we considered a CFI > .90, RMSEA < 0.08, and SRMR < .08 as indicative of good model fit (Kline, 2016). While chi-square statistics were available, in studies with sample sizes greater than 200 the chi-square tends to be significant even in models with very good fit and is not recommended when comparing models with different degrees of freedom (Brown, 2015). Therefore, we examined the AIC, a fit statistic that is robust to large sample sizes and valid for comparing non-nested models (Brown, 2015). However, when all other fit statistics are adequate, models with similar AIC values should both be considered a good fit to the data (Cavanaugh & Neath, 2019). In the event that more than one model was an adequate fit to the data, we relied on the principle of parsimony to determine a final model. We defined a more parsimonious model as having more degrees of freedom and fewer freely estimated parameters. Full information maximum likelihood was used to account for missing data. Parameter estimates were considered statistically significant if they met the p-value threshold of .05 or less. We confirmed these values by examining 95% confidence intervals to confirm that no interval overlapped with zero.

The guidelines set forth by Neale, Eaves, and Kendler (1994) represent the standard for power analyses for a coefficient alpha of .05 for continuous phenotypes, including the latent variables outlined above. Effects are expected to be moderate to large, given that previous findings revealed 28% to 61% of the variance specific to SUDs (Krueger et al., 2002; Slutske et al., 2000; Slutske et al., 2001; Tsuang et al., 1998; Xian et al., 2008; Xian et al., 2014) and 88% to 90% of the variance shared across SUDs (Krueger et al., 2002; Xian et al. 2008) is due to genetics. Calculations revealed that 3,372 twin pairs will provide

> 80% power to detect the "true" model when heritability = 25% and > 95% power to detect the "true" model when heritability is ≥ 30%.

Results

Sample Characteristics

The mean age of respondents was 42 years (SD = 2.8, range 33–55 years). The sample was 93.3% non-Hispanic/Caucasian, 6.3% African-American, and 0.4% identified as 'other'. In terms of education, 8% of respondents had not graduated from high school, 96% were high school graduates, and 23% college graduates. Most participants (95.6%) were employed, 75.9% were married, 16.4% widowed, separated or divorced and 7.7% had never been married.

Average symptom counts for MZ and DZ twin pairs as well as the total sample are reported in Table 2 (Chapter 3), and phenotypic correlations for the 15 disorders are reported in Table 3 (Chapter 3). On average, DZ twins reported significantly more symptoms of nicotine use ($t(6742) = 3.02$, $p = .003$, 95% CI [0.05, 0.25]) and conduct disorder ($t(6742) = 2.12$, $p = .034$, 95% CI [0.01, 0.12]) compared to MZ twins, although the mean differences were not particularly large (0.06 for conduct disorder and 0.05 for nicotine use).

Table 6 depicts within-trait, within-twin correlations for MZ and DZ twins. Of note, all MZ twin correlations were significantly stronger than those of DZ twins with the exception of co-twin correlations for hallucinogen use (z-score = 1.25, $p = .21$). Within-twin, within-trait correlations for cocaine use, conduct disorder, and post-traumatic stress disorder were modestly different between MZ and DZ twins. The strength of co-twin

correlations among MZ twins included mostly small (panic disorder, hallucinogen use, sedative use, cocaine use, generalized anxiety disorder, post-traumatic stress disorder, opioid use) and moderate (amphetamine use, conduct disorder, gambling disorder, major depressive disorder, cannabis use, alcohol use, and antisocial personality disorder) correlations, although nicotine use was highly correlated across MZ co-twins. DZ co-twins demonstrated small to moderate co-twin correlations, with the strongest correlation again for that of nicotine use. MZ and DZ twin correlations showed the greatest disparities (as assessed via z-score) in nicotine use, alcohol use, and antisocial personality disorder. Based on these findings we anticipated that disorder-specific genetic and/or shared environmental contributions to hallucinogen use, cocaine use, and conduct disorder might be minimal, whereas we anticipated greater genetic and/or shared environmental contributions to alcohol use, antisocial personality disorder, and nicotine use.

Table 6. Within-Trait, Within-Twin correlations

	MZ (n = 3,748)	DZ (n = 2,996)	z-score
CAN	0.44*	0.26*	8.41*
AMP	0.30*	0.09*	8.94*
SED	0.18*	0.08*	4.15*
COC	0.22*	0.15*	2.96*
OPI	0.26*	0.08*	7.58*
PCP	0.16*	0.13*	1.25
ALC	0.48*	0.27*	10.04*
NIC	0.55*	0.29*	13.04*
PG	0.33*	0.14*	8.23*
CON	0.32*	0.25*	3.10*
ASP	0.48*	0.27*	10.04*
DEP	0.35*	0.12*	9.99*
GAD	0.23*	0.04**	7.92*
PTS	0.24*	0.15*	3.82*
PAN	0.15*	0.04**	4.53*

Note: * = p <. 001; ** = p <.05

Table 7a. Cross-Trait, Cross-Twin Correlations-MZ Twins

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1 CAN	--													
2 AMP	0.47	--												
3 SED	0.34	0.39	--											
4 COC	0.30	0.36	0.22	--										
5 OPI	0.16	0.25	0.26	0.18	--									
6 PCP	0.39	0.53	0.40	0.30	0.17	--								
7 ALC	0.33	0.36	0.19	0.16	0.12	0.17	--							
8 NIC	0.23	0.18	0.10	0.12	0.07	0.09	0.43	--						
9 PG	0.10	0.10	0.11	0.07	0.00	0.07	0.16	0.12	--					
10 CON	0.24	0.22	0.15	0.16	0.08	0.17	0.28	0.21	0.18	--				
11 ASP	0.42	0.41	0.28	0.32	0.18	0.30	0.49	0.30	0.27	0.45	--			
12 DEP	0.28	0.23	0.18	0.16	0.09	0.18	0.34	0.27	0.17	0.29	0.40	--		
13 GAD	0.18	0.14	0.12	0.10	0.06	0.13	0.24	0.19	0.10	0.18	0.27	0.54	--	
14 PTS	0.18	0.18	0.11	0.12	0.09	0.10	0.26	0.24	0.11	0.25	0.29	0.48	0.38	--
15 PAN	0.20	0.21	0.15	0.11	0.04*	0.14	0.22	0.14	0.13	0.18	0.22	0.33	0.35	0.25

CAN = cannabis use disorder; AMP = amphetamine use disorder; SED = sedative use disorder; COC= cocaine use disorder; OPI = opioid use disorder; PCP = hallucinogen use disorder; ALC = alcohol use disorder; NIC = nicotine use disorder; PG = pathological gambling; CON = conduct disorder, ASP = antisocial personality disorder; DEP = major depressive disorder, GAD = generalized anxiety disorder, PTS = post-traumatic stress disorder, PAN = panic/agoraphobia,

Table 7b. Cross-Trait, Cross-Twin Correlations-DZ Twins

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1 CAN	--													
2 AMP	0.49	--												
3 SED	0.36	0.55	--											
4 COC	0.31	0.40	0.24	--										
5 OPI	0.28	0.33	0.41	0.27	--									
6 PCP	0.41	0.52	0.43	0.31	0.18	--								
7 ALC	0.34	0.28	0.21	0.17	0.14	0.22	--							
8 NIC	0.25	0.18	0.14	0.12	0.11	0.13	0.40	--						
9 PG	0.18	0.09	0.02	0.12	0.07	0.03	0.20	0.11	--					
10 CON	0.23	0.18	0.18	0.10	0.10	0.15	0.26	0.24	0.17	--				
11 ASP	0.39	0.38	0.32	0.33	0.23	0.35	0.48	0.29	0.25	0.42	--			
12 DEP	0.27	0.22	0.19	0.13	0.13	0.14	0.36	0.30	0.18	0.25	0.38	--		
13 GAD	0.19	0.17	0.18	0.08	0.06	0.12	0.25	0.16	0.14	0.17	0.24	0.51	--	
14 PTS	0.22	0.17	0.14	0.11	0.13	0.10	0.33	0.27	0.13	0.22	0.34	0.47	0.36	--
15 PAN	0.14	0.14	0.08	0.10	0.06	0.07	0.20	0.15	0.12	0.12	0.21	0.30	0.34	0.26

CAN = cannabis use disorder; AMP = amphetamine use disorder; SED = sedative use disorder; COC= cocaine use disorder; OPI = opioid use disorder; PCP = hallucinogen use disorder; ALC = alcohol use disorder; NIC = nicotine use disorder; PG = pathological gambling; CON = conduct disorder, ASP = antisocial personality disorder; DEP = major depressive disorder, GAD = generalized anxiety disorder, PTS = post-traumatic stress disorder, PAN = panic/agoraphobia

Cross-trait, cross-twin correlations are presented in Tables 7a (MZ twins) and 7b (DZ twins). Among MZ twins, all cross-trait correlations were significant at $p < .001$ with the exception of panic disorder and opioid use (both $p = .014$). In addition, pathological gambling and opioid use were not significantly correlated. Among DZ twins, pathological gambling and hallucinogen use ($p = .10$) and pathological gambling and sedative use ($p = .27$) were not significantly correlated. All other correlations were significant at $p \leq .001$.

MZ and DZ twins differed significantly between 20 cross-trait correlations. Correlations between cannabis and opioid use (z-score = -5.06, $p < .001$), pathological gambling and cannabis use (z-score = -3.27, $p < .001$), sedative and amphetamine use (z-score = -8.28, $p < .001$), opioid and amphetamine use (z-score = -3.51, $p < .001$), alcohol and amphetamine use (z-score = 3.58, $p < .001$), opioid and sedative use (z-score = -6.80, $p < .001$), generalized anxiety disorder and sedative use (z-score = -2.46, $p = .014$), opioid and cocaine use (z-score = -3.80, $p < .001$), opioid use and pathological gambling (z-score = 1.25, $p = .21$) opioid use and antisocial personality disorder (z-score = -2.09, $p = 0.04$), hallucinogen and alcohol use (z-score = -2.08, $p = 0.04$), hallucinogen use and antisocial personality disorder (z-score = -2.24, $p = .0.02$), post-traumatic stress disorder and alcohol use (z-score = -3.08, $p = .002$), and antisocial personality disorder and post-traumatic stress disorder (z-score = -2.23, $p = .026$) were significantly stronger among DZ twins. Inversely, associations between panic disorder and cannabis use (z-score = 2.48, $p = .01$), panic disorder and amphetamine use (z-score = 2.90, $p = .004$), panic disorder and sedative use (z-score = 2.85, $p = .004$), cocaine use and conduct disorder (z-score = 2.45, $p = .014$), hallucinogen use and panic disorder (z-score = 2.84, $p = .004$), and conduct disorder and

panic disorder (z-score = 2.46, p = .013) were significantly stronger among MZ compared to DZ twins.

Genetics of Psychopathology

Upon fitting the full ACE model, we found that several genetic and shared environmental variance estimates were equal to 0 (shared environmental contributions to internalizing, amphetamine use, sedative use, opioid use, major depressive disorder, generalized anxiety disorder, panic disorder, nicotine use, and antisocial personality disorder as well as genetic contributions to cocaine use and hallucinogen use), which resulted in overestimation of the model and negative residual variances. We fixed these parameters to zero, which resolved error messages related to non-identification. Next, we adjusted loadings to estimate the AE, CE, E, and modified ACE models. Notably, across all models, factor loadings for the internalizing and externalizing spectra as well as the illicit substance use subfactor derived in Study 1 remained stable, with loadings varying by no more than .02 compared to Study 1.

