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An examination of psychopathy and substance use disorders using magnetic resonance imaging and cluster analysis

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AN EXAMINATION OF PSYCHOPATHY AND SUBSTANCE USE DISORDERS USING MAGNETIC RESONANCE IMAGING AND CLUSTER ANALYSIS

BY

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ABSTRACT

Psychopathy is a personality disorder that is exemplified by affective and interpersonal characteristics such as grandiosity, pathological lying, manipulative use of others, and a profound lack of empathy, guilt, and remorse. Psychopaths also typically demonstrate a constellation of problematic and dangerous behavioral characteristics including sensation seeking, impulsivity, and both instrumental and reactive aggression. Psychopathy and substance use disorders (i.e., abuse and dependence) are significant sources of financial and emotional burden in the United States, as both are strongly linked to severe and repetitive criminal activity. They are also highly comorbid, with psychopaths being about two to three times more likely to have a drug use disorder than nonpsychopaths. Using structural and functional neuroimaging and cluster analysis, this comorbidity was investigated in a series of studies involving incarcerated adult males and females, incarcerated adolescent males and females, and nonincarcerated adult males and females. Across samples, structural differences related to psychopathic traits were largely consistent, lending support to the idea that a network of regions across the paralimbic system is abnormal, at least structurally. Several of the regions identified in the structural

studies were also hypoactive during the viewing of drug cues in a functional magnetic resonance imaging study of craving, suggesting a close link between structural and functional abnormalities. Finally, cluster analysis was used to identify typologies of substance users, and differential correlations with personality and individual differences variables were found. These results suggest that substance users are actually a heterogeneous group in terms of severity, drugs of choice, and personality correlates. This heterogeneity also suggests that individual differences should be taken into account when designing substance use treatment strategies. Analogous to the notion of personalized medicine, this philosophy could be at once both more effective and more efficient when applied to substance use treatment. In turn, the extreme financial and emotional burden that psychopathy and substance use disorders cause could be reduced.

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CHAPTER 1

INTRODUCTION

Psychopathy and substance use disorders are significant sources of financial and emotional burden in the United States, as both are strongly linked to severe and repetitive criminal activity. Indeed, the net annual burden of crime in the U.S. has been estimated at over $2.3 trillion (Anderson, 1999; Kiehl & Hoffman, 2011). And whereas psychopathy alone is strongly associated with severe offending, it is likely that psychopathy and substance use disorders act synergistically to substantially increase the frequency and severity of crime. A large-scale study on aggression and offending found that the best predictor of violence was psychopathic traits in conjunction with alcohol and/or drug abuse (Steadman et al., 2000). Given the substantial negative impact that these disorders have both singularly and in conjunction, research that examines them simultaneously is needed in order to better understand the behavioral and neurobiological characteristics of individuals with both psychopathy and substance use disorders.

Psychopathy

Psychopathy is a personality disorder that is exemplified by affective and interpersonal characteristics such as grandiosity, pathological lying, manipulative use of others, and a profound lack of empathy, guilt, and remorse (Cleckley, 1976; Hare, 2003). Psychopaths also typically demonstrate a constellation of problematic and dangerous behavioral characteristics including sensation seeking, impulsivity, and both instrumental and reactive aggression (Blair, 2007; Hare, 2003).

Psychopathy is typically assessed using the Hare Psychopathy Checklist-Revised (PCL-R; Hare 1991; 2003), the most widely accepted diagnostic instrument for

psychopathy in forensic populations. Individuals are rated on 20 items, and scores can range from 0 to 40 with higher numbers indicating higher levels of psychopathy. Factor analyses (Table 1) of the PCL-R revealed a two-factor structure (Hare, 2003; Harpur, Hare, & Hakstian, 1989), though other models have been proposed (Cooke & Michie, 2001), including a four-facet model that mirrors the two-factor structure (Hare, 2003). In the two-factor model, Factor 1 comprises interpersonal (e.g., grandiosity, deceitfulness) and affective traits (e.g., lack of empathy, shallow affect), whereas Factor 2 comprises behavioral and antisocial traits (e.g., impulsivity, irresponsibility, need for stimulation, poor behavioral controls). In the four-facet model, Facet 1 is comprised of the interpersonal items from Factor 1 (glibness/superficial charm, grandiosity, pathological lying, and manipulation) and Facet 2 is defined by the affective items from Factor 1 (lack of remorse, shallow affect, callousness, and failure to accept responsibility). Facet 3 is comprised of the lifestyle items from Factor 2 (need for stimulation, parasitic lifestyle, lack of realistic goals, impulsivity, and irresponsibility), and Facet 4 is defined by the antisocial items from Factor 2 (poor behavioral controls, early behavioral problems, juvenile delinquency, revocation of conditional release, and criminal versatility). In contrast to the two-factor and four-facet models, Cooke and Michie (2001) have argued for a three-factor model, where Facet 4 (Antisocial) is excluded, and the remaining three factors are identical to Facets 1-3 of the four-facet model. They claim that the three-factor model captures the core personality traits of psychopathy better than the original two-factor model by removing the emphasis on specific behaviors[1].

[1] The two-factor model was utilized in the present analyses in order to remain consistent with the literature cited here and to facilitate comparison with these previous studies. The four-facet model will also be used to further disentangle the effects of interpersonal vs. affective and lifestyle vs. antisocial features.

Table 1

Psychopathy Checklist-Revised (Hare, 2003) Items and Factor Models

	Item	Two-Factor Model[a]	Three-Factor Model[b]	Four-Factor Model[c]
1	Glibness/Superficial Charm	1	1	1
2	Grandiose Sense of Self-Worth	1	1	1
3	Need for Stimulation/Proneness to Boredom	2	3	3
4	Pathological Lying	1	1	1
5	Conning/Manipulative	1	1	1
6	Lack of Remorse or Guilt	1	2	2
7	Shallow Affect	1	2	2
8	Callous/Lack of Empathy	1	2	2
9	Parasitic Lifestyle	2	3	3
10	Poor Behavioral Controls	2	–	4
11	Promiscuous Sexual Behavior	–	–	–
12	Early Behavioral Problems	2	–	4
13	Lack of Realistic, Long-Term Goals	2	3	3
14	Impulsivity	2	3	3
15	Irresponsibility	2	3	3
16	Failure to Accept Responsibility for Own Actions	1	2	2
17	Many Short-Term Marital Relationships	–	–	–
18	Juvenile Delinquency	2	–	4
19	Revocation of Conditional Release	2	–	4
20	Criminal Versatility	–	–	4

Note. Adapted from "The Psychopath Magnetized: Insights From Brain Imaging," by N. E. Anderson and K. A. Kiehl, 2012, *Trends in Cognitive Sciences, 16*, p. 53. Copyright 2011 by Elsevier. Also adapted from "A Cognitive Neuroscience Perspective on Psychopathy: Evidence for Paralimbic System Dysfunction," by K. A. Kiehl, 2006, *Psychiatry Research, 142*, p. 109. Copyright 2006 by Elsevier Ireland.

Table 1 Notes Continued:

[a]From Harpur, Hakstian, and Hare, 1988; Harpur, Hare, and Hakstian, 1989 (Factor 1: Interpersonal/Affective, Factor 2: Social Deviance) [b]From Cooke and Michie, 2001 (Factor 1: Arrogant and Deceitful Interpersonal Style, Factor 2: Deficient Affective Experience, Factor 3: Impulsive and Irresponsible Behavioral Style) [c]From Hare, 2003 (Factor 1: Interpersonal, Factor 2: Affective, Factor 3: Behavioral Lifestyle, Factor 4: Antisocial). Items with an "–" did not load on any factor.

Relation to Antisocial Personality Disorder

The literature on psychopathy has been complicated by the fact that psychopathy is sometimes confused with antisocial personality disorder (APD), a related construct from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; APA, 2000). APD is a Cluster B personality disorder typified by "a pervasive pattern of disregard for, and violation of, the rights of others that begins in childhood or early adolescence and continues into adulthood" (p. 701). In order to be diagnosed with APD, an individual must meet at least three criteria out of seven (in addition to three other conditions); criteria include deceitfulness, impulsivity, consistent irresponsibility, and aggressiveness. Based on the nature of these criteria, it should be clear why many psychopathy researchers have criticized the construct of APD for relying too heavily on behavioral criteria and indexing mainly the social deviance component of psychopathy (Factor 2), while largely missing the interpersonal/affective component (Factor 1)[2]. Furthermore, with estimates as high as 71%, the majority of prison inmates meet diagnostic criteria for APD (Brinded & Mulder, 1999) rendering it virtually worthless for discriminating among individuals within prison populations. In contrast, psychopathy, as defined by an extensive clinical tradition and with the PCL-R, is a more severe and complicated disorder, and affects just 15-30% of prison inmates, with the rate increasing with increasing security level (Hare, 2003).

Female Psychopathy

Psychopathy is associated with violence, manipulation for personal gain, and impulsive behavior, and has traditionally been thought of as a disorder affecting primarily

[2] Two of the criteria (out of seven) for APD ("lack of remorse" and "deception") fit the interpersonal/affective factor (i.e., Factor 1) from the Hare PCL-R.

males, but research suggests that females are not immune. Though the vast majority of research on psychopathy has aimed at defining the disorder in men, recent work on the reliability and validity of assessment, personality and behavioral correlates, and neurocognitive and emotional functioning in women has clarified how psychopathy might manifest differently in women. In general, studies have found comparable interrater reliability but lower internal consistency in female samples (compared to the literature on male samples) when the PCL-R is used (Verona & Vitale, 2006). Bolt, Hare, Vitale, and Newman (2004) used item response theory and the PCL-R and found four items that functioned differently in men and women: *conning/manipulative*, *early behavioral problems*, *juvenile delinquency*, and *criminal versatility*. Despite differences in these four items, the overall impact on the overall score was not large, thus supporting the use of the PCL-R in female samples. The conclusion that researchers have drawn from numerous studies of females is that the PCL-R is a useful tool for assessment of psychopathy in women.

Both prevalence (Vitale, Smith, Brinkley, & Newman, 2002; Warren et al., 2003) and average PCL-R scores (Hare, 2003; Rutherford, Cacciola, Alterman, & McKay, 1996) have been found to be lower in females. In terms of violence, Kennealy, Hicks, and Patrick (2007) found similar patterns of association between psychopathy and behavioral correlates such as age of onset of criminal activity, number of violent and nonviolent crimes, institutional misconduct, and interpersonal violence and aggression as in male samples. Finally, whereas Factor 2 has been found to be a good predictor of recidivism in males (Salekin, Rogers, & Sewell, 1996), Factor 1 was found to be a significant, albeit weak, predictor of recidivism in females (Salekin, Rogers, Ustad, & Sewell, 1998).

In the present set of studies, there is one female-only sample (Study 1 [Sample 3]), and two samples that include both males and females (Study 1 [Sample 4] and Study 2). Though female psychopathy is not a primary focus of this research, similarities and differences in brain structural abnormalities will be addressed, and the effects of participant sex will be examined in these three samples.

Substance Use Disorders

Drug-related problems and substance use disorders are particularly prevalent among incarcerated populations. Indeed, of all state and federal prisoners in 2010, approximately 22% were serving time for a drug offense, not including drunk driving (Guerino, Harrison, & Sabol, 2011). Furthermore, nearly two-thirds of inmates in the U.S. in 2006 met DSM-IV-TR criteria for a substance use disorder, but only 11.2% of them had received professional substance use treatment since becoming incarcerated (CASA, 2010). It is likely that more research in this area could benefit treatment and prevention efforts.

Substance use disorders include abuse and dependence, and are characterized by "a maladaptive pattern of substance use manifested by recurrent and significant adverse consequences related to the repeated use of substances" (abuse), and "a pattern of repeated self-administration" that continues "despite significant substance-related problems," including tolerance, withdrawal, and/or compulsive drug-taking (dependence; APA, 2000). Abuse is a less severe disorder than dependence and the two should not be confused or used interchangeably[3]. Whereas DSM-IV-TR abuse is assessed with four

[3] The proposed DSM-V "Substance Use and Addictive Disorders" section will be quite different from the current DSM-IV-TR "Substance-Related Disorders" section. It is likely that there will no longer be a distinction between abuse and dependence; a diagnosis will be made if the individual meets two or more criteria out of 11, with a "moderate" use disorder corresponding to two-three criteria and a "severe" use

criteria (with diagnosis requiring the endorsement of at least one criterion), dependence is assessed with seven criteria and requires endorsement of three or more criteria. It should also be noted that dependence criteria have been divided into those describing *physiological dependence* and those describing *compulsive use* (Table 2). Among studies on substance use disorders, progress may be hampered by examining abuse or dependence as diagnoses (i.e., *present* or *not present*; e.g., Yuan et al., 2010). This procedure may be sufficient when using substance use as a control variable, but more direct examinations of substance use disorders should consider the specific symptoms/criteria when trying to characterize the behavioral and neurobiological correlates.

disorder corresponding to four or more criteria. The "legal problems" abuse criterion will be removed, and a craving criterion will be added. These proposed changes are based on extensive factor analytic, latent class, and item response theory studies. This does not suggest, however, that abuse and dependence – as they are currently assessed – can be collapsed into one "use disorder," as is sometimes done (e.g., Smith & Newman, 1990).

Table 2

Diagnostic and Statistical Manual of Mental Disorders Dependence Criteria

	Physiological Dependence (PD)
1	Tolerance, as defined by either (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect, or (b) markedly diminished effect with continued use of the same amount of the substance
2	Withdrawal, as manifested by either (a) the characteristic withdrawal syndrome for the substance, or (b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms
	Compulsive Use (CU)
3	The substance is often taken in larger amounts or over a longer period than was intended
4	There is a persistent desire or unsuccessful efforts to cut down or control substance use
5	A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
6	Import social, occupational, or recreational activities are given up or reduced because of substance use
7	The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance

Note. PD = physiological dependence; CU = compulsive use.

One problem with using diagnoses as opposed to criteria is that information regarding the specific criteria for diagnosis is lost. For instance, consider an individual who receives a diagnosis of cocaine dependence based on criteria A, B, and C; consider a second individual who receives the *exact same diagnosis*, but this time based on criteria D, E, and F. Consider a third individual whose same diagnosis is based on criteria B, E, and G. In many studies, these three individuals would be put into the same "cocaine dependence" group, despite having very different reactions to the same drug. This practice may be contributing to our lack of understanding about individual differences in reactions to – and motivations for – using drugs.

Several studies have investigated the structure of drug dependence using a latent class approach (e.g., Ghandour, Martins, & Chilcoat, 2008; Grant et al., 2006; Shand, Slade, Degenhardt, Baillie, & Nelson, 2010), though in each, criteria for only one drug were considered, despite there often being extensive abuse and dependence for other drugs present in the samples. Studies like these usually aim to determine whether abuse and/or dependence symptoms are best described by a severity spectrum (i.e., the classes form dimensions), or whether they are best described by discrete subtypes (i.e., individuals have different symptom profiles). For instance, applying a latent class analysis (LCA) and multinomial regression approach to male and female extramedical opioid analgesic users from the community, Ghandour et al. (2008) found evidence for four discrete classes. In their study, whereas Class 1 differed from Class 4 on severity, Classes 2 and 3 differed on symptom profiles, suggesting that both dimensions and subtypes may be present within a single sample. In contrast, Shand et al. (2010) used factor mixture modeling and opioid-dependent individuals and found that the best fitting

model was a one-factor, two-class solution, where the classes differed on severity. Similarly, using LCA and adult cannabis users, Grant et al. (2006) found evidence for a severity-based four-class solution. Thus, at least in studies that use criteria for just one drug type to develop mutually exclusive classes, severity seems to be the most common discriminating factor.

The procedure described in Study 3 will follow the essence of these approaches and, using cluster analysis of criteria from multiple drug types, seek to determine whether users of multiple substances form subtypes, and whether these subtypes are associated with relevant demographic and personality variables.