Table 8. Goodness of Fit for Biometrical Models

Model	RMSEA (<.08)	CFI (>.90)	SRMR (<.08)	AIC[a]	No. Estimated Parameters
E	0.034	0.83	0.11	327341.64	49
ACE	0.026	0.91	0.09	324828.57	74
AE	0.025	0.91	0.09	324833.77	67
CE	0.029	0.88	0.09	325803.25	58
Mod. ACE	0.025	0.91	0.08	324845.48	65

RMSEA = Root mean square error of approximation; CFI = Comparative fit index; SRMR = Standardized root mean square residual; AIC = Akaike Information Criteria
[a] Lower AIC indicates better model fit compared to E-only model.

Table 8 provides goodness of fit statistics for the biometrical models. Notably, E and CE models did not meet CFI or SRMR fit thresholds, although they were more parsimonious. The ACE model showed the greatest decrease in AIC, but SRMR did not meet the designated threshold, and the ACE model was the least parsimonious of all options. Between the AE and modified ACE models, fit indices were comparable, except that the modified ACE model was the only solution to demonstrate an acceptable SRMR. In addition, the modified ACE model was more parsimonious. Therefore, the modified ACE model was designated as the best fitting model.

The standardized factor loadings for the modified ACE model are presented in Figure 13. Notably, shared environment was not responsible for any of the common genetic variance shared among the 15 disorders (i.e., there were no significant effects for C at the spectrum or subfactor levels). At the disorder-specific levels, non-shared environmental factors contributed significantly to the residual variance for all 15 disorders, and genetic factors contributed significantly to the residual variance for 11 of the 15 disorders. For generalized anxiety disorder and hallucinogen use, only non-shared environmental effects were observed at the disorder-specific level. For conduct disorder and cocaine use, both shared environmental and non-shared environmental factors contributed to disorder-specific variance.

Table 9. Percent Total and Shared Variance by Disorder and Factor

	Total A (%)	Total C (%)	Total E (%)	Common A (%)	Common E (%)
INT	24		76		
EXT	46		54		
ILLICIT	37		63	62	44
CAN	36		64	50	48
AMP	30		70	77	51
SED	19		81	79	27
COC	11	11	78	100	18
OPI	27		73	22	12
PCP	16		84	100	31
ALC	44		56	9	9
NIC	49		51	14	16
PG	32		68	13	7
CON	12	13	75	100	19
ASP	36		64	83	56
DEP	18		82	83	56
GAD	10		90	100	36
PTS	19		81	42	32
PAN	10		90	40	17

Note: Total A, C, and E reflects the total genetic, shared environmental and non-shared environmental variance (both common and disorder-specific) attributable to each disorder, spectrum, and subfactor, respectively. Common A and E reflect the total proportion of each disorder, spectrum, or subfactor's genetic or non-shared environmental risk that is shared across multiple disorders.

CAN = cannabis use disorder; AMP = amphetamine use disorder; SED = sedative use disorder; COC= cocaine use disorder; OPI = opioid use disorder; PCP = hallucinogen use disorder; ALC = alcohol use disorder; NIC = nicotine use disorder; PG = pathological gambling; CON = conduct disorder, ASP = antisocial personality disorder; DEP = major depressive disorder, GAD = generalized anxiety disorder, PTS = post-traumatic stress disorder, PAN = panic/agoraphobia; INT = internalizing; EXT = externalizing; ILLICIT = illicit substance use

Table 9 reports total A, C, and E contributions to each of the 15 disorders as well as the illicit substance use subfactor and internalizing and externalizing spectra and provides proportions of total genetic and non-shared environmental risk attributable to common or shared influences for each disorder. Notably, all disorders were associated with some level of genetic risk, although heritability estimates varied widely from 10% (generalized anxiety and panic disorder) to 49% (nicotine use). Among internalizing disorders, much of the variance was attributable to non-shared environmental contributions and/or measurement error. Also of note, 100% of the genetic variance associated with risk for cocaine and hallucinogen use, conduct disorder, and generalized anxiety was associated with genetic influences shared at the spectrum or subfactor levels. Greater than 75% of the genetic variance associated with amphetamine use, sedative use, antisocial personality disorder, and depression was shared with other disorders.

Table 10. Common and Disorder-Specific Proportions of Variance

	Common INT %		Common ILLICIT %		Common EXT %		Disorder/Factor Specific %		
	A	**E**	**A**	**E**	**A**	**E**	**A**	**C**	**E**
INT							24		76
EXT							46		54
ILLICIT					23	28	14		35
CAN			7	17	11	14	18		33
AMP			9	20	14	16	7		34
SED			6	13	9	9	4		59
COC			4	8	7	6		11	64
OPI			2	5	4	4	21		64
PCP			6	15	10	11			58
ALC					4	5	40		51
NIC					7	8	42		43
PG					4	5	28		63
CON					12	14		13	61
ASP					30	36	6		28
DEP	15	46					3		36
GAD	10	32							58
PTS	8	26					11		55
PAN	4	15					6		75

CAN = cannabis use disorder; AMP = amphetamine use disorder; SED = sedative use disorder; COC= cocaine use disorder; OPI = opioid use disorder; PCP = hallucinogen use disorder; ALC = alcohol use disorder; NIC = nicotine use disorder; PG = pathological gambling; CON = conduct disorder, ASP = antisocial personality disorder; DEP = major depressive disorder, GAD = generalized anxiety disorder, PTS = post-traumatic stress disorder, PAN = panic/agoraphobia; INT = internalizing; EXT = externalizing; ILLICIT = illicit substance use

Table 10 further breaks down genetic and environmental contributions to the 15 disorders, spectra, and subfactor based on common and disorder-specific influences. Proportions were calculated by multiplying pathways and then squaring them to calculate total common A and E contributions to specific symptom sets. For example, illicit substance use shares genetic variance with externalizing, because of its factor loading. By multiplying and then squaring the product of the A-EXT and EXT-ILLICIT paths (.68 x

$.71)^2$ we determined that 23% of the variance associated with illicit substance use is due to genetic variance shared with the externalizing spectrum. Similar path tracing was used to calculate all shared genetic and environmental influences in Table 10.

Discussion

In this study, we found evidence to support our hypotheses that both common and disorder-specific genetic and non-shared environmental contributions contribute to psychopathology. Our findings also suggest that the structure derived from Study 1 helped to explain underlying sources of common variance for internalizing and externalizing disorders and for illicit substance use. However, we also found that disorder-specific shared environmental risks are associated with conduct disorder and cocaine use. We did not find evidence for significant disorder-specific genetic contributions to conduct disorder, cocaine use, hallucinogen use, or generalized anxiety disorder.

Our findings align well with previous studies using the same sample of Vietnam-era veteran twins. Figure 14 provides a side-by-side comparison of Tsuang and colleagues' 1998 study of shared genetics in illicit substance use and the current findings. The approaches differed in that the current study attempted to model an underlying structure to better describe common genetic risks and included 15 disorders, whereas the 1998 study examined only illicit substances and collapsed cocaine use and amphetamine use into a stimulant use variable. However, the total proportion of common variance among illicit substances is remarkably consistent across both studies. Our findings contribute new information to findings from the 1998 study; namely, we can further breakdown shared

genetic risk for illicit substance use into contributions from an externalizing spectrum as well as a unique subfactor representing liability to illicit substance use.

Overall, our heritability estimates for pathological gambling and alcohol use are somewhat lower than those derived in a previous study of alcohol use (h^2 = .55) and pathological gambling (h^2 = .49), but it is important to note that the two studies differed in how the target variables were operationalized (Slutske et al., 2000). Similarly, a prior study using the same sample found that 12% to 20% of the genetic variation in the risk for pathological gambling was shared with the risk for alcohol dependence (Slutske et al., 2001). We now add to those findings by suggesting that this common variance (13% for pathological gambling in our study) is attributable to the externalizing spectrum.

Our findings diverge somewhat from those of a prior study examining a common latent factor influencing alcohol, nicotine, and cannabis dependence (Xian et al., 2008). Xian and colleagues found evidence to support larger proportions of shared genetic variance (33% to 42%) among two of the three disorders compared to our findings (common variance of 5% and 14% for nicotine and alcohol use and 50% for cannabis use). However, the model utilized in the current study included 15 disorders, which means that sources of shared genetic variance are not directly comparable to the prior study, which modeled shared influences on three substance use variables. Finally, our heritability estimates are consistent with a study examining relationships between gambling and nicotine and cannabis dependence, with heritability estimates for the previous study ranging from .49 (pathological gambling) to .28 (cannabis use) compared to our findings

of .32 (pathological gambling) and .36 (cannabis use; Xian et al., 2014), although the modeling procedures were again different than those used in the current study.

Our results are also consistent with previous findings relating internalizing and externalizing to common genetic variance across common mental disorders. For example, our findings are comparable to Lahey and colleagues (2011), who reported small genetic contributions to generalized anxiety and depression via the internalizing spectrum. However, our findings diverge in our modeling of the externalizing spectrum. We found that genetic risks associated with conduct disorder were all associated with genetic variation shared with the externalizing spectrum; Lahey and colleagues identified significant disorder-specific genetic influences on the risk for conduct disorder. However, they did not model a substance use subfactor in their study.

Our findings also add to prior research findings that conduct disorder (common h^2 = .14 in a previous study and .12 in the current study) and antisocial personality disorder (common h^2 = .42 in a previous study and .30 in the current study) share significant genetic variance via a higher order factor that is also associated with illicit drug use and alcohol use (Kendler, Prescott, et al., 2003). We also found that opioid use shares comparably less common genetic risk with other illicit substance use (common additive genetics = 23% and 30% in prior studies and 22% according to current findings (Kendler, Jacobson, et al., 2003; Tsuang et al., 1998).

In the previous chapter we modeled a unique illicit substance use factor that in this study contributed common genetic and non-environmental variance to the risk for using six illicit substances. One previous study modeled licit and illicit substance use factors and

examined shared and disorder-specific A, C, and E across cannabis, cocaine, alcohol, caffeine, and nicotine dependence symptoms (Kendler et al., 2007). In the current study, we did not find evidence to support a licit substance use factor; however, we used pathological gambling as a legal addictive behavior in the current study and did not collect data on caffeine use. Our common heritability estimates for cannabis (h^2 = .50) are similar to those derived in the prior study (h^2 = .46), but we found that the modest heritability associated with cocaine use was common to illicit substance use (4%) and externalizing (7%). Because the studies utilized different models, it is difficult to draw conclusions about the existence of an illicit substance use subfactor and its contributions to common genetic and environmental risks for psychopathology. However, these findings do suggest the need to further research the unique genetic and environmental variance associated with illicit substance use.

Kendler (2006) noted that adherence to inaccurate nosology can obscure important genetic relationships, and this has likely contributed to difficulties in addressing genetic pleiotropy in the field of behavioral genetics. The current study attempted to bridge a quantitatively derived nosology with a quantitatively derived understanding of genetic contributions to psychopathology to better understand the magnitude of genetic and environmental contributions to risk of psychopathology as well as the constructs that inform those risks. This study is one of the first to combine these two approaches using 15 common mental disorders, and the findings replicate earlier research on heritability across illicit substances. With the knowledge that illicit SUDs share unique risks as well as risks common to other eternalizing disorders, it might be possible to design treatments that target

these shared risk factors with a particular focus on illicit substance use (Ruggero et al., 2019; Hopwood et al., 2020).

The current findings should be interpreted with the understanding that there are several limitations to this study. First, while it was an aim of the study to characterize psychopathology in a veteran sample, this particular sample consisted of male twin pairs who were majority white. There is evidence to suggest that women display different risk factors for pathological gambling (e.g., non-strategic gambling, "telescoping", and negative-reinforcement motivation; Potenza et al., 2019), so it is critical to examine how the genetic structure of psychopathology might differ in female samples. Likewise, given that racially and ethnically veterans are more likely to not seek treatment for SUDs (Golub et al., 2013), it is critical to better characterize unique risk factors impacting diverse veterans in order to better serve this important population.