Comorbidity Between Psychopathy and Substance Use Disorders

Given psychopaths' propensity for engaging in activities that are illegal, making impulsive and hedonistic decisions, seeking out stimulating and often dangerous activities, and ignoring the potential consequences of their actions, it is not surprising that psychopathy and substance use disorders are highly comorbid. It is less obvious why this heightened comorbidity exists even when compared to incarcerated nonpsychopaths, who also engage in illegal acts and tend to make impulsive and irresponsible decisions.

This psychopathy-substance abuse comorbidity has been relatively well described, but the causal mechanisms remain poorly understood. For instance, within inmate samples, psychopaths are up to 5.09 times more likely to have an alcohol use disorder (Smith & Newman, 1990) and 2.16 to 3.19 times more likely to have a drug use disorder than nonpsychopaths (Blackburn, Logan, Donnelly, & Renwick, 2003; Hemphill, Hart, & Hare, 1994; Smith & Newman, 1990; see Taylor & Lang, 2006 for a review). Smith and Newman (1990) found the prevalence of alcohol use disorders to be

much higher in psychopaths (93%) than nonpsychopaths (65%) in a large sample of Caucasian inmates. Similarly, they found the prevalence of drug use disorders to be much higher in psychopaths (74%) compared to nonpsychopaths (44%).

Another study found significant unique relationships between PCL-R Factor 2 scores and the number of dependence symptoms (i.e., controlling for Factor 1) for each of alcohol, cannabis, and opioids (but not cocaine) in a large sample of Caucasian and African American jail inmates (Walsh, Allen, & Kosson, 2007). Interestingly, when examining the PCL-R facets (where Factor 1 comprises Facets 1 and 2, and Factor 2 comprises Facets 3 and 4), Walsh et al. found that for cannabis and opioids, Facet 3 (containing items such as sensation seeking, irresponsibility, and impulsivity) was more strongly associated with the number of dependence symptoms than was Facet 4 (containing items such as poor behavioral controls, criminal versatility, and juvenile delinquency). This finding is consistent with theories that link substance use disorders and personality traits related to disinhibition (Trull, Waudby, & Sher, 2004), and suggest that the association between substance use disorders and psychopathy is not simply the result of antisociality. It should also be noted that Walsh et al. found a unique negative relation between Facet 2 (containing items such as shallow affect, callousness, and lack of remorse) and the number of dependence symptoms for one of the drugs they studied, cannabis. They predicted this unique negative association, citing research linking substance use to relief from negative affect (i.e., self-medicating behavior; Wills, Sandy, Shinar, & Yaeger, 1999).

Several studies have indicated a strong association between psychopathy and drug use disorders, but a weaker association with alcohol use disorders. For instance, Hart and

Hare (1989) found that PCL Total score and Factor 2 were significantly positively related to drug use disorders, but not alcohol use disorders. Similarly, Blackburn and Coid (1998) found higher drug abuse among psychopaths (31%) than among nonpsychopaths (13%), but they found no significant differences in alcohol use disorders in those groups[4]. Finally, in a sample of Swedish prisoners, psychopaths had higher rates of cannabis, inhalant, amphetamine, and opiate use disorders than nonpsychopaths, but there were no differences in alcohol use disorders (Rasmussen, Storaeter, & Levander, 1999).

Other Important Individual Differences Variables

The literature suggests that certain personality traits are correlated with substance use disorders, as least in community (i.e., student) populations (Trull et al., 2004). One of these traits is disinhibition, which is also an important construct for psychopathy. Two components of disinhibition, impulsivity and sensation seeking, are reflected in the lifestyle facet (Facet 3) of the PCL-R. Intelligence, which has been studied with regard to both substance use disorders and psychopathy, will also be reviewed here.

Impulsivity

Impulsivity is a complex construct that involves acting without appropriate forethought (Dickman, 1990), poor inhibitory control (Schachar & Logan, 1990), and choosing (smaller) short-term over (larger) long-term rewards (Kirby, Petry, & Bickel, 1999). Though some have suggested that impulsivity can be either functional or dysfunctional (e.g., Dickman, 1990), high impulsivity is often thought of as maladaptive, and has been associated with behaviors such as aggression and disorders such as attention-deficit hyperactivity disorder (ADHD) and APD. Principle components analysis

[4] The lack of significant findings for alcohol use disorders cannot be explained by a ceiling effect, as the base rate of alcohol use disorder in the Hart and Hare (1989) study was 52.5%; in the Blackburn and Coid (1998) study, 35% of psychopaths and 29% of nonpsychopaths had abused alcohol.

of one of the more commonly used psychometric assessments of impulsivity, the Barratt Impulsiveness Scale (BIS-11; Patton, Stanford, & Barratt, 1995), has confirmed the presence of three related components: Motor, Attentional, and Nonplanning impulsivity. Not surprisingly, impulsivity has been shown to be significantly higher in male prison inmates compared to both healthy college students and psychiatric patients (Patton et al., 1995), and impulsivity (at least the shortsightedness aspect) is considered to be an important component of psychopathy (Hare, 2003). Empirically, Snowden and Gray (2011) in a sample of adult male inmates found that PCL-R Total scores were significantly related to BIS-11 Motor impulsivity, and whereas Factor 2 was significantly related to BIS-11 Total, Motor, and Nonplanning impulsivity, Factor 1 was not related to any of the impulsivity scores (all were zero-order correlations and all reported significant correlations were positive).

Impulsivity has also been strongly linked to substance use. One early study found that participants with more than one dependence diagnosis had higher BIS scores than those with only one dependence diagnosis; BIS scores were also significantly correlated at $r = .44$ with the number of dependence diagnoses (O'Boyle & Barratt, 1993). Multiple studies have also found higher scores on various versions of the BIS in cocaine- (Coffey, Gudleski, Saladin, & Brady, 2003; Kjome et al., 2010), heroin- (Kirby et al., 1999), and alcohol- (Mitchell, Fields, D'Esposito, & Boettiger, 2005) dependent individuals[5]. Nonplanning impulsivity has also been associated with both quantity and frequency of drug use (see Stanford et al., 2009 for a review). Behaviorally, Hester and Garavan (2004) found that cocaine users had diminished ability to exert control over the prepotent

[5] A comparison of findings on the BIS subscales (Attentional, Motor, Nonplanning) is not easy due to the fact that many studies did not investigate or report the effects of the subscales.

go response in a go/no-go response inhibition functional magnetic resonance imaging (fMRI) paradigm. Although informative, these studies cannot address the question of whether premorbid impulsivity increases risk for initiating and developing a substance use disorder, whether chronic substance use causes deficits in behavioral inhibition through direct neurotoxicity or indirect changes in brain function, or whether both are true. In support of the view that impulsivity represents a vulnerability for substance use, Moeller and colleagues (2002) found a significant inverse relation between BIS-11 Total scores and age at first use of cocaine; similar evidence was found by Dom, D'haene, Hulstijn, & Sabbe (2006), where early onset alcoholics were more impulsive than late-onset alcoholics[6].

Sensation Seeking

Sensation seeking (also frequently referred to as "novelty seeking" in the literature[7]) is closely related to impulsivity, and involves "the preference for novel, complex, and ambiguous stimuli" (Bardo, Donohew, & Harrington, 1996, p. 26). Novelty or sensation seeking is frequently assessed with the Sensation Seeking Scale (Zuckerman, Eysenck, & Eysenck, 1978), a self-report measure that yields a general score and four subscales: Thrill and Adventure Seeking (TAS), Disinhibition (DIS), Experience Seeking (ES), and Boredom Susceptibility (BS). In addition to drug use, some types of sensation

[6] The Moeller et al. (2002) study controlled for age, but not duration of cocaine use, meaning participants who started using cocaine at an earlier age may have also used for a longer period of time, confounding the inverse correlation between age at first use and impulsivity. In the Dom et al. (2006) study, early-onset alcoholics did in fact abuse alcohol longer than the late-onset alcoholics, again allowing for the possibility that duration of abuse contributed to the differences in impulsivity, rather than the other way around.

[7] Though it might seem that novelty seeking and sensation seeking are distinct constructs, they are in fact sometimes used interchangeably in the literature (and Zuckerman [1988] went so far as to call them "practically identical"). Furthermore, Zuckerman's Sensation Seeking Scale is perhaps the most widely used instrument for measuring novelty seeking (Bardo et al., 1996). At the least, novelty seeking and sensation seeking are highly related, as sensation seeking is strongly correlated with the novelty seeking scale of Cloninger's Temperament and Character Inventory (Cloninger, Przybeck, Svrakic, & Wetzel, 1994).

seeking (i.e., General, TAS, and ES) are related to physically risky behaviors such as hang gliding (Straub, 1982), mountain/rock climbing (Cronin, 1991; Levenson, 1990; Robinson, 1985), and sky-diving (subscales not examined; Hymbaugh & Garrett, 1974). Some behaviors that are both physically and socially risky, such as sexual promiscuity, have also been linked to sensation seeking (General, TAS, ES, BS, and DIS; Zuckerman, Tushup, & Finner, 1976). On a theoretical level, novelty seeking has been linked to drug taking behavior because both act on neurobiological reward circuitry. In addition, individual differences in the propensity for novelty/sensation may predict the risk for drug abuse (Bardo et al., 1996).

Empirically, studies have found higher levels of novelty seeking among substance dependent individuals (Lukasiewicz et al., 2008). Other studies of novelty seeking have found associations with younger age of drug use initiation and dependence onset (Lim et al., 2008; Prisciandaro, Korte, McRae-Clark, & Brady, 2012; Schuckit & Smith, 2011)[8]. Important evidence for the link between novelty seeking and early drug use initiation comes from two longitudinal studies: Cloninger, Sigvardsson, and Bohman (1988) found that 11 year olds who were high on novelty seeking were more likely to abuse alcohol at age 27, and Webb, Baer, and McKelvey (1995) found that 5th graders who expressed an intention to try alcohol were higher on sensation seeking than those who did not. Novelty seeking may also be related to treatment failure and relapse. Helmus, Downey, Arfken, Henderson, and Schuster (2001) found that heroin-dependent cocaine users who were high on novelty seeking were more likely to drop out from a 17-week treatment trial than those who scored low on novelty seeking, though this difference was seen only in the

[8] *Initiation* of drug use is an important aspect of drug dependence, as an individual cannot become dependent on a drug that he/she has never tried.

latter weeks of the trial. Novelty seeking was also found to be higher in a relapsed group than a nonrelapsed group of alcohol-dependent individuals (Evren et al., 2012).

Intelligence

Several studies have linked high childhood IQ to later illicit drug use and dependence. For instance, Fergusson, Horwood, and Ridder (2005) found that IQ at age 8-9 was significantly positively related to illicit drug dependence at age 15-18 in a large longitudinal study of New Zealand children and adolescents. In a similarly large longitudinal study of British children born in 1970, higher IQ was associated with illegal drug use in adolescence and adulthood, regardless of parent social class, adolescent psychological distress, and adult socioeconomic status (White & Batty, 2012). Similar results were found in a 1958 British cohort (White, Gale, & Batty, 2012; though see White, Mortensen, & Batty, 2012).

Brain Function and Structure

Deficits in multiple domains of emotion and behavior (e.g., callousness, glibness, impulsivity, parasitic orientation) suggest that psychopathy is not the result of focal lesions to one or a few areas. Instead, it is likely that widespread emotional and behavioral dysfunction is related to widespread neural abnormalities. As such, the paralimbic hypothesis of psychopathy (Kiehl, 2006) asserts that multiple brain areas, encompassing both limbic and paralimbic regions, are involved in the disorder. It is important to note that other, less comprehensive, models have been proposed (e.g., Blair, 2008), but have received little empirical support. In line with the paralimbic model, work has identified abnormalities within the hippocampus and posterior cingulate during an affective memory task (Kiehl et al., 2001), parahippocampal gyrus during negative

picture viewing (Muller et al., 2003), and anterior cingulate during aversive conditioning (Veit et al., 2002). In addition, reduced amygdala activity has been reported during aversive delay conditioning (Birbaumer et al., 2005), emotional memory (Kiehl et al., 2001), and moral decision-making (Harenski, Harenski, Shane, & Kiehl, 2010). Finally, one study identified abnormalities in the orbitofrontal cortex (OFC) in psychopathic adults during an attention-related task (Veit et al., 2002).

Studies employing structural magnetic resonance imaging (sMRI) and analytic techniques such as voxel-based morphometry (VBM) have been successful at identifying gray matter differences related to psychopathy and substance use disorders. For instance, in psychopathy, studies have found abnormalities in the posterior cingulate (PCC)/precuenus (Boccardi et al., 2011; de Oliveira Souza et al., 2008), anterior cingulate (ACC; Boccardi et al., 2011; Muller et al., 2008), amygdala (Yang, Raine, Colletti, Toga, & Narr, 2010; Yang, Raine, Narr, Colletti, & Toga, 2009), and insula (de Oliveira-Souza et al., 2008; Gregory et al., 2012; Tiihonen et al., 2008), among others. Structural studies of drug use have found gray matter density reductions related to duration of heroin use in anterior cingulate and frontal regions (Yuan et al., 2009), as well as in cocaine-dependent individuals versus healthy controls in bilateral anterior insula, ventromedial OFC, right anterior cingulate, and bilateral superior temporal cortex (Franklin et al., 2002). Though the structure-function relationship remains poorly understood, it is likely that structural differences are at least partially related to personality; here we examine differences related to psychopathy in four independent samples, and account for the effects of pathological drug use. We also examine the effect

of substance dependence, accounting for psychopathy, in a large sample of adult male inmates.

Is There a Psychopathy-Substance Dependence Paradox?

Substance use disorders and psychopathy have been described as "syndromes of disinhibition" (Gorenstein & Newman, 1980), characterized by a lack of cognitive and emotional control (Patrick & Lang, 1999). But despite the substantial association between psychopathy and substance use disorders (reviewed above), an interesting paradox may exist. A body of evidence based on years of clinical experience with inmates suggests that psychopaths may have different motivations for – and responses to – using illicit substances. Whereas most individuals with severe drug problems experience craving and withdrawal upon becoming incarcerated, some psychopaths tend not to have this experience (Cleckley, 1988; K.A. Kiehl, personal communication, 2010)[9].

Drug craving is an intense desire or urge to use drugs, and is important in the development and maintenance of addiction. Craving has been associated with both repeated drug use and relapse after a period of abstinence (Weiss, 2005; though see Ehrman et al., 1998). Cue-elicited craving paradigms have been extremely fruitful in delineating brain regions involved in drug craving. In these paradigms, drug cues (e.g., visual, olfactory, or tactile stimuli) are presented to drug-abusing or drug-naïve participants, and brain activity to these drug cues versus neutral cues is recorded using functional imaging techniques. Several cortical and subcortical brain regions have been identified: anterior cingulate (ACC; Childress et al., 1999; Filbey, Schacht, Myers, Chavez, & Hutchison, 2009; Garavan et al., 2000; Heinz et al., 2004), OFC (Bonson et

[9] About one of his patients, Cleckley wrote, "Unlike nearly all real morphine addicts, he does not show ordinary withdrawal symptoms or other signs of physical illness and acute distress when, after being admitted to the hospital, he is deprived of opportunities to obtain the drug" (1988, p. 97).

al., 2002; Sell et al., 2000), insula (Brody et al., 2002; Myrick et al., 2004; Wang et al., 1999), ventral and dorsal striatum (i.e., nucleus accumbens [NAcc], caudate, and putamen; David et al., 2005; Garavan et al., 2000; Myrick et al., 2004), thalamus (Franklin et al., 2007), and amygdala (Bonson et al., 2002; Childress et al., 1999; Franklin et al., 2007). These areas largely overlap with those implicated as being dysfunctional or structurally abnormal in psychopathy. Thus, empirical evidence that psychopaths' lack of reported withdrawal and craving has a neurobiological basis will be examined here.

Drawing on Evolutionary Theory About Psychopathy

The idea that psychopathy is protective against drug craving fits well with the evolutionary perspective on psychopathy, which views the disorder as a potentially successful life-history strategy (e.g., Lalumiere, Harris, & Rice, 2001), where mating effort is favored over parenting effort (Ellis, 1988; Kinner, 2003). In line with this idea, Mealey (1997) described psychopathy as being "functional and adaptive for one individual in an interaction… but [has] dysfunctional, maladaptive consequences for one or more other participants" (p. 531). The strategy in which an individual moves around often and mates frequently but rarely stays long enough to help raise the offspring could lead to several adaptations, including not coming to rely on there being consistent resources (e.g., food, natural drugs) at every new location. Even modern psychopaths are thought of as being nomadic in order to escape detection as the societal cheaters that they often are.

A Historical Aside

Psychopathy has received considerable scientific attention in recent years, thanks in part to the development of reliable and valid assessments, coupled with the technological capability (e.g., fMRI, electroencephalography) to investigate the neural underpinnings. But psychopathy has undoubtedly existed for far longer, with references to its now well-known characteristics appearing in Ancient Greek text as early as the 4th-3rd centuries BCE (Kiehl, in press; Widiger, Corbitt, & Millon, 1992). Among the medical community, psychopathy was documented around 200 years ago, when French physician Philippe Pinel used the phrase, "*manie sans delire*" ("insanity without delirium") to describe individuals who exhibited antisocial behavior without any signs of hallucinations or delusions. The term "psychopath" was coined during the latter part of the nineteenth century, when German psychiatrist Emil Kraepelin used it in his influential psychiatry textbook (Kinner, 2003). Psychopathy appears to transcend not only time but culture: Both the Yorubas tribe in southwestern Nigeria and the Inuit have terms for individuals who regularly and without remorse violate societal norms (Murphy, 1976).

Great strides in our knowledge about psychopathy were made during the middle of the twentieth century, contributed mainly by American psychiatrist Hervey Cleckley. Cleckley collected years of clinical experience in psychiatric hospitals, and published *The Mask of Sanity* in 1941 based on his interviews with the adult male "psychopaths" who were institutionalized there. The sixteen characteristics that he outlined emerged from his studies of these individuals who are able to "know the words but not the music" (Johns & Quay, 1962, p. 217). Despite there being over 60 years since the first edition was

published, Cleckley's ideas remain as some of the most influential and definitive writings on the topic.

In 1975, the prominent antisocial personality and psychopathy researchers of the day convened in France to discuss the state of the field; around this time Robert Hare and his colleagues began psychometric analysis of the Cleckley criteria, and soon thereafter developed the Psychopathy Checklist. What followed was a period marked by substantially more valid and reliable assessment of psychopathy, and as a result, research in this area has exploded in recent years.

From this brief history of psychopathy it can be seen that the disorder has existed for thousands of years and in a variety of different types of societies. Indeed, psychopathy is not unique to recent, industrialized societies. The history of drug abuse is similar in some respects: Humans from all types of societies have been using natural substances to alter consciousness for thousands of years. For instance, beer was brewed as early as 6000 BCE (Hornsey, 2003), and poppy bulb was used beginning around 4000 BCE (Gahlinger, 2004). However, it should be noted that throughout history, drugs – either synthetic or natural – were typically legal at first, and only made illegal as their harmful properties were discovered. For instance, in the United States, drugs that were prescribed by physicians for maladies such as cough, diarrhea, and pain as recently as 100 years ago are now at the forefront of the $25 billion a year war on drugs (Porter, 2012). Through a series of drug control laws, beginning with the 1906 Pure Food and Drug Act[10], drugs of abuse were eventually criminalized (Gahlinger, 2004). Later addiction was medicalized, as illustrated by this recent definition from the National Institute on Drug Abuse:

[10] The Pure Food and Drug Act of 1906 required that the ingredients of patent medicines – often alcohol, cocaine, and/or morphine – be listed on the label. It was the Harrison Narcotics Tax Act of 1914 that regulated the production and distribution of opioids and cocaine (Gahlinger, 2004).

"Addiction is a chronic, often relapsing *brain disease* [emphasis added] that causes compulsive drug seeking and use, despite harmful consequences to the addicted individual and to those around him or her. *Similar to other chronic, relapsing diseases, such as diabetes, asthma, or heart disease* [emphasis added], drug addiction can be managed successfully" (NIDA, 2011). Not everyone agrees with this characterization, however, including many in the psychopathy research community. Whether addiction is a disease or a choice is not the focus of this manuscript. This issue does, however, raise interesting questions that are relevant to the comorbidity and neurobiological correlates of psychopathy and substance abuse, and should be kept in mind.

Overview of Studies and Aims

Psychopaths have a more protracted and severe trajectory of substance use (Corrado, Vincent, Hart, & Cohen, 2004; Mailloux, Forth, & Kroner, 1997; Smith & Newman, 1990), but are less likely to experience at least one of the physiological effects of drug use (Cope et al., 2013b). This paradox indicates that psychopaths may have different motivations for drug use, and highlights the need for further research that examines these disorders in conjunction. To this end, a series of studies were undertaken to investigate the differential contributions and comorbidity of psychopathy and substance use disorders using multiple methodologies: structural MRI (characterizing gray matter volume differences in psychopathy, accounting for substance use, and gray matter volume differences in substance use, accounting for psychopathy), functional MRI (characterizing neurobiological differences related to drug craving in psychopathy), and cluster analysis (correlations with personality variables to characterize typologies of substance users).

Study 1 (Sample 1)

Voxel-based morphometry was used to characterize regional gray matter volume differences related to psychopathy (controlling for age, brain volume, and substance dependence) and substance dependence (controlling for age, brain volume, and psychopathy) in a large sample of adult male inmates (n = 254).

Study 1 (Sample 2)

Voxel-based morphometry was used to characterize regional gray matter volume differences related to psychopathy in a large sample of juvenile male inmates (n = 191).

Study 1 (Sample 3)

Voxel-based morphometry was used to characterize regional gray matter volume differences related to psychopathy in a sample of juvenile female inmates (n = 39).

Study 1 (Sample 4)

Voxel-based morphometry was used to characterize regional gray matter volume differences related to psychopathy in a sample of male and female community substance abusers (n = 66).

Study 2

Functional MRI was used to characterize differences in the neurobiological craving response related to psychopathy in male and female inmates (n = 137).

Study 3

Cluster analysis and correlations with personality variables were used to evaluate the association between psychopathy and drug dependence in a large sample of adult male inmates (n = 380).

CHAPTER 2

STUDIES

General Method[11]

The data for Study 1 (Samples 1-3) and Studies 2 and 3 were drawn from ongoing research studies at mixed-security adult and youth correctional facilities in New Mexico. Sample 4 from Study 1 was recruited in Connecticut. For samples obtained in New Mexico, inmates were recruited through announcements made in the housing units and through word-of-mouth. Adult participants were excluded for any of the following: age younger than 18 years or older than 60, estimated full-scale IQ less than 70, less than a fourth grade English reading level, schizophrenia or other psychotic disorder or a first-degree relative with a psychotic disorder, head injury with loss of consciousness greater than one day, MRI incompatibility (e.g., metal implants, pace maker), and past or current central nervous system disease (e.g., stroke, multiple sclerosis, seizures). Similarly, juvenile participants were excluded if they had a history of seizures, psychosis, traumatic brain injury, other major medical problems, or failed to show fluency in English at or above a grade four reading level. Participants gave written informed consent (if $\geq$ 18 years old), or written informed assent and parent/guardian written informed consent (if <18 years old). All study materials and procedures were approved by the University of New Mexico Health Sciences Center Institutional Review Board. Participants were compensated $1.00 per hour for their time, commensurate with the rate of pay for general labor earned inside the correctional facilities.

[11] The general methodology described here applies to all studies unless described differently within the study-specific section. For all other information on study methods, see below.

Psychopathy was assessed using the Psychopathy Checklist-Revised (PCL-R; Hare, 2003) for participants ≥ 18 or Psychopathy Checklist-Youth Version (PCL-YV; Forth, Kosson, & Hare, 2003) for participants ≤ 17. Each psychopathy assessment consisted of an institutional file review and semi-structured interview. During each interview, information about the individual's family, school, work, and criminal histories was acquired, along with information about interpersonal and emotional functioning. Individuals were then scored on each of 20 items, where 0 *doesn't apply*, 1 *applies somewhat*, and 2 *definitely applies*; scores can range from 0 to 40. The typical diagnostic cut-off for research purposes is 30 (Hare, 2003). See Table 3 for sample information.

Table 3

Summary of Study Samples

	Study 1				Study 2	Study 3
	Sample 1	**Sample 2**	**Sample 3**	**Sample 4**		
N (% female)	254 (0)	191 (0)	39 (100)	66 (45.4)	137 (67.9)	380 (0)
Age	33.6 (9.1)	17.6 (1.1)	17.6 (1.1)	36.9 (7.9)	34.0 (8.2)	34.0 (9.4)
PCL Total	21.3 (7.0)	23.6 (6.2)	22.4 (6.4)	18.4 (8.0)	20.2 (6.1)	20.5 (6.8)
Factor 1	6.2 (3.4)	6.7 (3.1)	6.6 (3.4)	4.8 (3.4)	5.2 (2.9)	5.8 (3.2)
Facet 1	2.3 (2.0)	2.2 (1.9)	2.5 (2.0)	2.1 (1.6)	2.2 (1.7)	2.2 (1.9)
Facet 2	3.9 (2.1)	4.4 (1.8)	4.1 (2.2)	2.7 (2.1)	3.0 (1.8)	3.6 (2.0)
Factor 2	12.8 (3.9)	11.3 (2.7)	14.4 (3.3)	11.6 (4.7)	12.9 (3.3)	12.5 (3.8)
Facet 3	5.8 (2.2)	6.4 (2.0)	6.4 (1.9)	6.2 (2.4)	6.1 (1.8)	5.5 (2.2)
Facet 4	7.0 (2.3)	8.2 (1.7)	8.1 (1.6)	5.4 (2.8)	6.8 (2.1)	7.0 (2.3)
Substance Use	2.27 (1.64)[a]	2.23 (1.63)[b]	2.49 (1.62)[b]	42.00 (25.36)[c]	2.69 (1.36)[a]	2.18 (1.48)[d]
IQ	96.3 (13.8)	92.8 (12.1)	97.1 (12.7)	97.3 (9.8)	95.2 (10.2)	95.6 (13.0)

Note. PCL = Psychopathy Checklist

[a]From the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I; First, Spitzer, Gibbon, & Williams, 2002; scale: 0-8). [b]From the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (KSADS-PL; Kaufman et al., 1997; scale: 0-8). [c]From the modified Addiction Severity Index (ASI; McLellan et al., 1992; years of regular use). [d]From the SCID-I (scale: 0-7).

Study 1 (Sample 1)[12]

The body of research that now exists on psychopathy has been based largely on adult males. Indeed, psychopathy is more prevalent in males, especially incarcerated males. Thus, it seems appropriate to start our examination of structural differences in psychopathy with a large sample of incarcerated adult males. Here, voxel-based morphometry was used to characterize regional gray matter volume differences related to psychopathy, controlling for the effects of substance use. I acknowledge the contributions of the following coauthors and publisher in the publication of this study: Elsa Ermer, Prashanth Nyalakanti, Vince Calhoun, Kent Kiehl, and the American Psychological Association.

Method

Participants. Of those who volunteered for the various ongoing studies, 254 adult males (mean age = 33.63 years, *SD* = 9.10) completed a sufficient number of assessments required for the present study and were therefore included here. Via self-report, 84.3% were right-handed, 9.1% were left-handed, and 6.7% were ambidextrous. Participants were predominantly Hispanic/Latino (52.0%) or white/Caucasian (31.4%).

Psychopathy assessment. PCL-R interviews were videotaped for reliability assessment and double ratings were conducted on 14.6% of the sample, selected randomly. The intraclass correlation coefficient (ICC) was calculated using a one-way random effects model on a single rating with an absolute agreement definition. The ICC_1 was .91 for Total scores, indicating excellent reliability[13].

[12] Ermer, E., Cope, L.M., Nyalakanti, P.K., Calhoun, V.D., & Kiehl, K.A. (2012). Aberrant paralimbic gray matter in criminal psychopathy. *Journal of Abnormal Psychology, 121*, 649-658.

[13] The ICC_1 for a subset (n = 488) of N = 4891 male offenders (~10%) from the PCL-R manual was .86 (Hare, 2003).

Substance use assessment. The total number of substances (alcohol and drug) for which an individual met the lifetime dependence diagnostic criteria from the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I; First, Spitzer, Gibbon, & Williams, 2002) was calculated (scale: 0-8).

Other assessment. The Vocabulary and Matrix Reasoning subtests of the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997) were used to estimate full-scale IQ (Ryan, Lopez, & Werth, 1999). A post-head injury symptoms questionnaire (adapted from King, Crawford, Wenden, Moss, & Wade, 1995) was used to assess history and number of traumatic brain injuries (TBI) and duration of loss of consciousness. The SCID-I was used to diagnose history of psychotic disorders for exclusionary purposes.

MRI data acquisition and analysis. High-resolution T1-weighted structural MRI scans were acquired on the Mind Research Network Siemens 1.5T Avanto mobile scanner, stationed at the correctional facilities, using an MPRAGE pulse sequence (repetition time [TR] = 2530 ms, echo times [TE] = 1.64 ms, 3.50 ms, 5.36 ms, 7.22 ms, inversion time = 1100 ms, flip angle = 7°, slice thickness = 1.3 mm, matrix size = 256 × 256) yielding 128 sagittal slices with an in-plane resolution of 1.0 mm × 1.3 mm. Data were preprocessed and analyzed using Statistical Parametric Mapping software (SPM5; Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). T1 images were manually inspected by an operator blind to subject identity and reoriented to ensure proper spatial normalization. Images were then spatially normalized to the SPM5 T1 Montreal Neurological Institute (MNI) template using nonlinear registration, resampled to 2 × 2 × 2 mm, segmented into gray

matter, white matter, and cerebrospinal fluid (Ashburner & Friston, 2000; 2005). Voxels with a matter value of < 0.15 were excluded in order to remove possible edge effects between gray matter and white matter. Finally, segmented images were smoothed with a 10 mm full-width at half-maximum (FWHM) Gaussian kernel.

Analytic strategy. All analyses included substance dependence as a covariate to ensure we were assessing variation unique to psychopathy. Because gray matter volume also decreases with age (Good et al., 2001), we included age as a covariate in our analyses. Volumetric analyses require a control for individual variation in brain size; here, we included brain volume (BV; white matter + gray matter) as a covariate in all analyses, in addition to substance dependence and age. Multiple regression analyses were performed on a voxel-by-voxel basis over the whole brain using the general linear model to evaluate the relationship between psychopathy and regional gray matter volume. We also examined the effect of substance dependence on regional gray matter volume, controlling for age, BV, and PCL-R Total score. We employed AlphaSim (Ward, 2000) using AFNI software (http://afni.nimh.nih.gov/) to test for small, distributed gray matter effects. A Monte Carlo simulation determined that a 1308 voxel extent at $p < .05$ uncorrected yielded a corrected threshold of $p < .05$, accounting for spatial correlations between gray matter volumes in neighboring voxels.

Results

Controlling for the effects of age, BV, and substance dependence, gray matter analyses across the whole brain produced two large clusters negatively associated with psychopathy (Figure 1). One cluster is in the orbitofrontal cortex (OFC), extending into

parahippocampal cortex and the temporal poles, and the second is in the posterior cingulate cortex (PCC). There were no areas positively associated with psychopathy.

There were several areas negatively associated with a measure of substance dependence (Figure 2). These areas were primarily in posterior regions, and included the cerebellum, PCC/precuneus, and bilateral parietal areas. There were also posterior areas found to be positively associated with substance dependence in the bilateral middle and inferior occipital gyri and fusiform gyrus in the temporal lobe (Figure 3).