The substantial sample size for the current study represents a strength; however, due to the large sample size, objective chi-square testing to determine the best fitting model was not possible. This is because with large sample sizes chi-square tests are highly sensitive and tend to provide false significant results (Brown, 2015). However, this study did provide early evidence to support a HiTOP-derived structure of psychopathology that explains significant genetic and environmental contributions across 15 common mental disorders. Future research might consider collecting more data on licit and illicit substances to better characterize the structure of a substance use (or illicit) substance use subfactor. Likewise, future studies should attempt to model SUDs separately rather than as one collapsed drug dependence variable. Previous studies may have been missing out on

important genetic findings due to insufficient sample sizes or low base rates for illicit substance use. Finally, it is important to consider how patterns of use and associated beliefs and personality traits associated with use (see Zilberman et al., 2018) may change in response to the recent legalization of marijuana use in many states and the widespread expansion of legal gambling (e.g. online sports betting; Potenza, 2017).

CHAPER 5. General Discussion

While the DSM has allowed for the improved assessment and treatment of psychopathology, alternative nosologies and DSM revisions have also been a regular feature of mental health research (Cuthbert, 2015). The goals of these alternative taxonomies are to 1) improve clinical practice and 2) to better understand underlying biological mechanisms that contribute to psychopathology. To achieve these goals, research will need to deviate from traditional classification models and combine new taxonomic frameworks with existing analytic techniques to better understand and treat common mental disorders.

As this project has demonstrated, SUDs and pathological gambling are a potential area of research where the use of alternative classification systems might clarify underlying relationships. SUDs and pathological gambling are highly comorbid and share common neurological underpinnings, particularly via the dopaminergic systems that influence reward circuitry in the brain (Linnet, 2020). Moreover, twin studies have revealed shared genetic risks among SUDs and pathological gambling, although candidate gene and genome wide association studies have yet to identify those genetic relationships at the molecular level (Comings et al., 2001; Nivard et al., 2016; Slutske et al., 2000; Xian et al., 2014). This project leveraged an alternative, quantitatively derived, dimensional classification of psychopathology (HiTOP) to model common and disorder-specific influences on 15 common mental disorders, including 8 SUDs and pathological gambling.

In Study 1, we attempted to determine where pathological gambling fit into the HiTOP-proposed structure of psychopathology using a sample of Vietnam-era twins, all of

whom served in the active-duty military. Based on a small body of prior research and theory, we hypothesized a best fitting model where pathological gambling would load onto the externalizing spectrum via an addictive behaviors subfactor (Bresin, 2020; King et al., 2019; Oleski et al., 2011). Our findings partially supported our hypotheses in that pathological gambling and other SUDs loaded onto the externalizing spectrum. However, rather than a broad subfactor representing liability to addictive disorders (our hypothesis) or a substance use subfactor influencing liability to any substance use (Bailey & Finn, 2019, 2020; Kotov et al., 2017), we found evidence to support a subfactor unique to illicit substance use (Figure 11).

While our study provides evidence to support the dimensional nature of psychopathology as outlined within the HiTOP framework, there are some important points to consider. First, we found that a model including the 'p' factor resulted in overestimation of the model. In other words, internalizing and externalizing accounted for the same variance as the 'p' factor and adding this super spectrum to the model resulted in an explanation of greater than 100% of the model variance. Fried and colleagues (2021) suggested that the 'p' factor represents severity or comorbidity rather than liability, in the way that flu symptom counts might reflect severity rather than liability for the flu. However, research in the field of adolescent psychopathology suggests that a general factor of psychopathology shares more in common with neuroticism than with social desirability or evaluation bias measures (Tackett et al., 2013). Overall, our findings add to the mixed evidence both refuting and supporting the existence of a 'p' factor. While future research might continue to focus on elucidating the underlying constructs associated with the 'p'

factor, Watts and colleagues argue that the ever-changing operationalization of the concept requires that its existence be questioned. Instead, they argue that confirmatory factory analysis will not in itself prove the existence of a 'p' factor and that unique approaches to characterization of this dimension of psychopathology will be required to provide strong evidence of its existence.

Our findings support the strong body of evidence suggesting the existence of an externalizing spectrum that influences SUDs and antisocial behavior (e.g., Arcos-Burgos et al., 2012; Bailey & Finn, 2019; Kendler et al., 2011; Krueger et al., 2002). However, we found that only illicit SUDs loaded onto a subfactor, which is contrary to the proposed HiTOP framework suggesting a SUD subfactor (Blanco et al., 2015; Kotov et al., 2017). There is at least one study that modeled illicit and licit substance use factors, although this previous study used only two illicit and three licit substances in analyses and focused on modeling genetic variance using common pathway models rather than identifying latent dimensions and modeling their genetic and environmental variance (Kendler, Prescott, et al., 2003). Most studies examining the existence of a SUD subfactor model a limited number of illicit SUDs or collapse illicit substance use into one drug dependence variable (see King et al., 2019; Krueger et al., 2002; Oleski et al., 2011 for examples). The current findings suggest the importance of modeling illicit SUDs separately rather than as a composite illicit drug dependence variable to better understand dimensional traits underlying their co-occurrence and to potentially differentiate shared susceptibility unique to illicit SUDs and susceptibility shared with legal SUDs that may be partially attributable to externalizing traits.

With liability for pathological gambling most strongly related to the externalizing spectrum in this study, we add to the evidence suggesting that pathological gambling shares underlying dimensional liability with SUDs and other externalizing behaviors. These findings can and should have a significant impact on clinical practice. The National Institute of Health Science of Behavior Change Program has emphasized the importance of identifying mechanistic targets, particularly those that underlie multiple disorders, with the hopes of using these targets to better design effective treatments (Nielsen et al., 2018). This sentiment has been echoed in calls for medication management aimed at shared mechanistic targets rather than traditionally classified categorical disorders (Owen, 2014).

Moreover, Ruggero and colleagues (2019) have outlined specific ways in which the framework of HiTOP can be integrated into clinical practice. The authors note that clinicians might 1) consider a move to dimensions with ranges of symptoms rather than yes/no categorical diagnoses and 2) consider treatment both at the disorder-specific (e.g., phobia of spiders) and dimensional levels (e.g., impulsivity as a treatment target for externalizing; Beauchaine et al., 2017). This study lends support to the theory that externalizing is one of those shared mechanistic targets of SUDs and pathological gambling, and future research might consider how treatment programs aimed at promoting change in externalizing behaviors might decrease symptoms across these disorders. Such a research program would particularly benefit veterans, who struggle with particularly high rates of comorbid pathological gambling and SUD (Westermeyer et al., 2013).

In Study 2, we combined the confirmatory factor analysis from Study 1 with biometrical twin modeling of latent and observed variables. The resulting model largely

aligned with Lahey and colleagues' (2011) generalist genes, specialist environment model in that additive genetics contributed to both latent dimensions of psychopathology as well as specific disorders uniquely. Conduct disorder and cocaine use symptoms both demonstrated significant shared environmental variance at the disorder-specific level, however (Figure 13). Overall, we found evidence to add support to the theory that externalizing is heritable and contributes to shared genetic variance across SUDs and pathological gambling in adolescent and adult samples (Slutske et al., 2001; Hicks et al., 2004, 2011; Iacono et al., 1999; Kendler et al., 2011; Krueger et al., 2002). However, we further characterized the magnitude of common and disorder-specific variance for each of 15 common mental disorders, including contributions from a subfactor representing liability to illicit substance use.

The current findings support existing theories that externalizing might represent a mechanism through which shared genetic factors influence both SUDs and pathological gambling, and we further characterized the genetic and environmental influences unique to each disorder. Our calculations of common genetic variance using a complex structural model largely replicated an earlier study of illicit substance use in the same sample of Vietnam-era twins using a simpler modeling procedure (Tsuang et al., 1998; Figure 14), which lends confidence to our results. We add to this previous study by presenting evidence that a liability to illicit substance use and externalizing explains that common genetic variance.

One benefit of the HiTOP consortium is that researchers have provided recommendations for "how to HiTOP" both in clinical practice (Hopwood et al., 2020;

Ruggero et al., 2019), neuroscientific research (Latzman et al., 2020), and in psychiatric genetics (Waszczuk et al., 2020). In this study, we attempted to adhered to these guidelines by creating lower-order quantitative variables in the form of symptoms counts. Our findings lend support to the use of HiTOP as a tool for modeling pleiotropic relationships in psychiatric genetics. Both molecular and behavioral genetics approaches would benefit from using quantitative phenotypes, which improve statistical power compared to categorical diagnoses by taking advantage of all available phenotypic information (van der Sluis et al., 2013). Using HiTOP phenotypes in future psychiatric and behavioral genetics research can also help to overcome the difficulty in discerning significant genetic relationships across heterogenous presentations of common mental disorders (Wray & Maier, 2014).

This project has several strengths worth considering. First, these studies demonstrate the utility of combining traditional structural equation modeling and biometrical modeling to better characterize theorized HiTOP spectra and super spectra in existing data sets. As such, our research provides some indication that the twin study is still a useful model for characterizing underlying mechanistic targets that contribute to the common and disorder-specific variance across mental disorders (Friedman et al., 2021). In addition, the results of studies 1 and 2 replicate prior findings on the structure of dimensional psychopathology underlying SUDs and pathological gambling and the common and disorder-specific genetics associated with these and other common mental disorders. Finally, this research utilized a sample of veteran males who are at particularly

high risk for comorbid SUDs and pathological gambling and for some of the harm associated with these disorders (Levy & Tracy, 2018; Abbott, 2017).