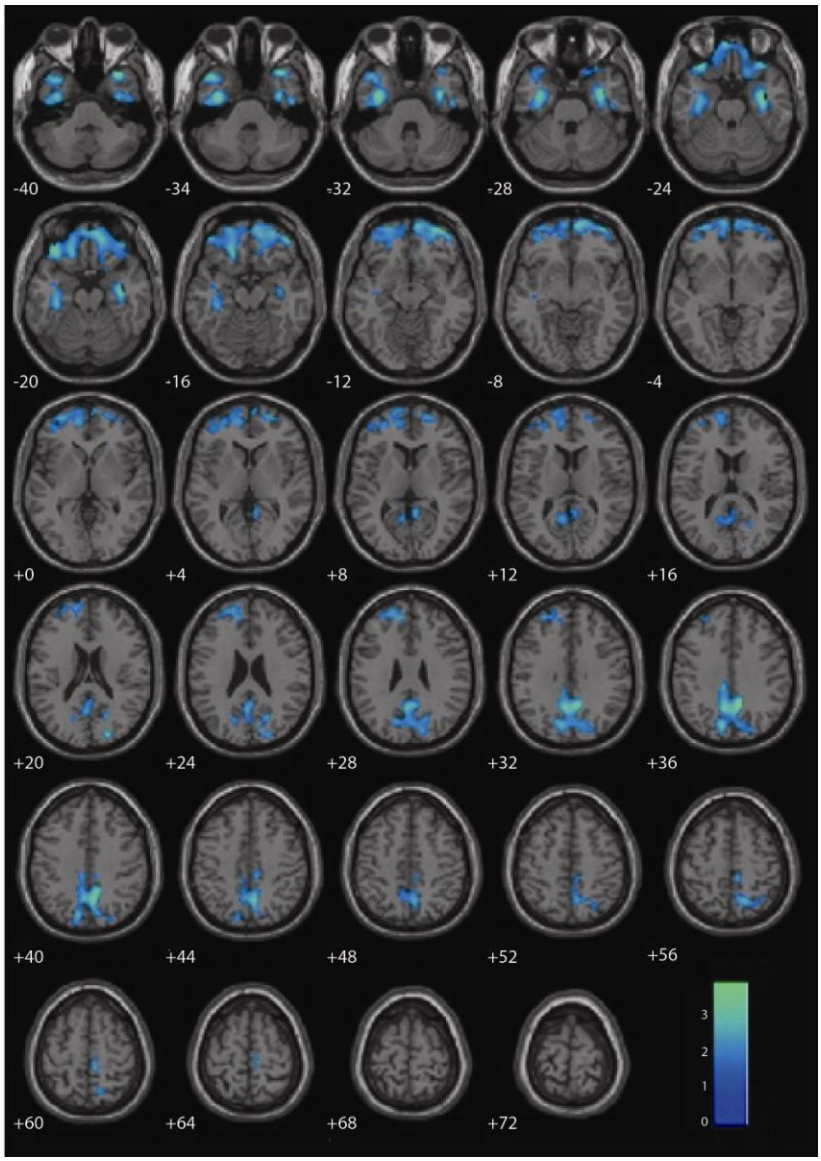

Figure 1. Regional gray matter volumes negatively associated with Psychopathy Checklist-Revised (Hare, 2003) Total scores, controlling for brain volume (BV), age, and substance dependence. These regions are significant in the whole brain at $p < .05$ and 1308-voxel extent (selected using AlphaSim; Ward, 2000). Numeric values indicate the Montreal Neurological Institute (MNI) *z*-coordinate of the slice, and the color bar represents *t*-values. Adapted from "Aberrant Paralimbic Gray Matter in Criminal Psychopathy," by E. Ermer, L. M. Cope, P. K. Nyalakanti, V. D. Calhoun, & K. A. Kiehl, 2012, *Journal of Abnormal Psychology, 121*, p. 654. Copyright 2011 by the American Psychological Association.

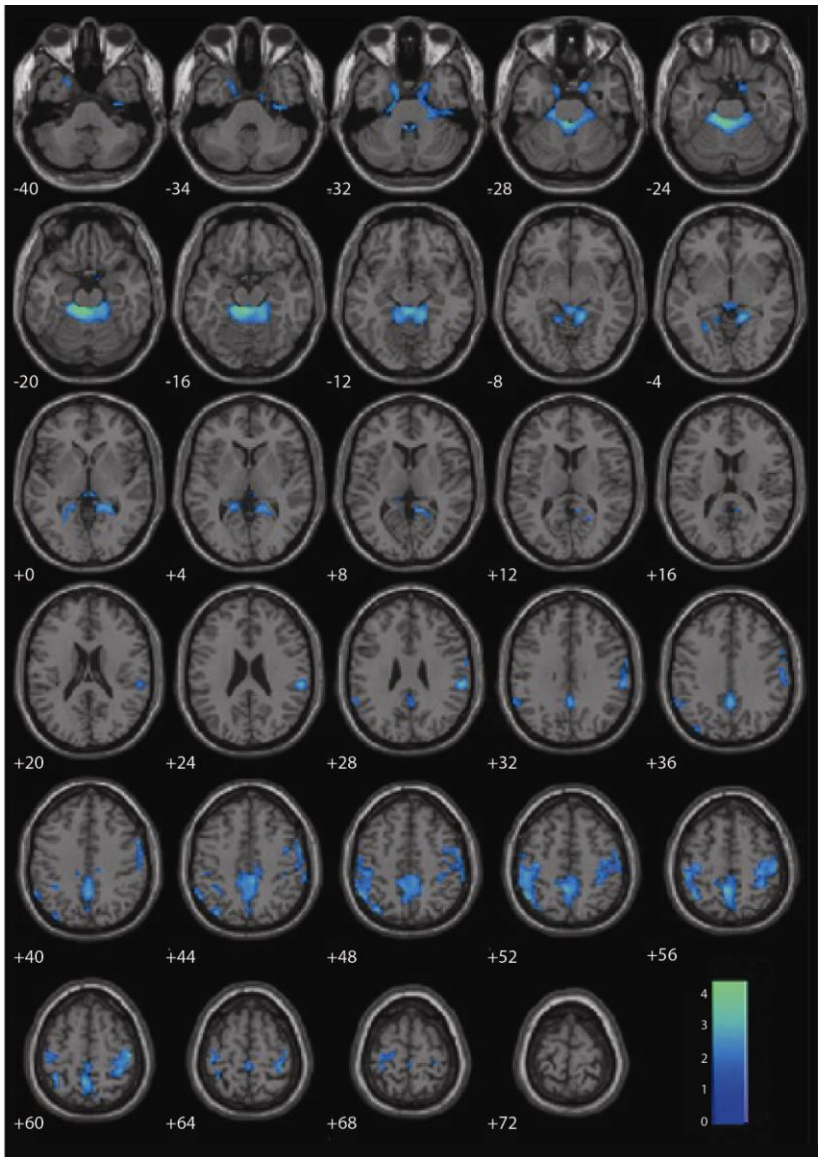

Figure 2. Regional gray matter volumes negatively associated with substance dependence, controlling for brain volume (BV), age, and Psychopathy Checklist-Revised (Hare, 2003) Total scores. These regions are significant in the whole brain at $p < .05$ and 1308-voxel extent (selected using AlphaSim; Ward, 2000). Numeric values indicate the Montreal Neurological Institute (MNI) *z*-coordinate of the slice, and the color bar represents *t*-values.

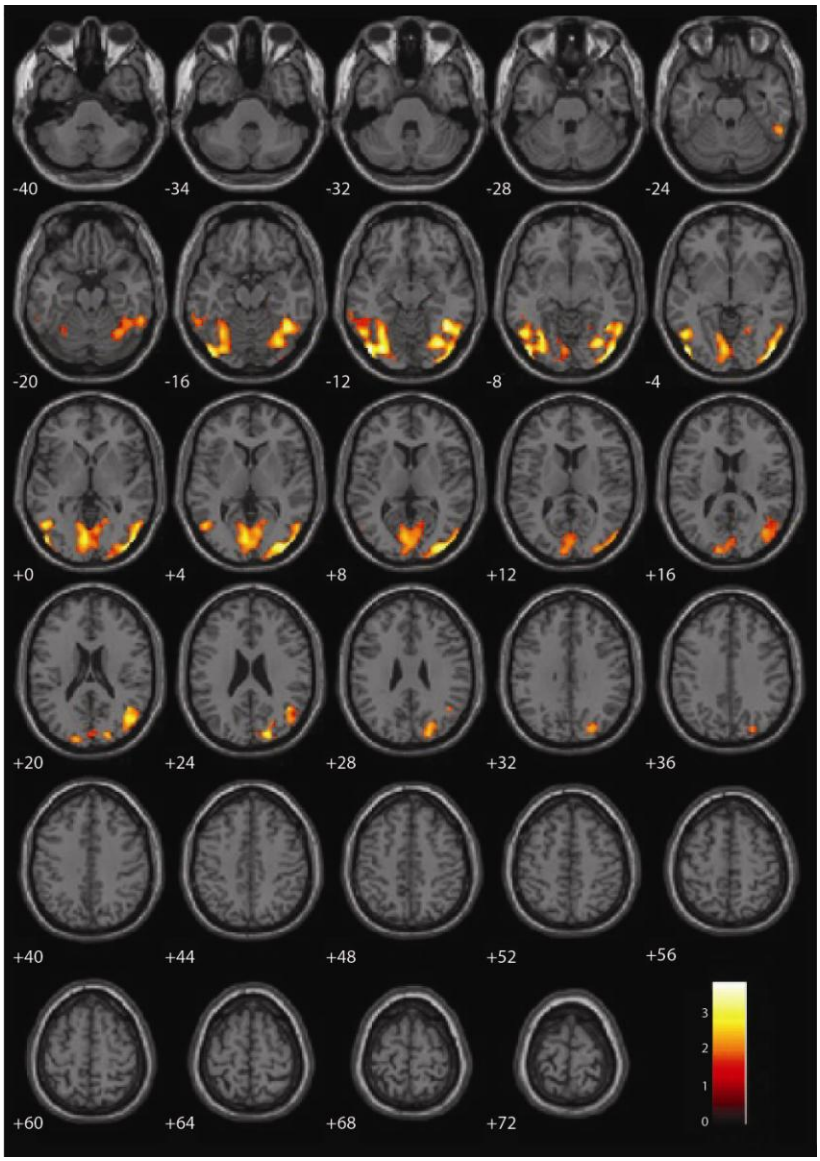

Figure 3. Regional gray matter volumes positively associated with substance dependence, controlling for brain volume (BV), age, and Psychopathy Checklist-Revised (Hare, 2003) Total scores. These regions are significant in the whole brain at $p < .05$ and 1308-voxel extent (selected using AlphaSim; Ward, 2000). Numeric values indicate the Montreal Neurological Institute (MNI) *z*-coordinate of the slice, and the color bar represents *t*-values.

Discussion

The present study adds to literature on structural differences in psychopathy by using VBM in a large sample of incarcerated men (n = 254) assessed for psychopathy using the PCL-R, and controlling for the potentially toxic effects of pathological substance use. These findings suggest that structural abnormalities in psychopathy are subtle, yet widespread, and that these abnormalities reflect distributed networks of impairment, rather than focal lesions. In contrast to the findings in psychopathy, regions associated with substance dependence were primarily in posterior areas, and there were positive associations between regional gray matter volume and substance dependence, in addition to the negative associations.

Differences were observed in the PCC, which is involved in emotional and moral processing and judgment (Glenn et al., 2009; Greene et al., 2004; Muller et al., 2003). PCC activity was also reduced in violent criminal psychopaths during an emotional memory task (Kiehl et al., 2001). The temporal poles also showed reduced gray matter in the present sample. The temporal poles are involved in theory of mind (Gallagher et al., 2000), and were also found to be underreactive for emotional stimuli during an affective memory task (Kiehl et al., 2001). There was a large cluster of reduced gray matter in the OFC in the present sample. The OFC is involved in processing information in the context of decision-making and planning (e.g., Walton et al., 2004), and medial aspects of the OFC are implicated in emotion-governed decision-making and regulation tasks (e.g., Rolls, 2004). OFC dysfunction has also been found in psychopathy studies of emotional processing and aversive conditioning (Muller et al., 2003; Veit et al., 2002), and is characteristic of brain-lesioned patients who display psychopathic-like behaviors

(Anderson, Bechara, Damasio, Tranel, & Damasio, 1999; Bechara, Damasio, Damasio, & Anderson, 1994). Finally, reduced gray matter was found in parahippocampal cortex in the present sample. Previously, reduced activation was found in psychopaths compared to controls while viewing negative pictures (Muller et al., 2003) and during the processing of affective stimuli (Kiehl et al., 2001).

It is unknown at this time how these structural differences map onto functional abnormalities observed in psychopathy, but the findings presented here are consistent with the functional literature. Future work should attempt to address this structure-function relationship more fully. It also remains to be seen how early these structural differences can be observed. Whereas age-typical gray matter findings in adolescents might suggest more of a "use-it-or-lose-it" model, reduced or abnormal gray matter in male adolescents with psychopathic traits would support a neurodevelopmental account of psychopathy, as has been proposed (e.g., Blair, Peschardt, Budhani, Mitchell, & Pine, 2006).

Study 1 (Sample 2)[14]

The body of research on adolescents with psychopathic traits has grown substantially in recent years. This work is being done in an effort to determine when and how the disorder begins to manifest. The PCL-YV (Forth et al., 2003) was developed as a downward extension of the PCL-R in order to reliably and validly assess adolescents for psychopathic traits. Here, voxel-based morphometry was used to characterize regional gray matter volume differences related to psychopathic traits in a large sample of juvenile male incarcerated offenders, assessed for psychopathy using the PCL-YV and controlling for substance use. I acknowledge the contributions of the following coauthors and publisher in the publication of this study: Elsa Ermer, Prashanth Nyalakanti, Vince Calhoun, Kent Kiehl, and Elsevier.

Method

Participants. Of those who volunteered for the various ongoing studies, 191 adolescent males (mean age = 17.60, *SD* = 1.12) completed a sufficient number of assessments required for the present study and were therefore included here. Participants were predominantly Hispanic/Latino (56.6%), white/Caucasian (14.8%), or Native American (11.7%). From self-report, 89.0% of participants were right-handed, 9.4% left-handed, and 1.6% ambidextrous.

Psychopathy assessment. PCL-R interviews were videotaped for reliability assessment and double ratings were conducted on 11.5% of the sample, selected randomly. The intraclass correlation coefficient (ICC) was calculated using a one-way

[14] Ermer, E., Cope, L.M., Nyalakanti, P.K., Calhoun, V.D., & Kiehl, K.A. (2013). Aberrant paralimbic gray matter in incarcerated adolescents with psychopathic traits. *Journal of the American Academy of Child & Adolescent Psychiatry, 52*, 94-103.

random effects model on a single rating with an absolute agreement definition. The ICC_1 was .87 for Total scores, indicating good reliability.

Substance use assessment. The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (KSADS-PL; Kaufman et al., 1997) was used to count the total number of substances (alcohol and drug) for which an individual met the lifetime dependence diagnostic criteria ("substance dependence"; scale: 0-8). A modified version of the Addiction Severity Index (ASI; McLellan et al., 1992) was also administered. The ASI is a brief interview that asks details about the duration, frequency, and amount of use of multiple types of drugs. Years of regular use were summed for each substance (alcohol and drug) that the participant reported using regularly (three or more times per week for a minimum period of one month). Total scores were then divided by age (to control for opportunity to use), multiplied by 100, and a square root transformation was applied to correct for skew ("regular substance use").

Other assessment. Full-scale IQ was estimated from the Vocabulary and Matrix Reasoning subtests of the WAIS-III (Ryan et al., 1999; Wechsler, 1997) for participants older than 16 years of age and from the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV; Sattler & Dumont, 2004; Wechsler, 2003) for participants younger than 16 years of age. The adapted King et al. (1995) post-head injury symptoms questionnaire was used to evaluate history of TBI and the KSADS-PL was used to evaluate history of psychotic disorders.