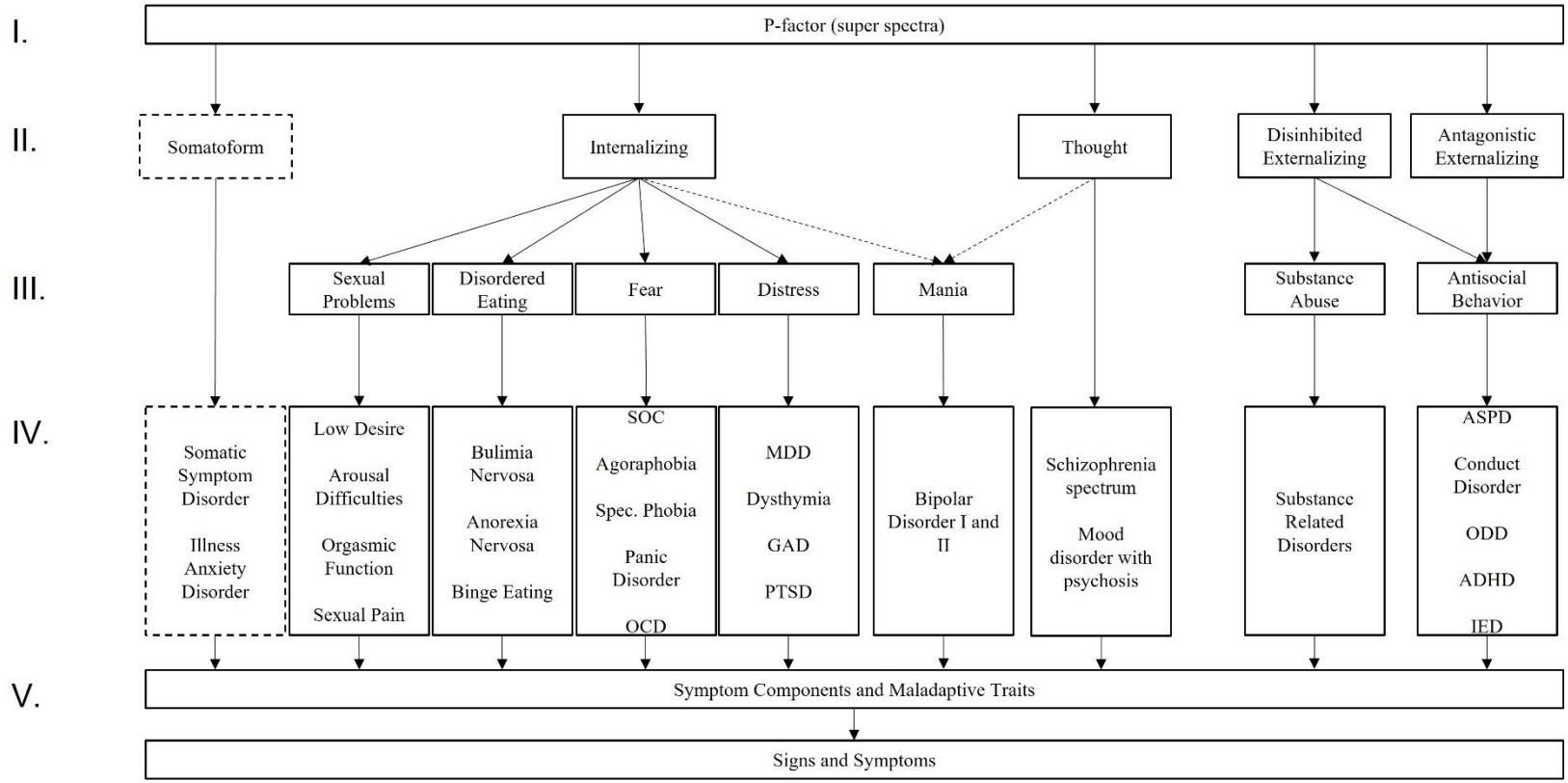
Limitations to the current study are also noteworthy. First, the HiTOP consortium outlines best practices for using HiTOP phenotypes in psychiatric genetics research, and while we did utilize symptom counts to better capture a range of severity in 15 common mental disorders, we did not build a new data set for this study. The gold standard for integrating HiTOP dimensional constructs into genetics research involves collecting data on the subfactor, spectra, and super spectra levels (Waszczuk et al., 2020), which was outside the scope of the current project. Further, while there is a need for research examining comorbid SUDs and pathological gambling in veteran populations, we were demographically limited to a male sample that was majority (93.3%) white. There is evidence to suggest that females and people of color also struggle with comorbid SUDs and pathological gambling that often go untreated, particularly among veteran populations (Golub et al., 2013; Vazan et al., 2013; Werner et al., 2020). Moreover, there is no known research that extends the current findings outside of the confines of biological sex to explore gender identity. These populations represent important targets to include in future research with the goal of providing better care to these marginalized communities. Finally, Kendler (2006) noted that improving phenotypic constructs can improve genetics research. However, twin studies do not define a threshold past which a genetic correlation can be considered sufficient evidence that two disorders are subtypes of a latent subfactor, spectra, or super spectra. In other words, this study clarified genetic and environmental

contributions to SUDs and pathological gambling but did not definitively carve nature at its joints.

There are several takeaways from the current study that can inform future research designs. First, we modeled six illicit SUDs separately rather than collapsing them into one diagnostic category. This may explain the finding of an illicit substance use subfactor in Study 1. However, it is less clear what the shared mechanisms of liability are among illicit SUDs. Modeling illicit SUDs separately in future studies may help to clarify the current findings and their importance to understanding the dimensional nature of SUDs. Second, there are other non-substance related addictive behaviors (e.g., compulsive sexual behavior, excessive shopping, internet gaming) that may result in negative consequences, distress, and impairment. However, these behaviors have not been well characterized in terms of prevalence or their relationship, if any, to pathological gambling, SUDs, and/or externalizing behaviors (Potenza et al., 2019). Future research might consider including these behaviors in research to assess prevalence, harm, and relationship to the externalizing spectrum. Finally, future research should consider other novel ways of combining statistical approaches to both validate the proposed HiTOP structure and better understand shared underlying mechanistic targets that contribute to common mental disorders.

FIGURES

Figure 1. The Hierarchical Taxonomy of Psychopathology



Note: Adapted from Kotov, R., Krueger, R. F., Watson, D., Achenbach, T. M., Althoff, R. R., Bagby, R. M., . . . Zimmerman, M. (2017). The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *Journal of Abnormal Psychology*, *126*(4), 454-477. Adapted to exclude personality disorders, which are not included in the current study.

I = Super Spectra; II = Spectra; III = Subfactor; IV = Syndromes; V = Symptom components and signs and symptoms SOC = social anxiety disorder; Spec Phobia = specific phobia; OCD = obsessive-compulsive disorder; MDD = major depressive disorder; GAD = generalized anxiety disorder; PTSD = post-traumatic stress disorder; ASPD = antisocial personality disorder; ODD = oppositional defiant disorder; ADHD = attention deficit hyperactivity disorder; IED = intermittent explosive disorder

Figure 2. HiTOP Elements that Address Limitations in Genetics Research

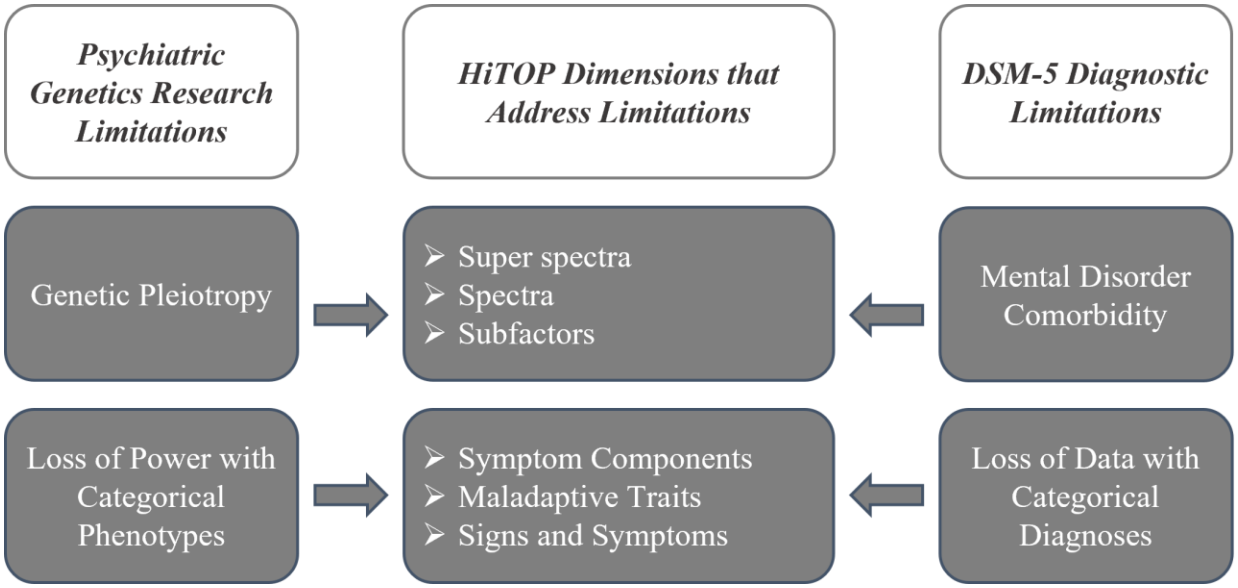


Figure 3. Examples of Independent and Common Pathway Models

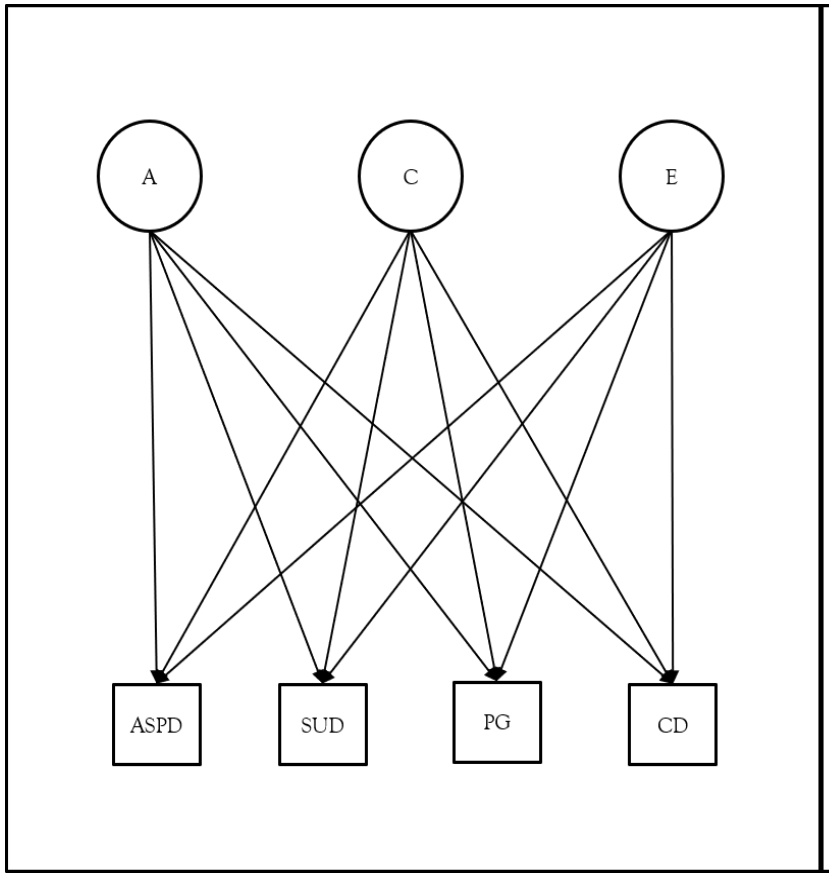


Figure 3a. Independent pathway model.