MRI data acquisition and analysis. The imaging parameters and preprocessing procedures were the same as in Sample 1, except for the following difference to account

for juveniles' smaller brains. After segmentation and modulation, gray matter segments were averaged to create a study-specific template. Then, the original gray matter segments were normalized to the customized template.

Analytic strategy. All analyses included a measure of substance use as a covariate. Because of the rapid developmental changes in brain structure over adolescence (Giedd, 2004) and because gray matter volume in particular decreases with age (Good et al., 2001), age was also included a covariate in all analyses. We also included BV (as in Sample 1) as an additional covariate in all analyses to account for individual variation in brain size (Pell et al., 2008) and to focus on regionally specific changes.

Multiple regression analyses were performed on a voxel-by-voxel basis over the whole brain using the general linear model to evaluate the relationship between PCL-YV and regional gray matter volume, including BV, age at scan, and substance dependence (or years of regular use) in the model as covariates. We estimated the cluster size necessary to correspond to a desired statistical threshold. Monte Carlo simulation conducted using AlphaSim (Ward, 2000) determined that a 1643 voxel extent at height threshold of $p < .05$ uncorrected yielded a corrected threshold of $p < .05$, accounting for spatial correlations between gray matter volumes in neighboring voxels.

Results

Cluster-extent analyses (1643 voxel threshold) across the whole brain showed that gray matter volume in paralimbic regions was negatively associated with PCL-YV scores, controlling for age at scan, BV, and substance dependence. Two clusters, in PCC and OFC (extending into the parahippocampal cortex and the temporal poles), were

found. In addition, a significant cluster in prefrontal cortex was positively associated with PCL-YV Total scores (Figure 4). When regular use was used as the covariate instead, results for cluster extent analyses were substantively the same for negative associations with psychopathy scores. However, there was no evidence of a positive association between gray matter volume in the mPFC and Total PCL-YV scores. These results suggest a potentially large extent of structural abnormalities in psychopathy.

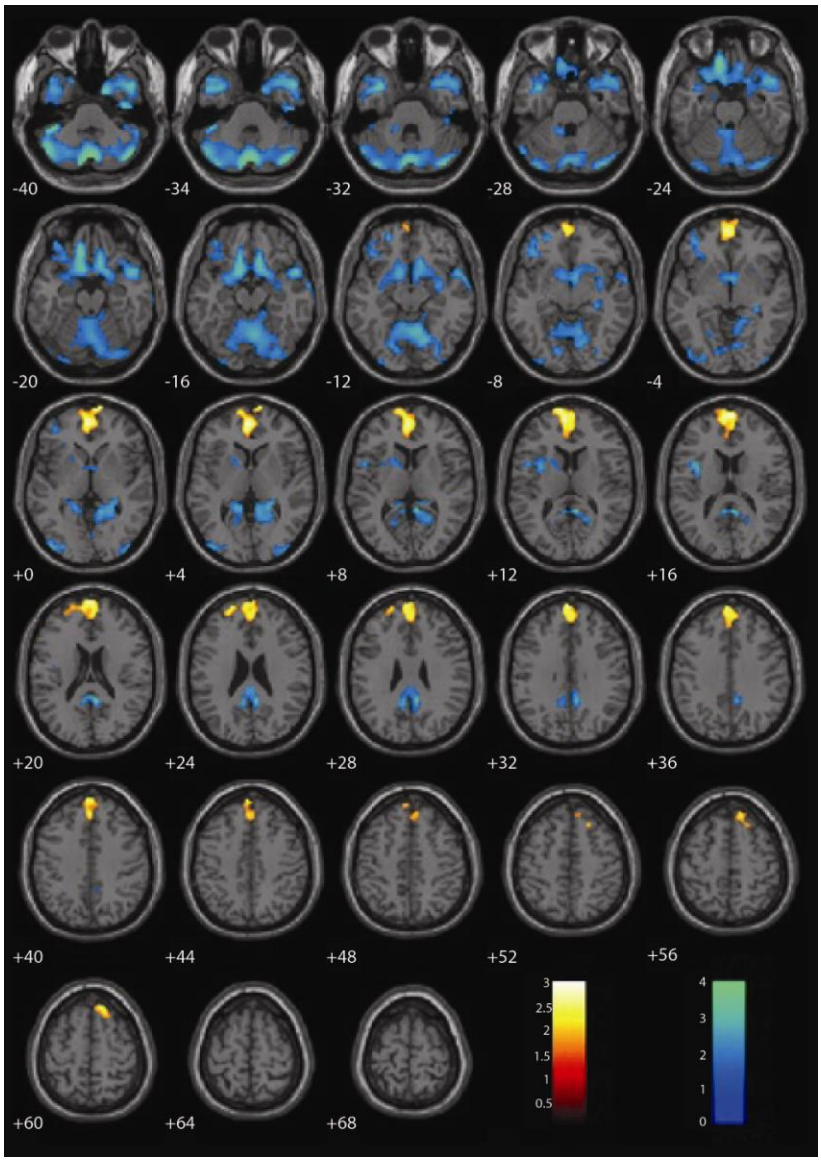

Figure 4. Regional gray matter volumes significantly associated with Psychopathy Checklist-Youth Version (PCL-YV) Total scores, controlling for brain volume (BV), age at scan, and substance dependence. These regions are significant in the whole brain at $p <$ .05 and 1643-voxel extent (selected using AlphaSim; Ward, 2000). Numeric values indicate the Montreal Neurological Institute (MNI) *z*-coordinate of the slice, and the color bar represents *t*-values. Gray matter volume increases are in yellow/orange/red and decreases are in green/blue. Adapted from "Aberrant paralimbic gray matter in incarcerated adolescents with psychopathic traits," by E. Ermer, L. M. Cope, P. K. Nyalakanti, V. D. Calhoun, & K. A. Kiehl, 2013, *Journal of the American Academy of Child & Adolescent Psychiatry, 52*, p. 98. Copyright 2012 by Elsevier.

Discussion

To our knowledge, this was the first structural MRI study of adolescents assessed using the PCL-YV. Here we found several commonalities with the results from Sample 1: Gray matter volume decreases were found in the temporal poles, parahippocampal cortex, PCC, and lateral OFC in both adults and adolescents, when the same covariates were used.

In contrast to Sample 1 (n = 254 male adults) however, positive associations between psychopathic traits and prefrontal gray matter volumes were identified in the adolescents. This finding is in line with evidence from functional MRI that found abnormal medial PFC activity in adolescents with psychopathic traits (Finger et al., 2008).

The consistent negative associations found in adolescents with psychopathic traits and in adults with psychopathy support the hypothesis that this disorder is neurodevelopmental in nature. These results suggest that the brain abnormalities associated with psychopathy are present as early as age 14. Furthermore, these results provide further support for the construct validity of psychopathic traits assessed in adolescence.

Study 1 (Sample 3)[15]

Little work has been done with adolescent females. Indeed, traditional theories of youth antisociality were developed specifically about males (e.g., Moffitt, 1993), leading some to question whether these theories can be generalized to females (Silverthorn & Frick, 1999). To address this gap, voxel-based morphometry was used to characterize regional gray matter volume differences related to psychopathic traits in a sample of juvenile female incarcerated offenders, assessed for psychopathy using the PCL-YV and controlling for substance use. I acknowledge the contributions of the following coauthors preparation of this study: Elsa Ermer, Prashanth Nyalakanti, Vince Calhoun, and Kent Kiehl.

Method

Participants. Of those who volunteered for the various ongoing studies, 39 adolescent females (mean age = 17.58, *SD* = 1.10) completed a sufficient number of assessments required for the present study and were therefore included here. Participants were predominantly Hispanic/Latino (61.5%), white/Caucasian (30.8%), or Native American (23.1%). From self-report, all participants were right-handed.

Psychopathy assessment. PCL-R interviews were videotaped for reliability assessment and double ratings were conducted on 12.8% of the sample, selected randomly. The intraclass correlation coefficient (ICC) was calculated using a one-way random effects model on a single rating with an absolute agreement definition. The ICC_1 was .83 for Total scores, indicating good reliability.

[15] Cope, L.M., Ermer, E., Nyalakanti, P.K., Calhoun, V.D., & Kiehl, K.A. (2013a). *Paralimbic gray matter reductions in incarcerated adolescent females with psychopathic traits*. Manuscript in preparation.

Substance use assessment. We assessed substance use in our subjects with the KSADS-PL (Kaufman et al., 1997); the total number of substances (alcohol and drugs) for which an individual met the lifetime dependence diagnostic criteria was calculated (scale: 0-8).

Other assessment. Full-scale IQ was estimated from the Vocabulary and Matrix Reasoning subtests of the WAIS-III (Ryan et al., 1999; Wechsler, 1997) for participants older than 16 years of age and from the WISC-IV (Sattler & Dumont, 2004; Wechsler, 2003) for participants younger than 16 years of age. The adapted King et al. (1995) post-head injury symptoms questionnaire was used to evaluate history of TBI and the KSADS-PL was used to rule out psychosis.

MRI data acquisition and analysis. Imaging parameters and preprocessing procedures were the same as in Study 1 (Sample 2).

Analytic strategy. Multiple regression analyses were performed on a voxel-by-voxel basis over the whole brain using the general linear model to evaluate the relationship between PCL-YV and regional gray matter volumes. All analyses included substance dependence as a covariate to control for the potential effect of this variable. As before, age at scan was also included a covariate in all analyses (Giedd, 2004; Good et al., 2001). We included BV as a covariate in all analyses in order to control for brain size and to focus on regionally specific changes (Pell et al., 2008). We estimated the cluster size necessary to correspond to a desired statistical threshold using Monte Carlo simulation with AlphaSim (Ward, 2000). We determined that a 371 voxel-extent at a height threshold of $p < .05$ (uncorrected) yielded a corrected threshold of $p < .05$, accounting for spatial correlations between gray matter volumes in neighboring voxels.

Results

Consistent with hypotheses, cluster threshold (371 voxels) analyses across the whole brain showed that gray matter volume in paralimbic regions was negatively associated with PCL-YV Total scores, controlling for BV, substance dependence, and age at scan. Two clusters in the (1) OFC, extending into right parahippocampal cortex and temporal pole, and in the (2) left parahippocampal cortex, extending into the temporal pole, were found (Figure 5). There were no clusters that were positively associated with PCL-YV Total scores.

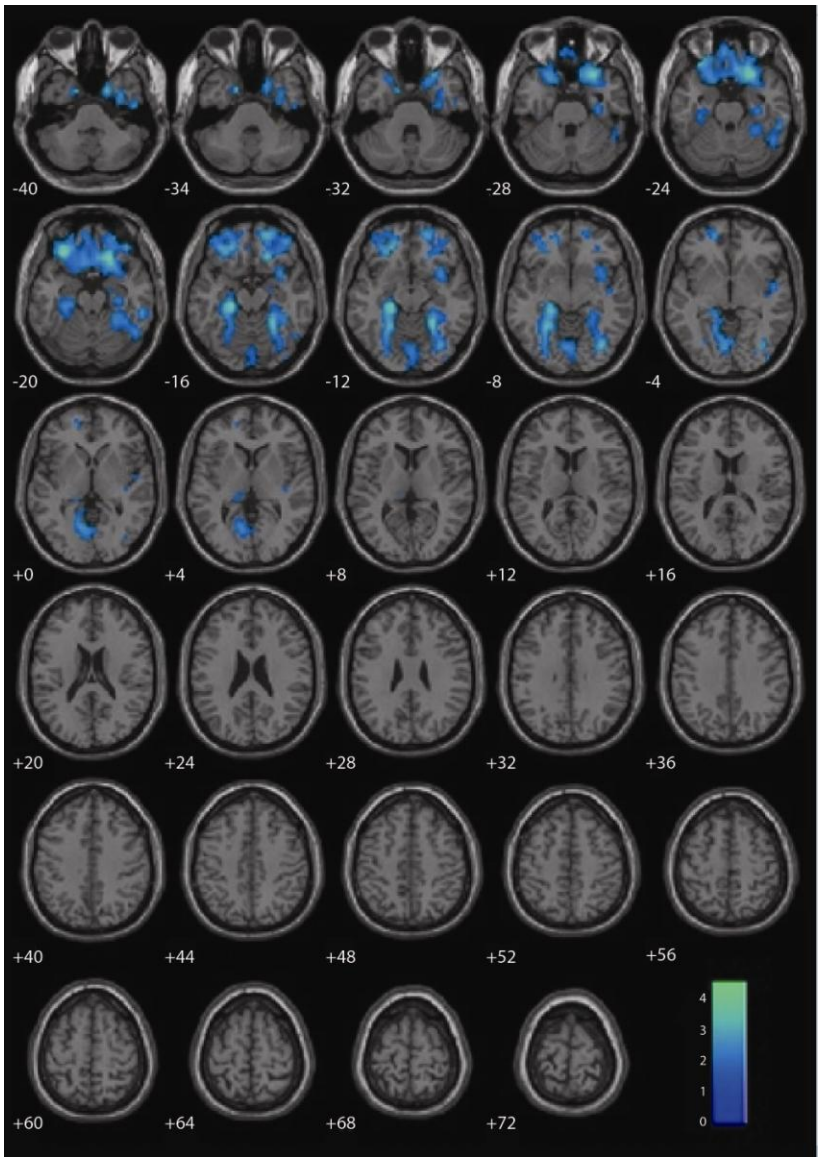

Figure 5. Regional gray matter volumes significantly associated with Psychopathy Checklist-Youth Version (PCL-YV) Total scores, controlling for brain volume (BV), age at scan, and substance dependence. These regions are significant in the whole brain at $p <$ .05 and 371-voxel extent (selected using AlphaSim; Ward, 2000). Numeric values indicate the Montreal Neurological Institute (MNI) *z*-coordinate of the slice, and the color bar represents *t*-values. Adapted from "Paralimbic Gray Matter Reductions in Incarcerated Adolescent Females with Psychopathic Traits," by L. M. Cope, E. Ermer, P. K. Nyalakanti, V. D. Calhoun, & K. A. Kiehl, 2013a (Manuscript in preparation).

Discussion

Consistent with hypotheses, regional gray matter volumes were negatively related to psychopathic traits in limbic and paralimbic areas, including OFC, parahippocampal cortex, temporal poles, and left hippocampus in an incarcerated female adolescent sample. These results are consistent with previous structural MRI findings in adults (Sample 1; Ermer et al., 2012) and adolescent males (Sample 2; Ermer et al., 2013), thus lending further support for the OFC, parahippocampal cortex, and temporal poles being abnormal in psychopathy. In contrast with males, however, adolescent females in the present study did not show any significant abnormalities in the PCC. One potential reason for this difference is the difference in sample sizes among the adolescent male (n = 191), adult male (n = 254) and adolescent female (n = 39) studies.

The present results are also relevant for the issue of whether psychopathy in females is a valid and useful construct. In addition to the findings reported in the introduction, a few previous studies have indicated both similarities and differences with male psychopathy in terms of emotional and neurocognitive aspects. For instance, as in men, deficient emotional responding (Sutton, Vitale, & Newman, 2002) and dysfunctional selective attention (Vitale, Brinkley, Hiatt, & Newman, 2007) have been reported in female samples. In contrast, one study (Vitale & Newman, 2001) found that response perseveration may not be a prominent feature of female psychopathy, as it is in male psychopathy (Newman, Patterson, & Kosson, 1987). The present neuroanatomical findings may be related to these behavioral and affective deficits, and lend further support to the validity of female psychopathy.

To our knowledge, this is the first study of regional gray matter differences in adolescent females using the PCL-YV. Though these females have significant comorbidities, including ADHD, anxiety, and depressive disorders, they are representative of incarcerated adolescents in general, and thus these results allow for generalizability to other samples. Given the relatively small sample size in comparison with other recent studies, these results should be considered preliminary. However, the consistency (in both methods and results) with other populations provides strong evidence of a unitary disorder across both age and sex.