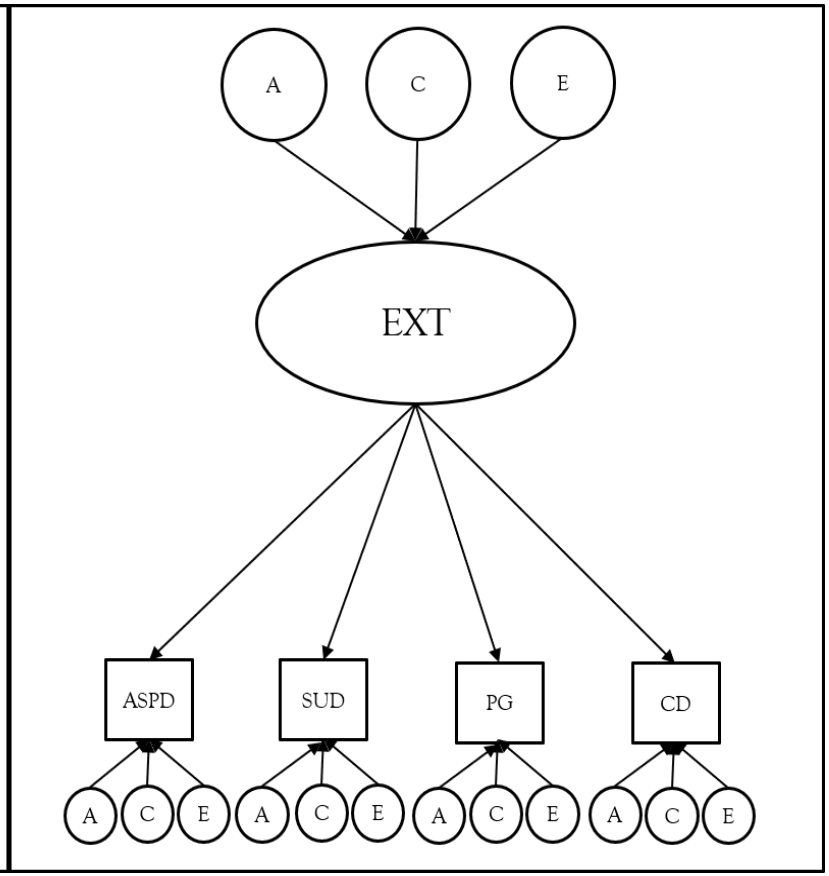
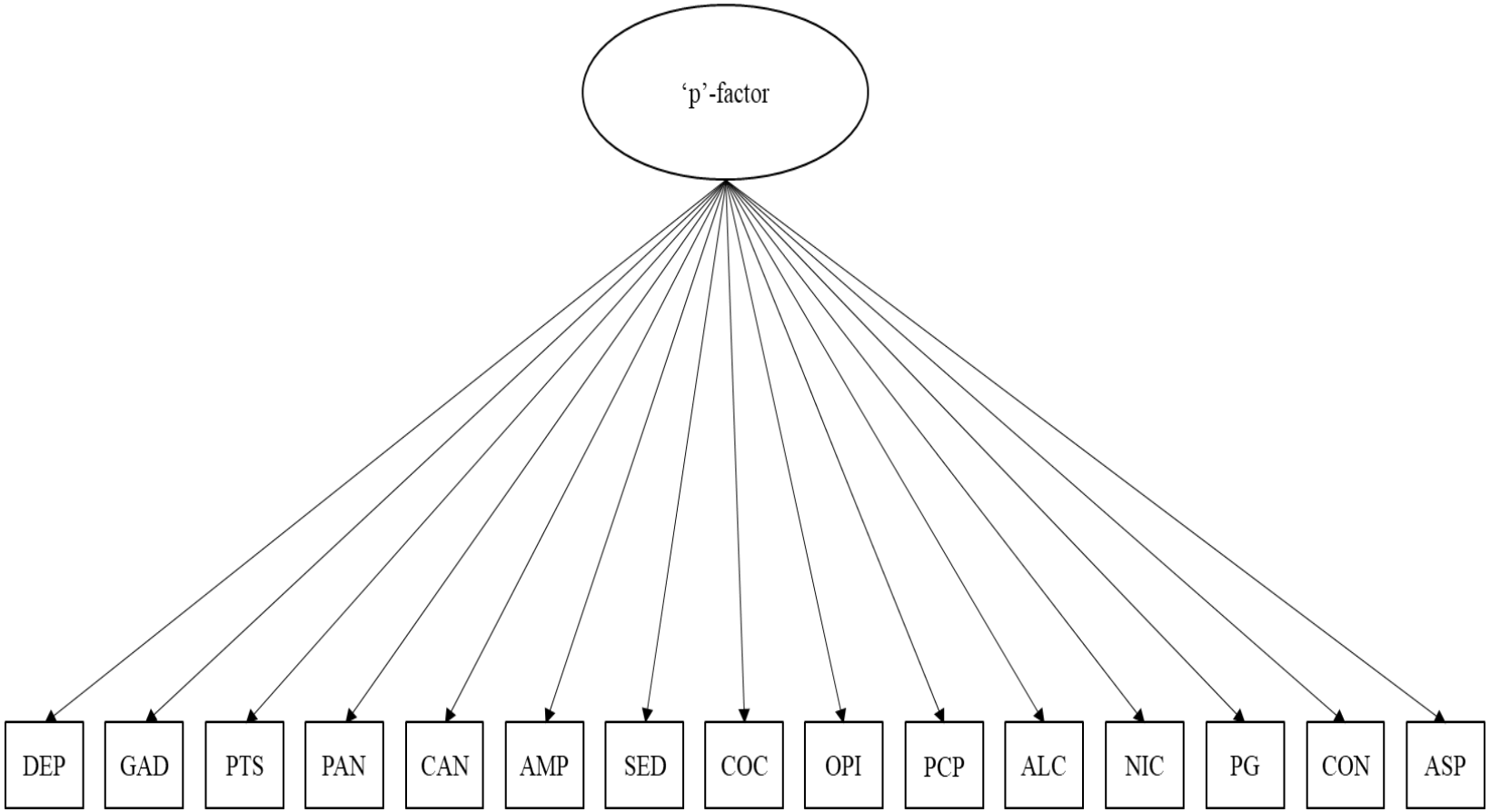


Figure 3b. Common pathway model.

ASPD = antisocial personality disorder; SUD = substance use disorder; PG = pathological gambling; CD = conduct disorder, EXT = externalizing

Figure 4. M1: Single-factor Model



DEP = major depressive disorder, GAD = generalized anxiety disorder, PTS = post-traumatic stress disorder, PAN = panic/agoraphobia, CAN = cannabis use; AMP = amphetamine use; SED = sedative use; COC= cocaine use; OPI = opioid use; PCP = hallucinogen use; ALC = alcohol use; NIC = nicotine use; PG = pathological gambling; CON = conduct disorder, ASP = antisocial personality disorder

Figure 5. M2: Correlated Factors Model

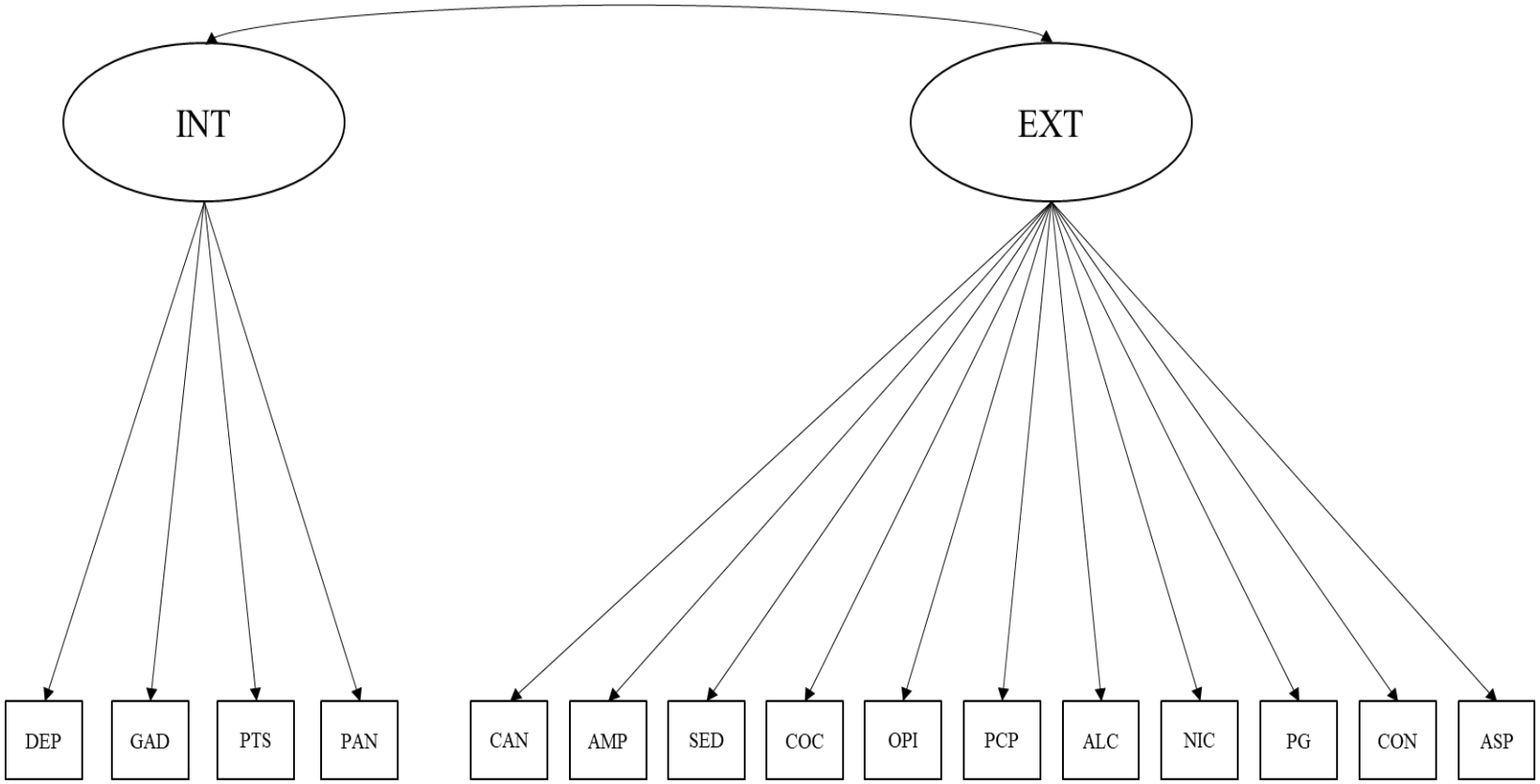


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Figure 6. M3: Higher-Order Factor Model (‘p’ factor)

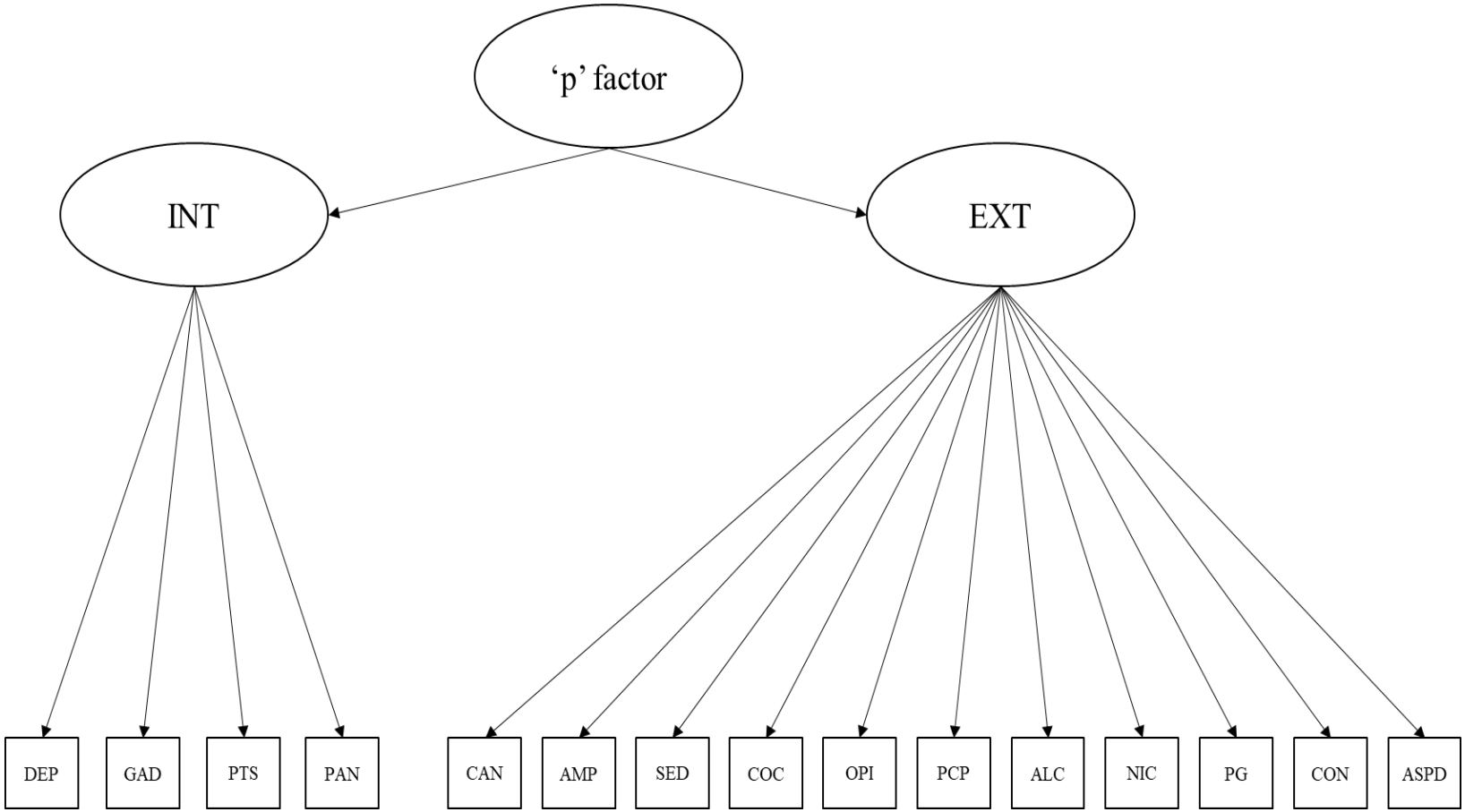

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Figure 7. M4a: Correlated Factors Model with Pathological Gambling on Addiction Subfactor

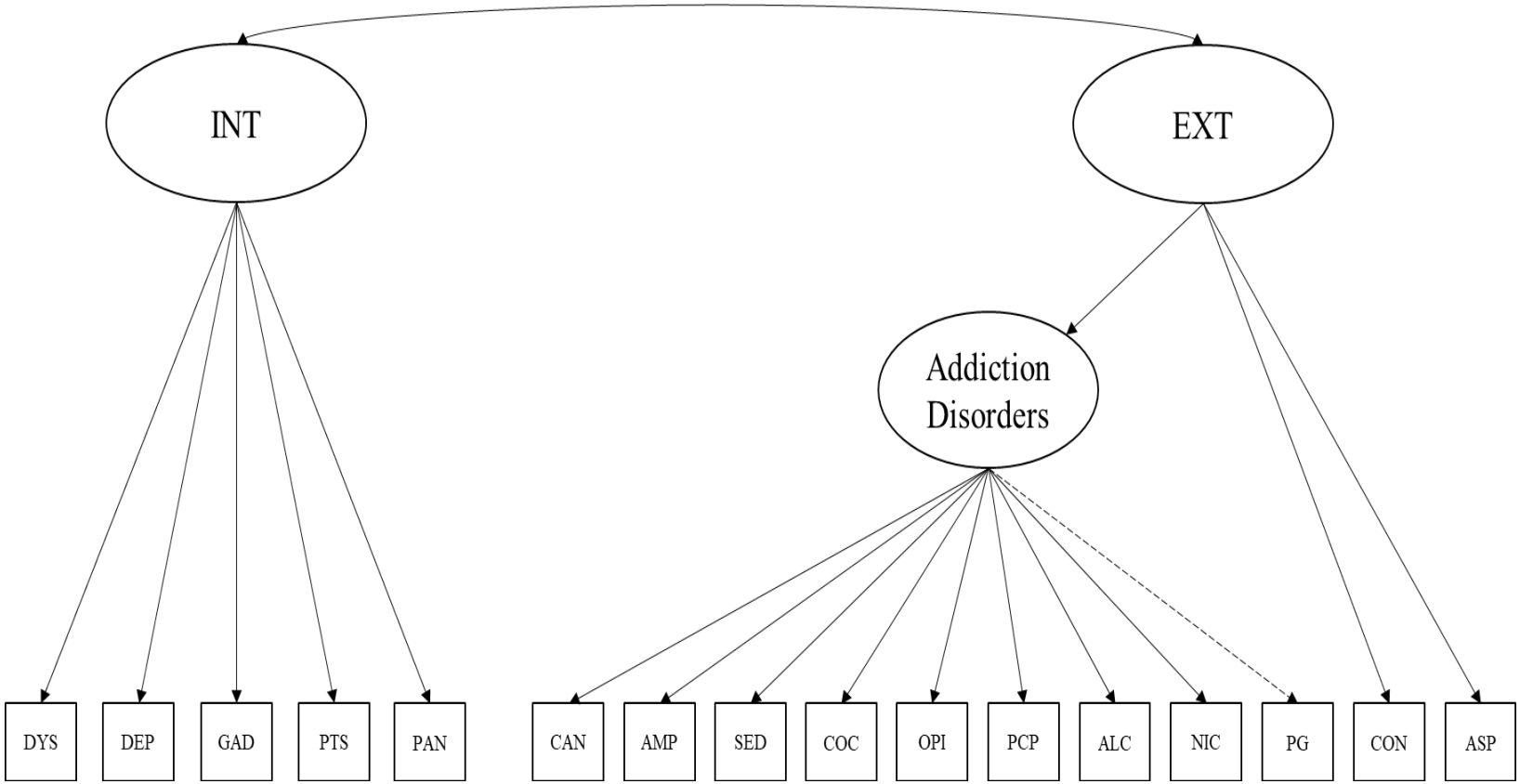

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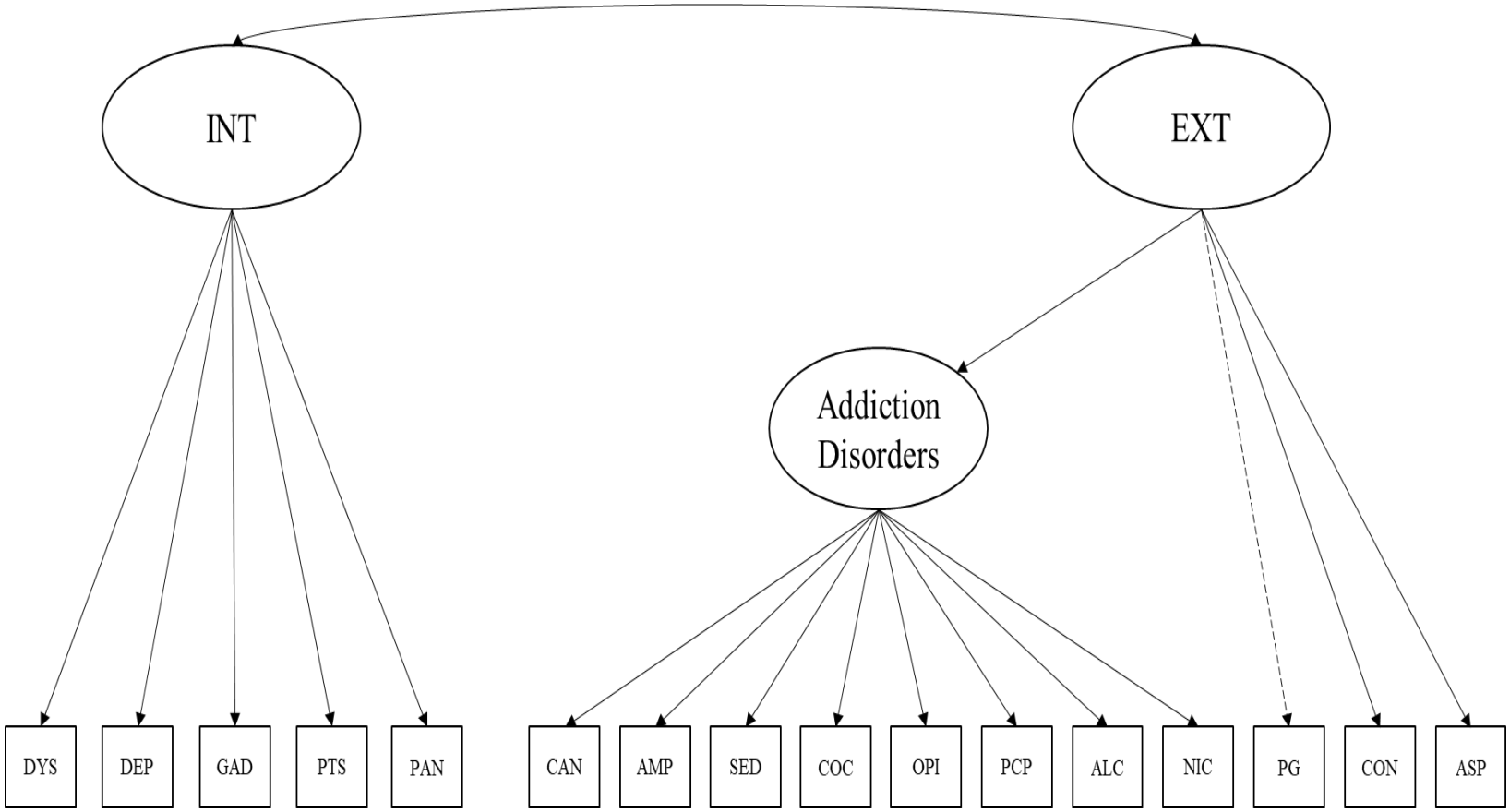
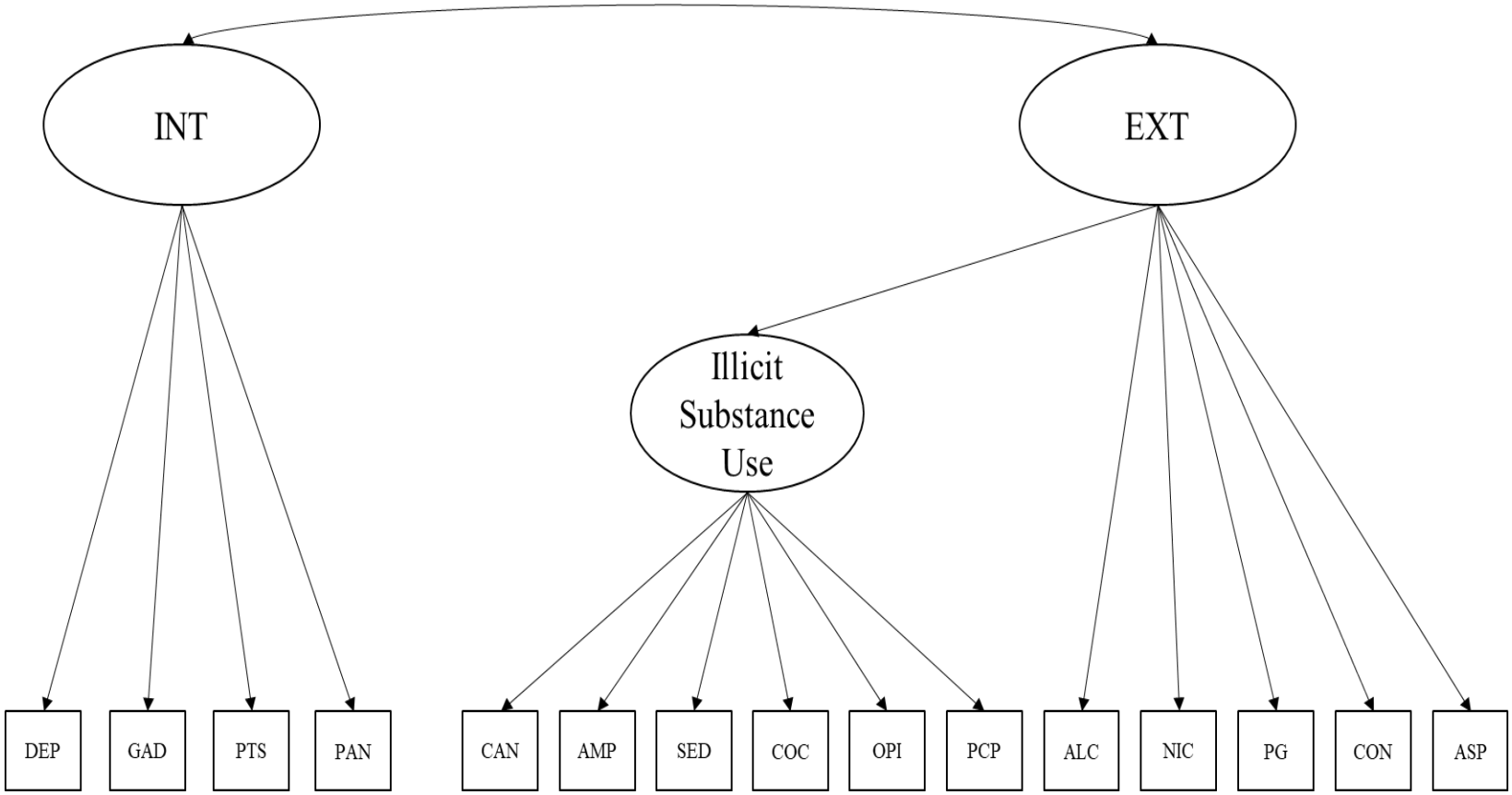
Figure 8. M4b: Correlated Factors Model with Pathological Gambling on Externalizing Spectrum