Study 1 (Sample 4)[16]

Studying psychopathy in different groups (e.g., males versus females, adults versus adolescents, prisoners versus community corrections residents) allows us to characterize the disorder more comprehensively. Whether psychopathy is dimensional or categorical is still being debated; thus, studying both incarcerated and nonincarcerated individuals could be informative. Here, voxel-based morphometry was used to characterize regional gray matter volume differences related to psychopathy in a sample of community substance abusers, controlling for substance use. I acknowledge the contributions of the following coauthors and publisher in the publication of this study: Matt Shane, Judith Segall, Prashanth Nyalakanti, Mike Stevens, Godfrey Pearlson, Vince Calhoun, Kent Kiehl, and Elsevier.

Method

Participants. Sixty-six participants (30 female; mean age: 36.9 years, *SD* = 7.9) from probation, parole, and drug-treatment centers in the Hartford, CT, area completed a sufficient number of assessments required for the present study and were therefore included here. Participants were 47% Caucasian, 32% African American, 17% Hispanic, and 1.5% Asian. Seventeen percent of the sample participants did not wish to respond to questions of race or ethnicity, and race or ethnicity information was not available for an additional 3% of the sample. Left-handed participants were excluded in the present analyses. All aspects of the study were performed in accordance with the Hartford Hospital Institutional Review Board's guidelines and regulations. Participants also provided informed consent and were compensated for their time.

[16] Cope, L.M., Shane, M.S., Segall, J.M., Nyalakanti, P.K., Stevens, M.C., Pearlson, G.D., Calhoun, V.D., & Kiehl, K.A. (2012). Examining the effect of psychopathic traits on gray matter volume in a community substance abuse sample. *Psychiatry Research: Neuroimaging, 204*, 91-100.

Psychopathy assessment. For participants recruited from local probation/parole offices, official criminal files were obtained; these files contained detailed criminal histories, as well as background information regarding school, family, and work histories. For participants recruited through drug and alcohol treatment facilities, professional credit and background checks were completed by SSC Inc. (Hartford, CT), which provided information regarding criminal, driving, employment, and credit history.

Substance use assessment. The modified ASI (McLellan et al., 1992) was used to obtain lifetime drug and alcohol use severity measures. Drug (methamphetamine, cocaine, and heroin) history was defined as the cumulative years of "regular use" (defined as three or more times per week). Alcohol history was likewise calculated as the number of cumulative years of regular use. All participants self-reported no current drug or alcohol use.

Other assessment. A measure of IQ was estimated using the Hopkins Adult Reading Test (HART; Schretlen et al., 2009). To evaluate for comorbid DSM-IV Axis I and Axis II disorders, participants were assessed using the SCID-I (First et al., 2002). In terms of SCID-I diagnoses, only participants diagnosed with a lifetime psychotic disorder were excluded; 38 individuals met criteria for lifetime mood and/or anxiety disorders. No participants had a current severe mood or anxiety disorder according to DSM criteria.

MRI data acquisition and analysis. High-resolution T1-weighted structural MRI scans were acquired on a Siemens 3T Allegra scanner at the Olin Neuropsychiatry Research Center in Hartford, CT, using an MPRAGE pulse sequence (repetition time = 2500 ms, echo time = 2.74 ms, inversion time = 900 ms, flip angle = 8°, slice thickness = 1 mm, matrix size = 176 × 256) yielding 256 sagittal slices with an in-plane resolution of

1 mm × 1 mm. Data were preprocessed and analyzed using Statistical Parametric Mapping software (SPM5; Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). T1 images were manually inspected by an operator blind to subject identity and realigned if improper spatial normalization was likely due to gross misalignment. In SPM5, tissue classification, bias correction, and image registration are performed in one integrated step (Ashburner & Friston, 2005). Images were spatially normalized to the SPM5 T1 template, segmented into gray matter, white matter, and cerebrospinal fluid, modulated to preserve total volume, and resampled to 2 × 2 × 2 mm. Voxels with a matter value of < 0.15 were excluded in order to remove possible edge effects between gray matter and white matter. Finally, segmented images were smoothed with a 10 mm full-width at half-maximum (FWHM) Gaussian kernel.

Analytic strategy. Multiple regression analyses were performed on a voxel-by-voxel basis using the general linear model. We used total gray matter volume (GM) to account for individual variation in brain size (Bassitt et al., 2007; De Brito et al., 2009; Tanabe et al., 2009). Drug and alcohol history were also entered as control covariates. All whole-brain analyses were thresholded at $p < .005$, uncorrected for multiple comparisons, with an extent threshold of 5 voxels (after de Oliveira-Souza et al., 2008). Given that nearly half of this sample was female, we also controlled for participant sex in a supplemental analysis (with PCL-R Total score predicting regional gray matter volume, controlling for GM, drug and alcohol history, and participant sex).

Results

PCL-R scores were negatively correlated with regional gray matter in temporal and limbic areas, specifically left inferior temporal gyrus, left middle temporal gyrus, left

uncus, and right hippocampus. PCL-R scores were also positively correlated with regional gray matter in frontal and subcortical areas, specifically medial OFC, bilateral superior frontal gyrus, and bilateral thalamus (Figure 6). The additional analysis with participant sex as a covariate (with PCL-R predicting regional gray matter volume, controlling for drug and alcohol use, total GMV, and participant sex) yielded similar results to those of the primary analysis.

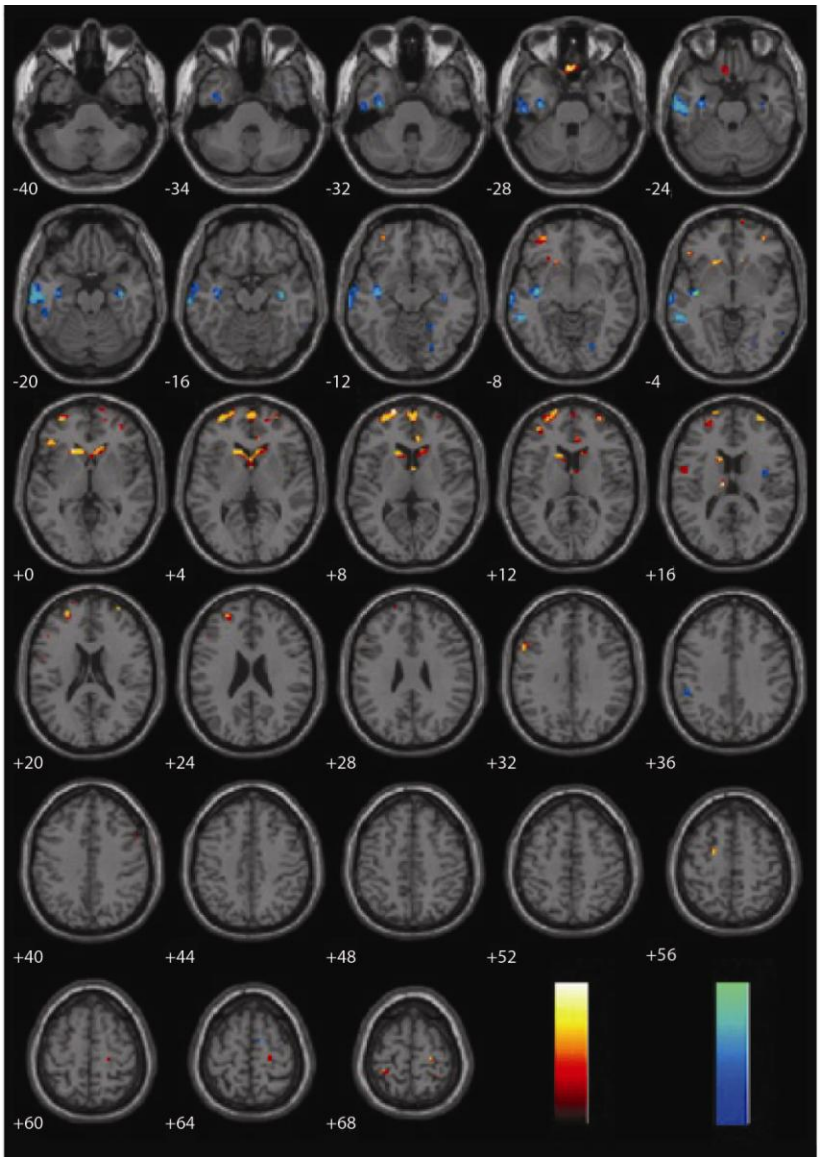

Figure 6. Regions where gray matter volume is related to Psychopathy Checklist-Revised (Hare, 2003) Total, Factor 1, or Factor 2, controlling for total gray matter volume, drug history, and alcohol history. Negative associations are depicted in blue colors and positive associations are depicted in red colors. Results are overlaid on a canonical high-resolution structural image and thresholded at $p < .005$, uncorrected for multiple comparisons. Adapted from "Examining the Effect of Psychopathic Traits on Gray Matter Volume in a Community Substance Abuse Sample," by L. M. Cope, M. S. Shane, J. M. Segall, P. K. Nyalakanti, M. C. Stevens, G. D. Pearlson, V. D. Calhoun, & K. A. Kiehl, 2012, *Psychiatry Research: Neuroimaging, 204,* p. 98. Copyright 2012 by Elsevier Ireland.

Discussion

Here we found negative associations between regional gray matter volumes and psychopathic traits in a community corrections sample. We also found positive associations with psychopathic traits in several regions, including the anterior cingulate (ACC). The rostral ACC is connected to the amygdala, anterior insula, hippocampus, and OFC, and is known to be involved in a wide variety of affective processes, including emotion regulation and assessing the salience of affective information (Bush et al., 2000). This region was also found to be dysfunctional during fear conditioning in psychopaths compared to healthy controls (Birbaumer et al, 2005). In addition to the ACC, we found a positive relationship between OFC volumes (BAs 11 and 47) and psychopathic traits. This latter finding can be contrasted with the negative associations found in these areas in adult males and adolescent females.

Unlike our previous findings in Samples 1-3, we found a positive association between regional gray matter volumes and severity of psychopathy in the striatum (caudate nucleus and putamen), consistent with Glenn and colleagues (2010). More recently, using radial distance mapping (RDM), Boccardi et al. (in press) found complex patterns of enlargement and reduction in the caudate, putamen, and nucleus accumbens in medium to high scorers on the PCL-R versus age-matched healthy controls. Locally abnormal subcortical morphology, such as the kind found by Boccardi et al., could potentially explain the disparate results in these areas found in multiple studies of psychopathy (e.g., Boccardi et al., in press; Cope et al., 2012 [Sample 4]; Ermer et al., 2012 [Sample 1]; Glenn et al., 2010).

It is worth noting that we found generally decreased volume within temporal and limbic regions, yet generally increased volume within frontal and subcortical structures. One potential explanation for the observed results is that psychopathic traits are associated with abnormal interactions between frontal/subcortical and temporal/limbic structures. In support of this idea, a recent study of white matter in psychopathy found abnormalities in the amygdala-OFC network (Craig et al., 2009). Giorgio and colleagues (2010) have shown in a sample of healthy adolescents that gray matter volume decreases with age in several distinct clusters, including medial and lateral prefrontal cortex, whereas in the present study, gray matter increases were observed in these regions. Similarly, it has been shown that in healthy individuals caudate volumes decrease during adolescence (Giedd, 2004) while amygdala and hippocampal volumes increase during this time (Giedd et al., 1996). It is thus possible that abnormal neurodevelopment lies at the heart of the manifestation of psychopathic traits. This explanation is supported by the findings of De Brito et al. (2009), where boys with callous-unemotional traits had increased gray matter concentration in the medial orbitofrontal cortex and anterior cingulate compared to typically developing boys. Disruption in the normal developmental trajectory during adolescence could result in increased frontal and subcortical but decreased temporal and limbic gray matter in adulthood, leading to dysfunction such as the kind seen in psychopathy. One possibility is that the dysfunction occurs at the cellular level, where a premature arrest in synaptic and neuronal pruning in some areas, coupled with deficient growth in others, results in ineffective and/or dysfunctional processing. Our data do not address this level of analysis directly, but they do suggest an interesting avenue to investigate.

The results from the present sample can be contrasted with those from Sample 1 (n = 254, with 39 individuals scoring at or above 30; Ermer et al., 2012). In both studies, negative associations between PCL-R Total scores and regional gray matter volumes were found in the left inferior temporal gyrus (BA 20), left parahippocampal gyrus (uncus/hippocampus; BA 20), and right hippocampus specifically[17]. More generally, negative associations were found in temporal and limbic/paralimbic regions in both samples. One difference between the two results is the positive association found in the present community corrections sample between PCL-R Total scores and regional gray matter volumes in frontal and subcortical areas and the negative correlation found in these regions in Ermer and colleagues. Due to the small size of the present sample and inconsistent nature of findings in the OFC in previous studies (including this one), these frontal gray matter increases should be replicated before definitive conclusions are drawn regarding the structure-function relationship in psychopathy. Differences between the results of the present study and those of the Ermer et al. study could be due to any number of the following methodological factors: population (community versus prison), participant gender (54.5% versus 100% male), number of individuals scoring at or above 30 on the PCL-R (5 versus 39), and covariates in the whole-brain analysis (GM and regular substance use vs. BV, substance dependence, and age). Note that sample size, race/ethnicity, mean PCL-R scores (p = .005), and reported thresholds were also different. Although the small sample size (n = 30 females) does not allow direct comparisons to be made between males and females in this sample, we controlled for participant sex in a supplemental analysis, and future studies should indeed examine

[17] These later areas were identified in region of interest analyses in the Ermer et al. study.

whether structural abnormalities in adult females with psychopathic traits differ from those in males.

Given strong evidence that psychopathy is a dimensional construct (Edens, Marcus, Lilienfeld, & Poythress, 2006; Guay et al., 2007), studying both incarcerated and nonincarcerated individuals, as well as samples scoring at all levels of the PCL-R, could be fruitful endeavors (Kirkman, 2002). It should be noted that these individuals were recruited from community corrections centers, and as such, should be considered part-way between the general population and prison populations. One potential limitation of this study is that we were not able to statistically control for depression and anxiety scores in the imaging analysis. Additionally, we did not perform drug tests to definitively rule out the possibility that participants were using drugs or alcohol at the time of the study (though note that they self-reported no current use). On the other hand, comorbidities including drug and alcohol use history and anxiety and mood disorders make this sample both heterogeneous and representative.

These results support the hypothesis that psychopathic traits are associated with structural abnormalities in a number of related brain regions, including parahippocampal gyrus, OFC, insula, ACC, and striatum. Undoubtedly, the relation between functional abnormalities and volumetric increases or decreases needs to be more fully elucidated, as does the functional and structural connectivity of regions important in psychopathy. In line with Craig and colleagues (2009), imaging analyses that evaluate white matter volume and integrity, such as diffusion tensor imaging, might be useful in this regard. It is important to keep in mind the potential differences between studies that have a large number of individuals scoring high on the PCL-R (i.e., that address psychopathy *per se*)

versus those that address *heightened psychopathic traits*. Indeed, future studies should continue to investigate the role of paralimbic and limbic regions in the manifestation of psychopathic traits, as well as the precise relationship between morphometric and functional abnormalities.

Study 2[18]

Given the structural differences described in Study 1, we now turn to functional differences in these areas. Abnormal functioning related to substance use is a logical place to start, because studies indicate that individuals with psychopathy start using substances at an earlier age (Corrado et al., 2004) and are more likely to develop polysubstance dependence (Mailloux et al., 1997; Smith & Newman, 1990) but do not experience drug craving to the same extent as nonpsychopaths (Cleckley, 1988). The present study utilized fMRI and a cue-induced drug craving paradigm to examine the modulatory effect of psychopathy on the brain's craving response in a sample of male and female incarcerated offenders. I acknowledge the contributions of the following coauthors in the preparation of this study: Gina Vincent, Justin Jobelius, Prashanth Nyalakanti, Vince Calhoun, and Kent Kiehl.