DEP = major depressive disorder, GAD = generalized anxiety disorder, PTS = post-traumatic stress disorder, PAN = panic/agoraphobia, CAN = cannabis use; AMP = amphetamine use; SED = sedative use; COC= cocaine use; OPI = opioid use; PCP = hallucinogen use; ALC = alcohol use; NIC = nicotine use; PG = pathological gambling; CON = conduct disorder, ASP = antisocial personality disorder; INT = internalizing; EXT = externalizing

Figure 9. M4c: Correlated Factors Model with Illicit Substance Use Subfactor and Pathological Gambling on Externalizing Spectrum



DEP = major depressive disorder, GAD = generalized anxiety disorder, PTS = post-traumatic stress disorder, PAN = panic/agoraphobia, CAN = cannabis use; AMP = amphetamine use; SED = sedative use; COC= cocaine use; OPI = opioid use; PCP = hallucinogen use; ALC = alcohol use; NIC = nicotine use; PG = pathological gambling; CON = conduct disorder, ASP = antisocial personality disorder; INT = internalizing; EXT = externalizing

Figure 10. M4d: Three Correlated Factors Model with Pathological Gambling on Externalizing Spectrum

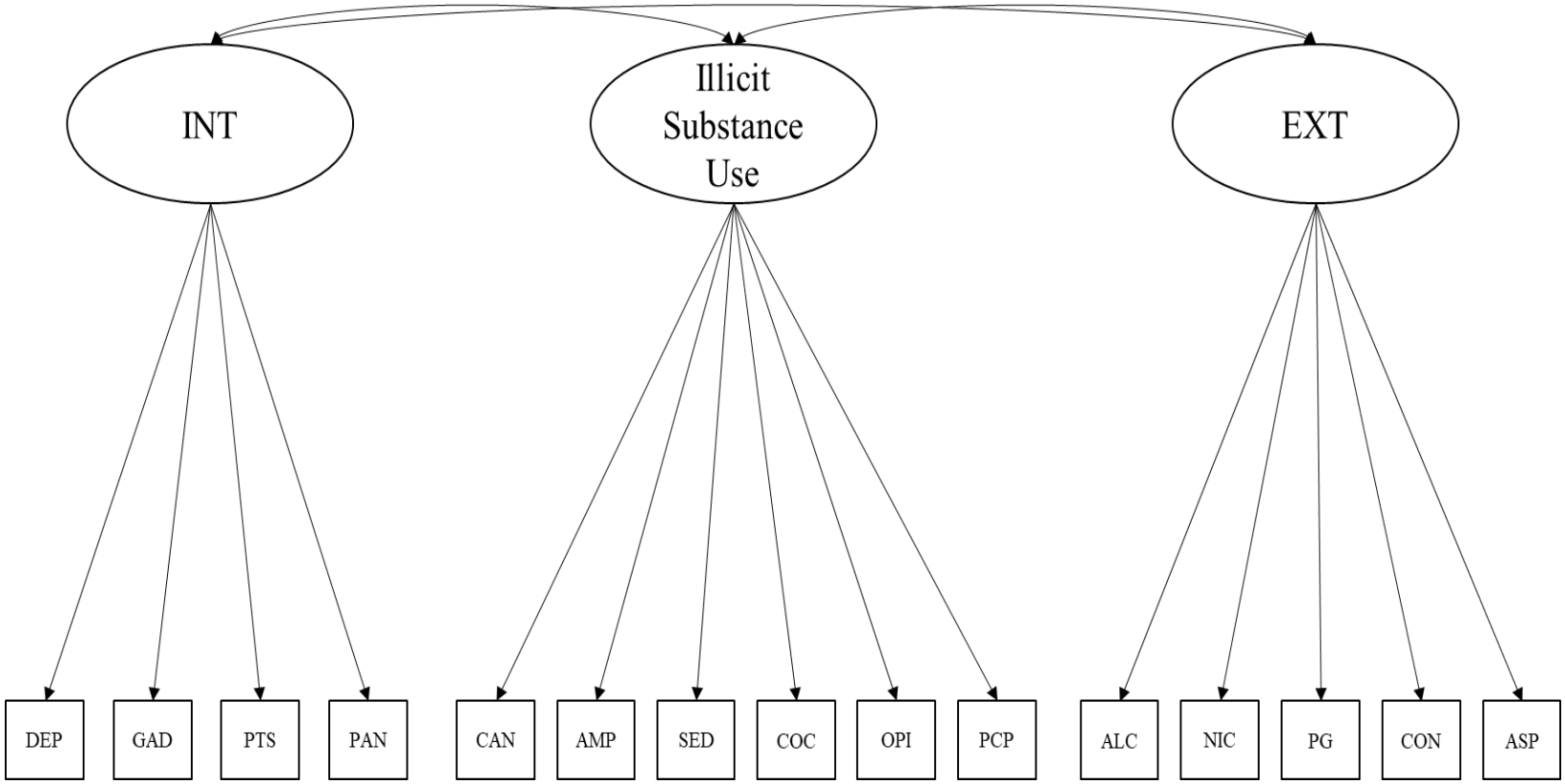


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Figure 11. Final Structural Model (4c) with Standardized Factor Loadings

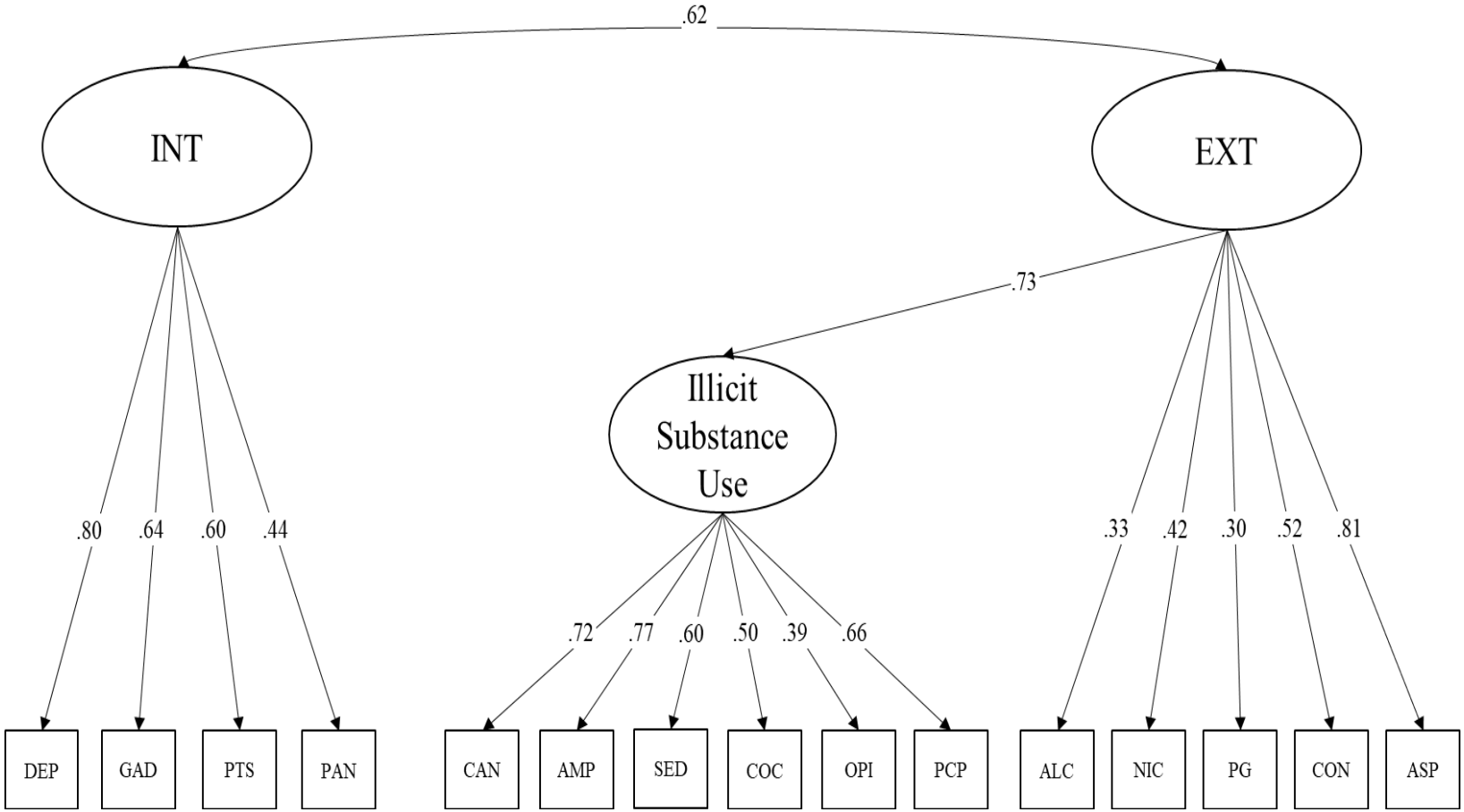

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Figure 12. Outline of Biometrical Model Using Structure Derived from Study 1