Method

Participants. These data were drawn from a National Institute on Drug Abuse (NIDA)-funded substance abuse treatment trial conducted at two (one male and one female) adult multi-security correctional facilities in New Mexico. To be eligible, participants had to volunteer, meet DSM-IV (APA, 2000) criteria for lifetime dependence on methamphetamine, heroin, or cocaine, and had to have used the drug within three months prior to their incarceration. Participants were given drug tests before each treatment session[19], but due to ethical considerations, were given the opportunity to continue treatment and study participation regardless of test results. Exclusion criteria

[18] Cope, L.M., Vincent, G.M., Jobelius, J.L., Nyalakanti, P.K., Calhoun, V.D., & Kiehl, K.A. (2013b). *Psychopathy modulates brain responses to drug cues*. Manuscript in preparation.

[19] Substance abuse treatment began within 1 week of the initial fMRI scan, barring personal or institutional circumstances (e.g., participant sickness, disciplinary action, institutional lock-down) that precluded the participant from keeping the appointment.

included: estimated full-scale IQ less than 70, less than a sixth grade reading level, current antipsychotic medication use, psychotic disorder diagnosis for self or a first-degree relative, or past or current central nervous system disease. The final sample consisted of 137 adults (mean age = 34.03, *SD* = 8.18; 93 females).

Psychopathy assessment. PCL-R interviews were videotaped to conduct reliability assessments. Double ratings were conducted on 16.8% of the sample, selected randomly. The intraclass correlation coefficient (ICC_1 one-way random effects model) was .83 for PCL-R Total scores, indicating good reliability.

Substance use assessment. Trained researchers interviewed participants using the SCID-I (First et al., 2002) to assess lifetime substance dependence according to DSM-IV criteria. The total number of substances (out of alcohol, sedatives/hypnotics/anxiolytics, cannabis, stimulants, opioids, cocaine, hallucinogens/PCP, other) for which an individual met lifetime dependence criteria was calculated (scale: 0-8).

Other assessment. Vocabulary and Matrix Reasoning subtests of the WAIS-III (Wechsler, 1997) were used to estimate the full-scale IQ (Ryan et al., 1999). The Wide Range Achievement Test Word Reading subtest (WRAT-3; Wilkinson, 1993) was used to assess reading level. The SCID was used to assess past and current Axis I disorders. Individuals also self-reported their primary drug of choice (i.e., methamphetamine, cocaine, or heroin).

Stimuli and task. All fMRI data used in the present analyses were collected prior to the participants' initiating the omnibus study's NIDA-funded 12-week drug abuse treatment program. Two types of pictures (32 drug craving-inducing and 32 neutral) were

selected from the popular media. Craving-inducing pictures depicted drugs or drug paraphernalia (e.g., rows of white powder with a razor blade, a hand holding a syringe, a pipe); these pictures depicted or were related to cocaine, heroin, and/or methamphetamine only. Neutral pictures depicted nondrug objects and scenes (e.g., white fluffy clouds, folded hands, a pen). Participants were instructed that they would see a series of pictures presented one at a time for 6 s. For each picture they were told to determine if anything in the picture gave them a craving feeling or desire to use drugs. Participants were told that their ratings should be based on their immediate level of desire, not how they think they should feel or would hope to feel. Following the offset of each picture participants were provided with a rating scale (in the form of a growing red bar) and told to rate the intensity of their drug craving on a scale from 1 (no craving) to 5 (extreme craving) by making a button press to stop the bar. After the rating screen, a black screen with a white fixation cross was presented for 4 s. In addition to craving-inducing and neutral pictures, 20 null fixation trials, which were the same duration as picture trials (i.e., picture + rating + fixation = 14 s), were interspersed to create jitter in the hemodynamic response and to minimize the development of any preparatory motor responses. Presentation of craving-inducing and neutral pictures and null fixation trials was randomized. Each participant completed two runs of 52 trials (16 craving-inducing, 16 neutral, and 20 null fixation stimuli per run). The task was designed, presented, and behavioral craving ratings were recorded for each picture using Presentation software v11 (http://www.neurobs.com/).

MRI data acquisition and analysis. Participants were scanned on the Mind Research Network 1.5T Siemens Avanto mobile MRI scanner, stationed at the

correctional facilities, using an EPI gradient-echo pulse sequence (TR 2000 ms, TE 39 ms, flip angle 75°, FOV 24 x 24 cm, 64 x 64 matrix, 3.8 x 3.8 mm in-plane resolution, 4 mm slice thickness, 27 slices).

Data were preprocessed and analyzed using Statistical Parametric Mapping software (SPM5; http://www.fil.ion.ucl.ac.uk/spm). The ArtRepair Toolbox in SPM (Mazaika, Hoeft, Glover, & Reiss, 2009) was used to detect and remove severe artifacts. Percent signal change was measured relative to the mean image intensity within the head mask. ART detected voxel-wise spikes that were greater than a given percent signal change (4% in this case), replaced the outliers with the mean in order to allow for proper subsequent realignment, and created a regressor to remove the effects of the outliers in the statistical analyses. Following ArtRepair each run was realigned to the first scan of the run using INRIAlign, a motion-correction algorithm that is unbiased by local signal changes (Freire, Roche, & Mangin, 2002). The six realignment parameters (three translations and three rotations) and second-order movement parameters were entered as covariates in the statistical models below in order to remove variance due to movement. Realigned images were spatially normalized to the Montreal Neurological Institute (MNI) template and smoothed with an 8 mm FWHM Gaussian smoothing kernel. Low frequency noise was removed using a high pass filter (cutoff: 1/128 s). Pictures (craving and neutral), ratings, and null fixation trials were modeled separately. Pictures were modeled with the standard SPM hemodynamic response function. For each participant, images that represented the hemodynamic response associated with viewing craving or neutral pictures were computed.

One-sample *t*-tests in SPM5 were used to detect differences in viewing craving-inducing pictures versus neutral pictures. To evaluate the relationship between psychopathy and drug craving, multiple regression analyses were also performed. PCL-R Total score was the predictor of most interest in order to observe the effect of psychopathy as a unitary disorder. Factors and facets were also examined to observe the unique variance accounted for by each factor and facet. In addition to these three primary regression analyses (one for Total score, one for the two factors, and one for the four facets), four secondary analyses were performed to evaluate the robustness of the effect of PCL-R Total score. Three of these four analyses included a control variable (participant sex, age, number of substance dependence diagnoses) and one secondary analysis was performed to address the fact that some participants had a positive (n = 12) or invalid/missing (n = 10) urinalysis just prior to the first treatment session. The whole-brain corrected statistical threshold was determined by performing a Monte Carlo simulation in AlphSim (Ward, 2000) to test for small, distributed effects, as have been previously found (Cope et al., 2013a; Ermer et al., 2012; Ermer et al., 2013). A cluster of 353 contiguous voxels (at peak height $p < .05$ uncorrected) corresponded to a corrected-for-multiple-comparisons cluster threshold of $p < .05$. Final results were overlaid on a canonical single subject T1-weighted high resolution structural scan from SPM5.

Results

Consistent with previous literature, the comparison of hemodynamic activity associated with viewing drug cues relative to neutral cues (cluster corrected $p < .05$) showed engagement of ACC, bilateral anterior/mid insula, bilateral hippocampus,

bilateral amygdala, PCC, bilateral striatum (i.e., caudate, putamen, NAcc), and bilateral thalamus (Figure 7).

PCL-R Total scores were entered as a covariate of interest in the craving versus neutral contrast in order to test for the modulatory effect of psychopathy on the hemodynamic response elicited by drug stimuli. There was a negative association between PCL-R Total scores and craving (cluster corrected $p < .05$) in the ACC, PCC, mid-insula, thalamus, caudate, and lentiform nucleus (medial and lateral globus pallidus and putamen) (Figure 8). There were no clusters showing a positive association between PCL-R Total scores and craving. These effects were driven primarily by Factor 2 (Figure 9) and Facet 4 (Figure 10).

Four secondary analyses were performed to control for potential covariates (participant sex, age, number of substance dependence diagnoses) and to control for the potential effect of a positive or invalid/missing drug urinalysis on hemodynamic activity associated with viewing craving pictures. Each of the three covariates was added as a nuisance variable to three separate models that compared craving pictures to neutral pictures, with PCL-R Total score as the main predictor. Participants with a positive or invalid/missing drug urinalysis were excluded from a fourth analysis. Results were substantively the same when each of these potential confounders was evaluated. The only notable difference was the lack of posterior engagement (i.e., PCC, inferior parietal lobule) when participant sex was covaried.

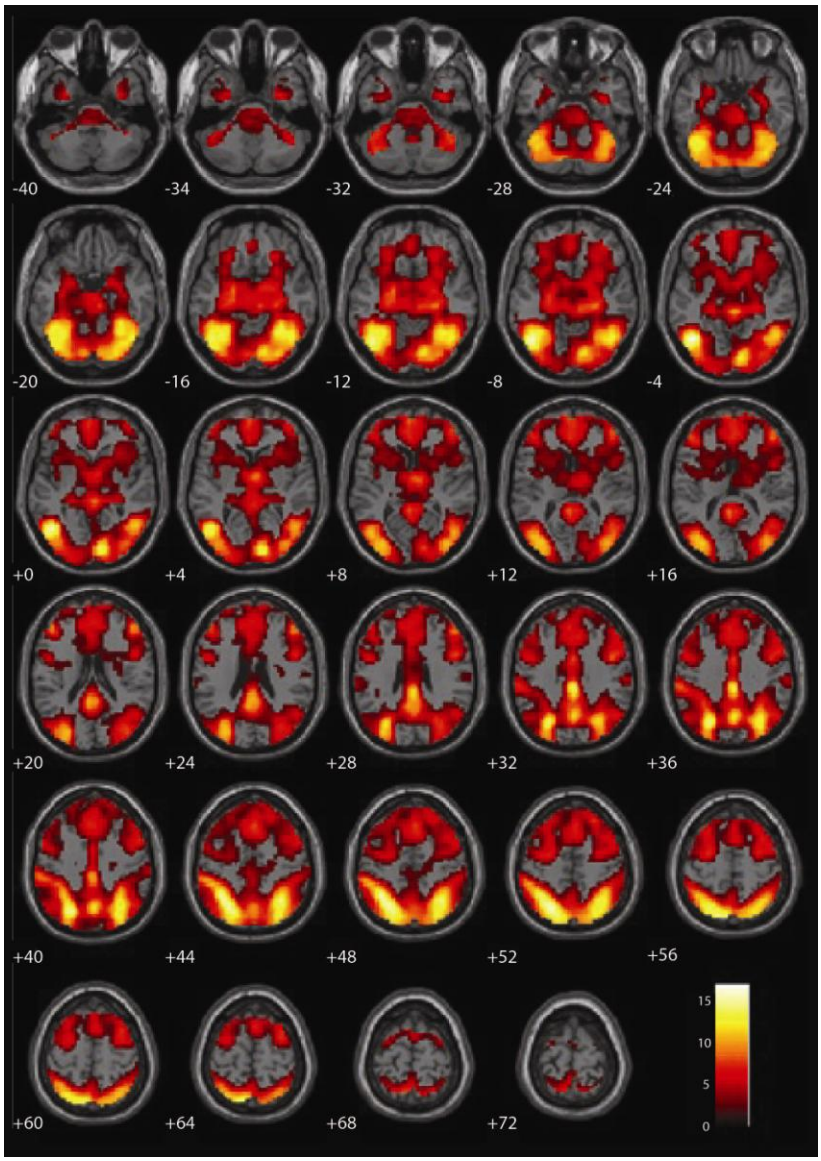

Figure 7. Regions associated with the main effect of viewing drug cues versus neutral cues. These regions are significant in the whole brain at $p < .05$ and 353-voxel extent (selected using AlphaSim; Ward, 2000). Numeric values indicate the Montreal Neurological Institute (MNI) *z*-coordinate of the slice, and the color bar represents *t*-values. Adapted from "Psychopathy Modulates Brain Responses to Drug Cues," by L. M. Cope, G. M. Vincent, J. L. Jobelius, P. K. Nyalakanti, V. D. Calhoun, & K. A. Kiehl, 2013b (Manuscript in preparation).

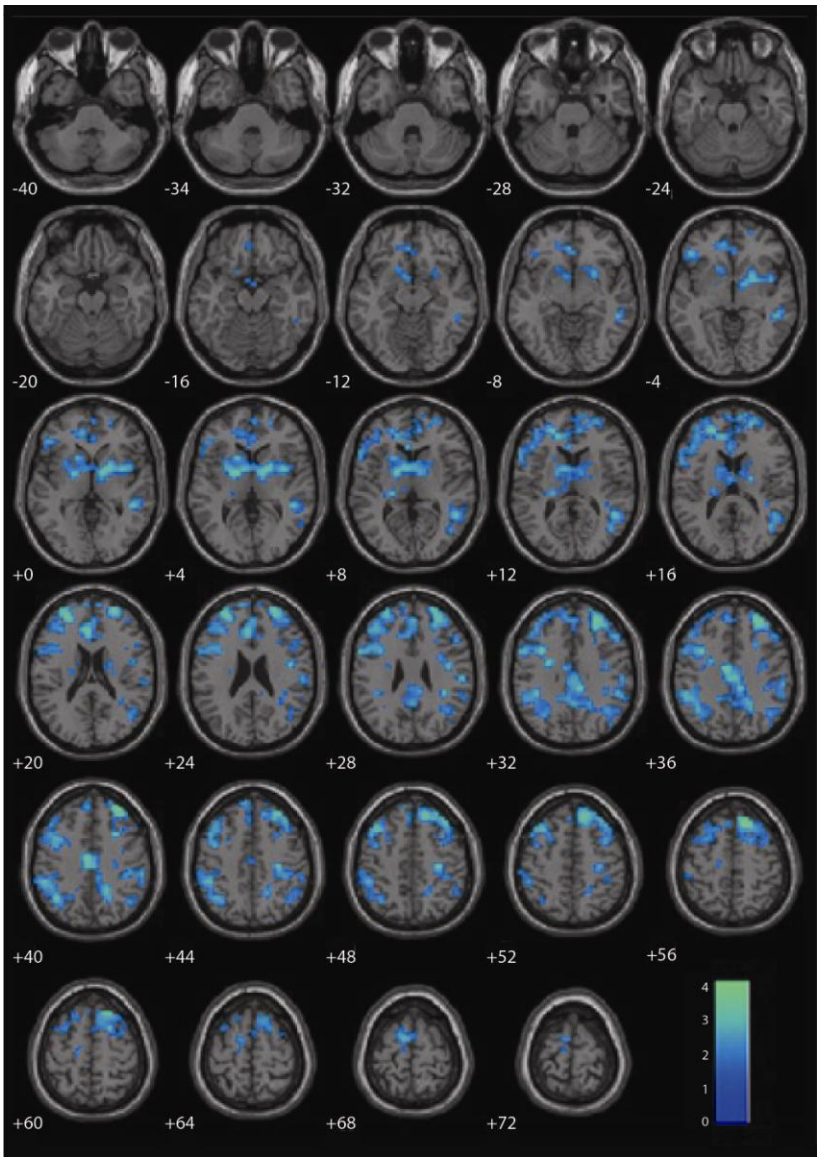

Figure 8. Negative associations between Psychopathy Checklist-Revised (PCL-R; Hare, 2003) Total scores and hemodynamic activity for viewing drug cues versus neutral cues. These regions are significant in the whole brain at $p < .05$ and 353-voxel extent (selected using AlphaSim; Ward, 2000). Numeric values indicate the Montreal Neurological Institute (MNI) *z*-coordinate of the slice, and the color bar represents *t*-values. Adapted from "Psychopathy Modulates Brain Responses to Drug Cues," by L. M. Cope, G. M. Vincent, J. L. Jobelius, P. K. Nyalakanti, V. D. Calhoun, & K. A. Kiehl, 2013b (Manuscript in preparation).