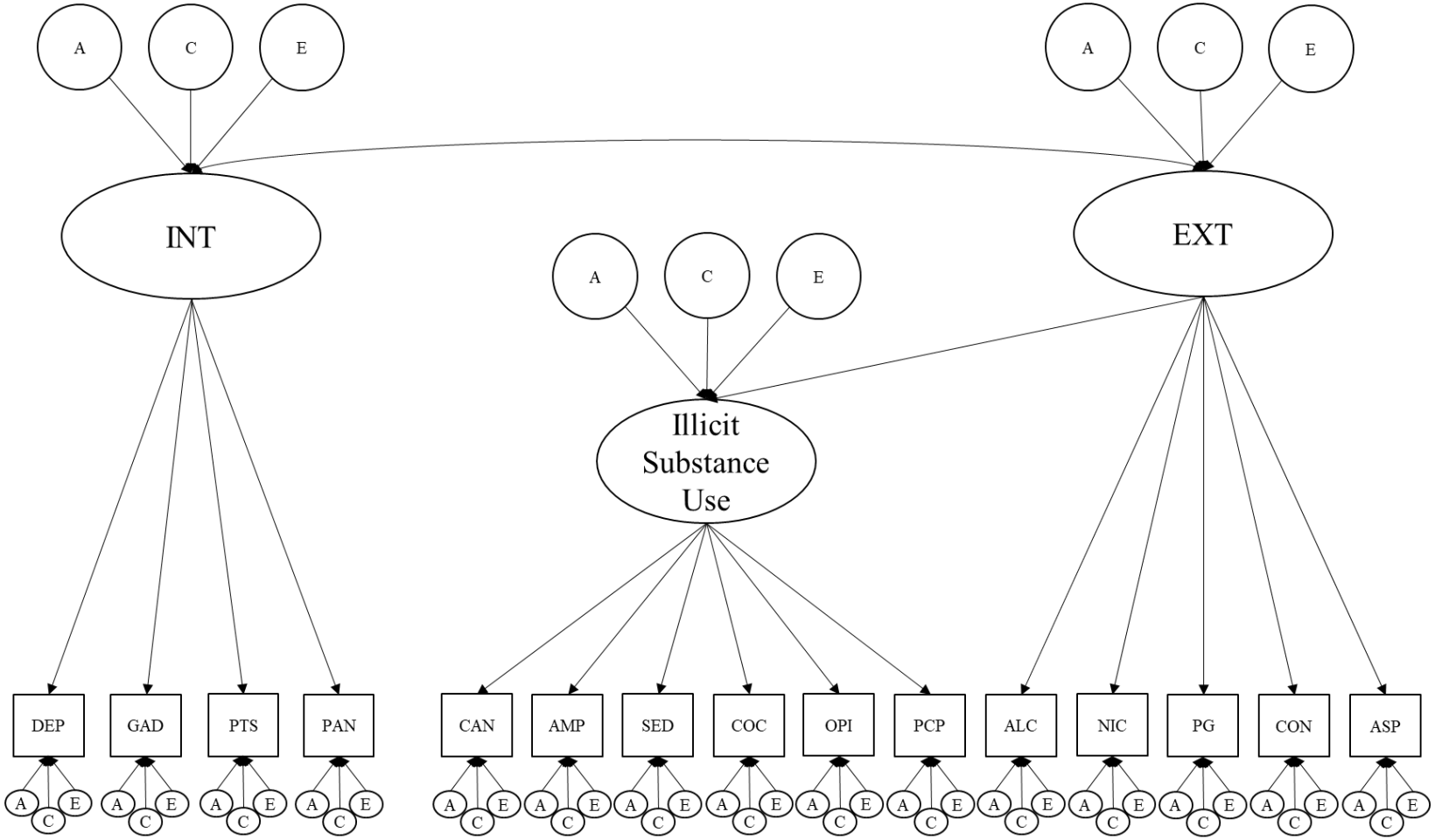

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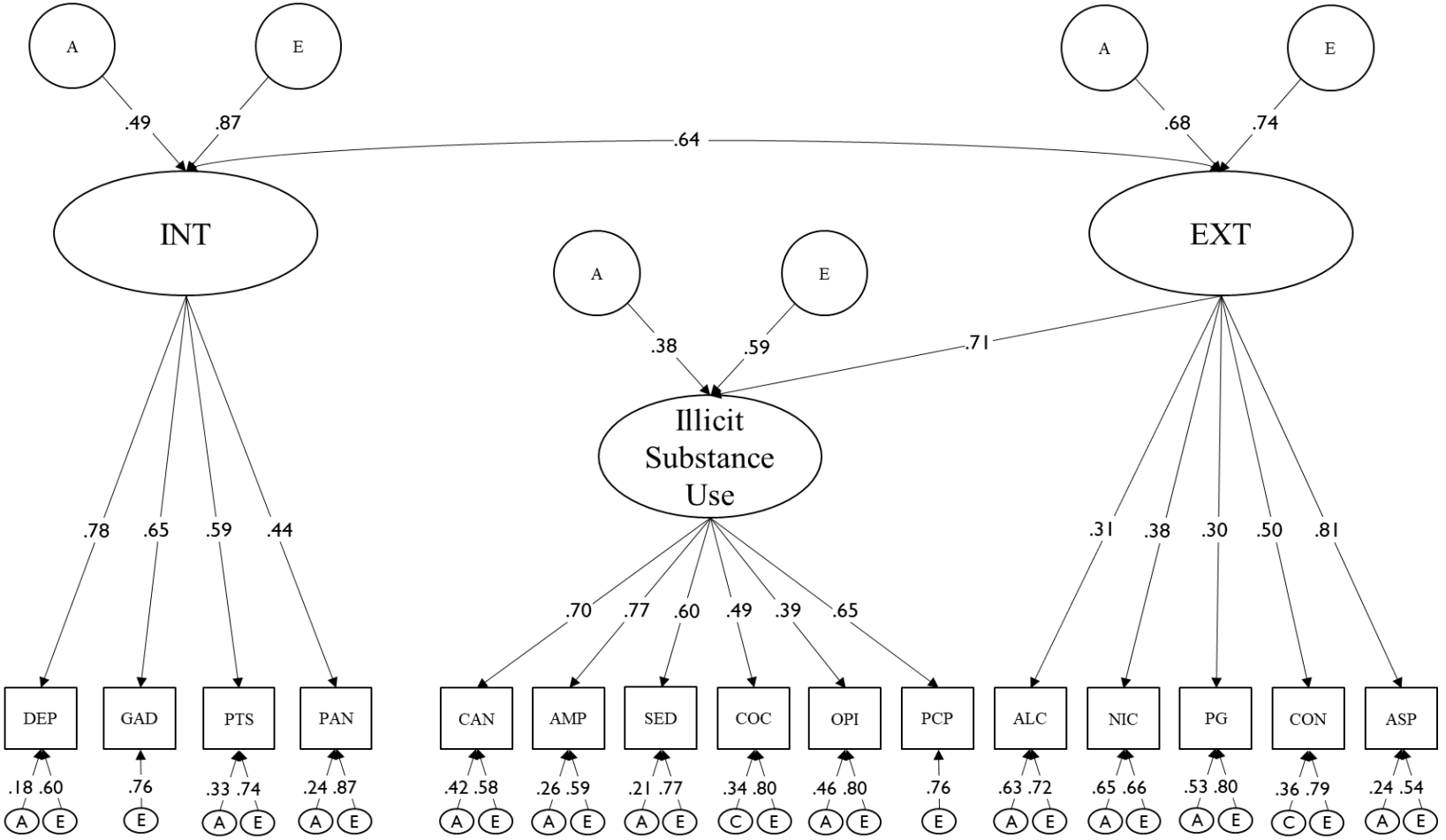
Figure 13. Final Biometrical Model (Modified ACE with Non-Significant Loadings Dropped)



DEP = major depressive disorder, GAD = generalized anxiety disorder, PTS = post-traumatic stress disorder, PAN = panic/agoraphobia, CAN = cannabis use; AMP = amphetamine use; SED = sedative use; COC= cocaine use; OPI = opioid use; PCP = hallucinogen use; ALC = alcohol use; NIC = nicotine use; PG = pathological gambling; CON = conduct disorder, ASP = antisocial personality disorder; INT = internalizing; EXT = externalizing

Figure 14. Common Genetics of Illicit Substance Use: Comparability Across Two Studies

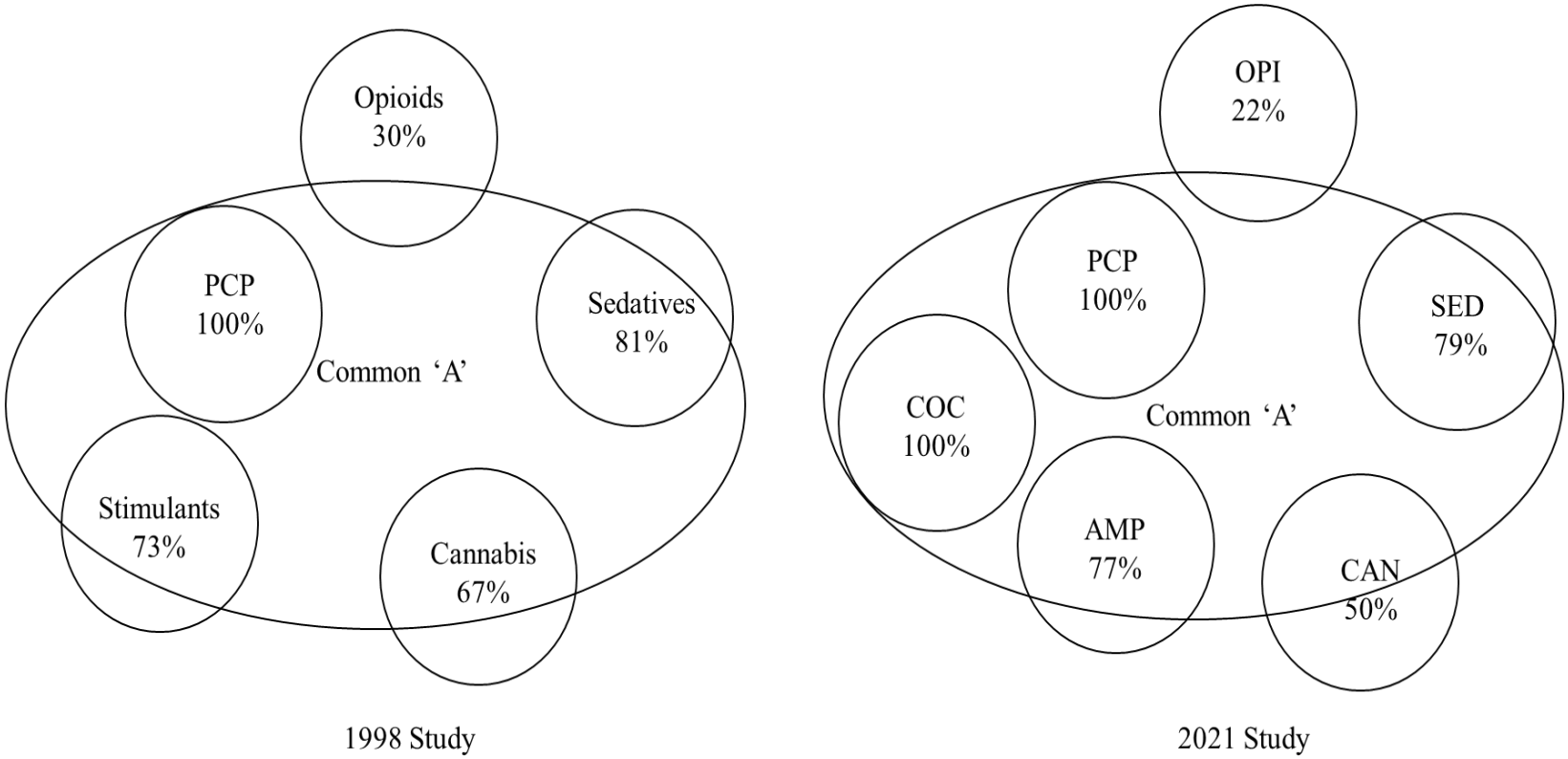


Figure reproduced with permission from Tsuang, M. T., Lyons, M. J., Meyer, J. M., Doyle, T., Eisen, S. A., Goldberg, J., True, W., Lin, N., Toomey, R., & Eaves, L. (1998). Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. *Archives of General Psychiatry*, *55*(11), 967-972. https://doi.org/10.1001/archpsyc.55.11.967

CAN = cannabis use; AMP = amphetamine use; SED = sedative use; COC= cocaine use; OPI = opioid use; PCP = hallucinogen use

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