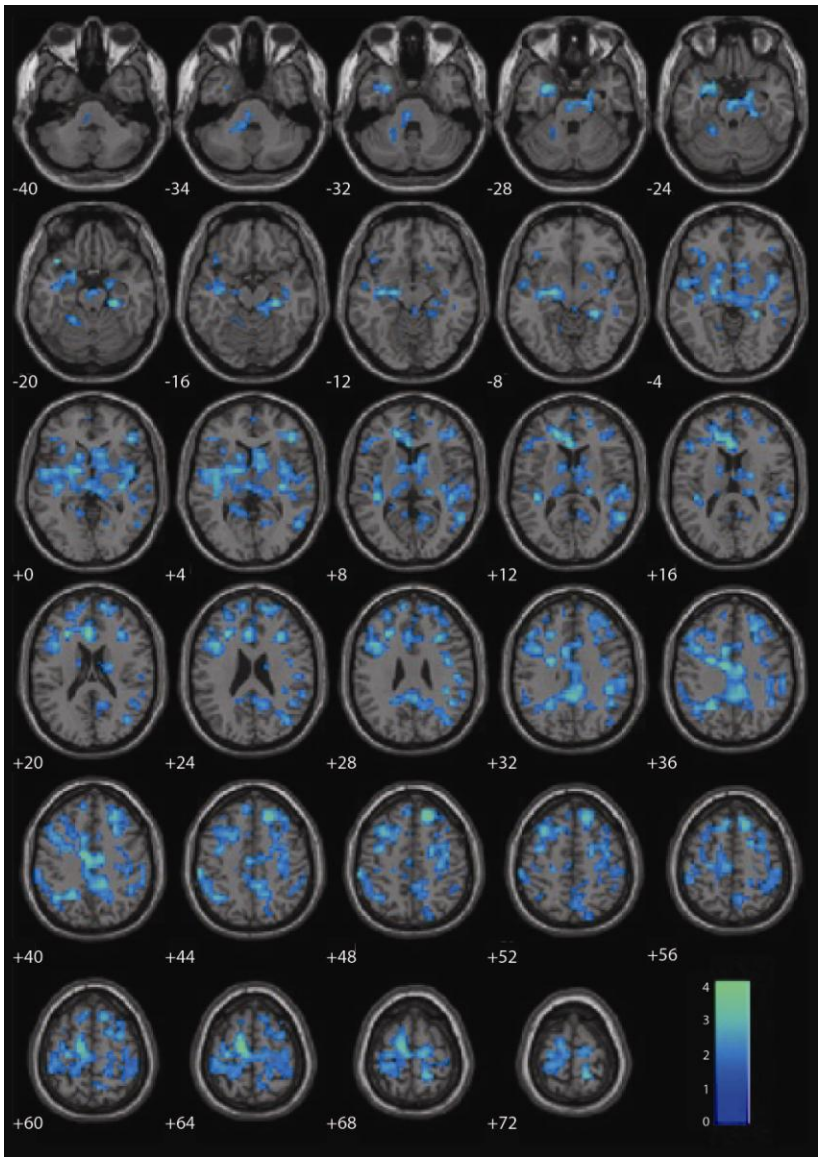

Figure 9. Negative associations between Psychopathy Checklist-Revised (PCL-R; Hare, 2003) Factor 2 scores (controlling for Factor 1) and hemodynamic activity for viewing drug cues versus neutral cues. These regions are significant in the whole brain at $p < .05$ and 353-voxel extent (selected using AlphaSim; Ward, 2000). Numeric values indicate the Montreal Neurological Institute (MNI) *z*-coordinate of the slice, and the color bar represents *t*-values. Adapted from "Psychopathy Modulates Brain Responses to Drug Cues," by L. M. Cope, G. M. Vincent, J. L. Jobelius, P. K. Nyalakanti, V. D. Calhoun, & K. A. Kiehl, 2013b (Manuscript in preparation).

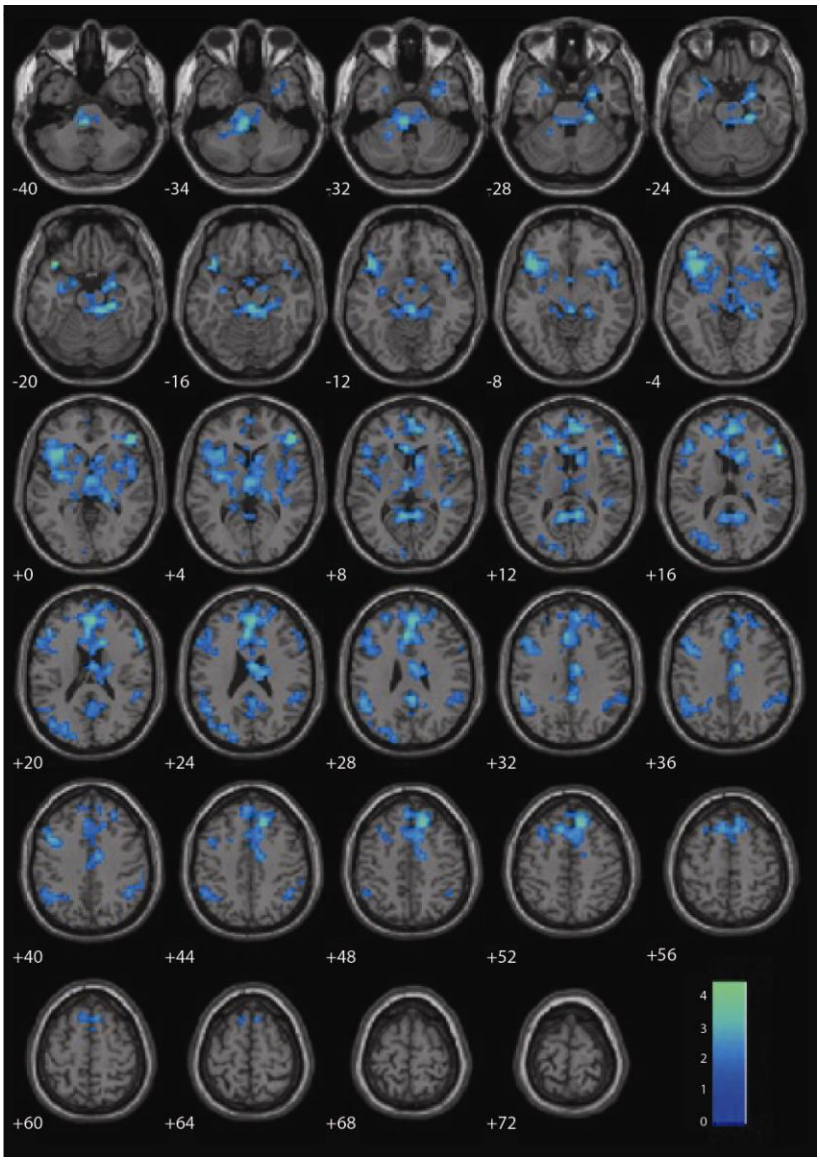

Figure 10. Negative associations between Psychopathy Checklist-Revised (PCL-R; Hare, 2003) Facet 4 scores (controlling for the other three facets) and hemodynamic activity for viewing drug cues versus neutral cues. These regions are significant in the whole brain at $p < .05$ and 353-voxel extent (selected using AlphaSim; Ward, 2000). Numeric values indicate the Montreal Neurological Institute (MNI) *z*-coordinate of the slice, and the color bar represents *t*-values. Adapted from "Psychopathy Modulates Brain Responses to Drug Cues," by L. M. Cope, G. M. Vincent, J. L. Jobelius, P. K. Nyalakanti, V. D. Calhoun, & K. A. Kiehl, 2013b (Manuscript in preparation).

Discussion

Consistent with hypotheses, psychopathic traits were negatively correlated with the hemodynamic response in areas that include the ACC, PCC, caudate, and right insula during the viewing of drug-related pictures compared to neutral pictures. The negative effect on craving was driven primarily by Factor 2 and Facet 4 of the PCL-R, which capture the developmental and life-course persistent aspects of psychopathy. Results were substantively the same when participant sex, age, urinalysis results, and number of substance dependence diagnoses were included.

One interpretation of these results may be found in the incentive sensitization theory of addiction (Robinson & Berridge, 1993). The incentive sensitization theory describes three distinct processes involved in the development of reward learning: (1) *pleasure* (i.e., "liking"), (2) *associative learning* of the link between targets and their hedonic value, and (3) *attribution of incentive salience* to those targets (i.e., "wanting/craving"). In individuals who are addicted to drugs, it is thought that the sensitization of the incentive salience system mediates compulsive drug-seeking and drug-taking (Robinson & Berridge, 1993). The self-reported subjective pleasure associated with drug-taking, on the other hand, does not become sensitized. This distinction is supported by individuals' reports that they *like* drugs less and less the more they take them, but they *want* the drugs more and more (i.e., they crave drugs).

The three processes involved in the development of reward learning can be distinguished in both time and space. Multiple studies in rats have shown that as experience with a rewarding stimulus (e.g., food, drug) increases, dopamine systems become activated earlier and earlier, signaling anticipation of the reward rather than the

reward itself (e.g., Blackburn, Phillips, Jakubovic, & Fibiger, 1989; Kiyatkin & Rebec, 1997). Other studies have attempted to distinguish "liking" from "wanting"[20] by capitalizing on reliable behaviors that rats perform when exposed to certain tastes: Rats protrude their tongues to sweet tastes like sucrose and gape and shake their heads to bitter tastes like quinine. In line with Darwin (1872/1998) and James (1884), researchers have used these expressions as an indicator of the hedonic aspect of a stimulus, and determined that morphine (an opioid agonist) increases "liking" to sweet tastes (Doyle, Berridge, & Gosnell, 1993; Pecina & Berridge, 1995). In contrast, dopamine antagonists like pimozide decrease the incentive value of food, as measured by reduced intake, preference, and instrumental behaviors (Wise, Spindler, deWit, & Gerberg, 1978), but do not have an effect on taste reactivity (Treit & Berridge, 1990). Taken together, these and many other studies suggest that dopamine does not signal the hedonic aspects of reward ("liking"), but rather the incentive salience of reward ("wanting"). Regions that may be involved in signaling the hedonic quality of stimuli include the shell of the nucleus accumbens and the ventral pallidum (Berridge & Robinson, 1998).

The results of the rat studies described above have been replicated, at least conceptually, in humans. For instance, one study found that coadministration of pimozide (a dopamine antagonist) with amphetamine did not decrease the euphorigenic quality of the amphetamine (Brauer & de Wit, 1996; 1997). Along the same lines, cocaine's hedonic quality was not decreased by prior administration of haloperidol, another dopamine antagonist (Ohuoha, Maxwell, Thomson, Cadet, & Rothmau, 1997). Dopamine

[20] It is commonly assumed that if an object or substance is wanted (as measured by voluntary intake and instrumental behavior, for example) then it is also liked. But incentive sensitization theory argues that these processes are not indelibly linked. This idea is supported by substance users' accounts of *liking* drugs less and less over time, but *craving* them more and more (Robinson & Berridge, 2008).

antagonists have been found, however, to reduce subjective ratings of wanting and craving (Brauer & deWit, 1997; Modell, Mountz, Glaser, & Lee, 1993). Administration of pergolide, a dopamine agonist, increased subjective ratings of wanting but decreased subjective ratings of liking in human cocaine addicts (Haney, Foltin, & Fischman, 1998). Finally, there exist some drugs that are more potent than cocaine at blocking dopamine reuptake, and yet are not at all euphorigenic (Berridge & Robinson, 1998).

Individual differences in the attribution of incentive salience have been suggested (Berridge, 2012). Perhaps psychopaths' incentive sensitization (i.e., "wanting" system) fails to be sensitized due to abnormal neurodevelopment in critical areas, while the motivating factor in their drug use is positive reinforcement for drugs' pleasurable effects. Thus, compared to nonpsychopaths, psychopaths may have different motivations for using drugs, where craving (i.e., intense "wanting") does not act as the usual potent motivator.

That psychopaths have a hypoactive mesolimbic dopamine system is contrary to the results of at least one study that found a positive association between psychostimulant dopamine release and psychopathic traits (Buckholtz et al., 2010), though several methodological choices may complicate the interpretation of these findings in the present context (e.g., participants were community volunteers with no history of drug use, psychopathy was measured with the Psychopathic Personality Inventory [PPI; Lilienfeld & Andrews, 1996]). Also note that in the Buckholtz et al. study, it was the Impulsive Antisociality factor of the PPI (which most closely maps onto PCL-R Factor 2) that was related to dopamine release. The results of the present study in relation to the Buckholtz

et al. findings and dopamine functioning in psychopathy in general certainly deserves further attention.

From these findings it follows that psychopaths may differentially experience the symptoms that comprise the diagnostic criteria for substance use disorders. Some differences in substance use related to psychopathy have already been characterized: Studies indicate that individuals with psychopathy start using substances at an earlier age (Corrado et al., 2004) and are more likely to develop polysubstance dependence (Mailloux et al., 1997; Smith & Newman, 1990). Directly testing these ideas in the fMRI scanner will be difficult, given the substantial overlap between regions responsive to drug stimuli and to evocative nondrug stimuli (Garavan et al., 2000). Additionally, opioid and dopamine receptors are often found within the same structure (e.g., shell of the nucleus accumbens, ventral pallidum), and the two systems may even directly synapse, making differentiating them difficult in humans. Despite these difficulties, future work should attempt to disentangle processes related to physiological dependence from compulsive use. This question leads us finally to Study 3, which used cluster analysis to investigate typologies of substance users and differential correlations with individual differences variables.

Study 3

Given the results of Study 2, more work needs to be done on distinguishing differential responses to (and motivations for) drug use in psychopaths and nonpsychopaths. Here, cluster analysis was used to create typologies of substance users based on SCID criteria for substance dependence; these groups were then compared on personality variables to further investigate how substance users differ along these dimensions.

Method

Participants. Of those who volunteered for the various ongoing studies, 380 adult males (mean age = 34.0 years, *SD* = 9.4) completed a sufficient number of assessments required for the present analyses and were therefore included here. Via self-report, 82.9% were right-handed, 7.9% were left-handed, and 7.1% were ambidextrous; handedness was unavailable for 2.1%. Participants were predominantly of Hispanic or Latino ethnicity (56.1%); 40.3% were not Hispanic or Latino, and information was unavailable for 3.7%. Racially, 40.8% were White, 6.6% were Black or African American, 0.3% were Asian, 9.5% were American Indian or Alaska Native, and 38.4% selected Do Not Wish to Provide This Information or Other; race information was unavailable for an additional 4.5%.

Psychopathy assessment. PCL-R interviews were videotaped for reliability assessment and double ratings were conducted on approximately 13% of the sample, selected randomly. The intraclass correlation coefficient (ICC) was calculated using a one-way random effects model on a single rating with an absolute agreement definition. The ICC_1 was .84 for Total scores, indicating good reliability.

Substance use assessment. Substance use was assessed using the SCID-I (First et al., 2002). Abuse and dependence were assessed for each of eight types of substances: alcohol, cannabis, sedatives/hypnotics/anxiolytics, stimulants (e.g., methamphetamine), opioids, cocaine, hallucinogens/PCP, and "other." DSM-IV-TR (APA, 2000) dependence is assessed with seven criteria that have been divided into those describing physiological dependence and those describing compulsive use. For each criterion for each substance, the individual can be given a 1 (*absent or false*), 2 (*subthreshold*), or 3 (*threshold or true*). Abuse items were not included in the present analyses due to the nature of the assessment procedure (i.e., dependence is assessed before abuse; if the individual meets diagnostic criteria for dependence, abuse criteria are not assessed). Sedatives/hypnotics/anxiolytics and hallucinogens/PCP criteria were also not included in the present criteria-level analyses due to very low rates of endorsement (i.e., 6.8% and 7.1% met dependence diagnostic criteria for sedatives/hypnotics/anxiolytics and hallucinogens/PCP, respectively, compared to 46.8% for cocaine; see Figure 11), indicating that the individuals in this sample generally did not experience problems with these substances. "Other" criteria were also not included as the substances that comprise this category are too heterogeneous for meaningful interpretation (e.g., anabolic steroids, nitrous oxide).

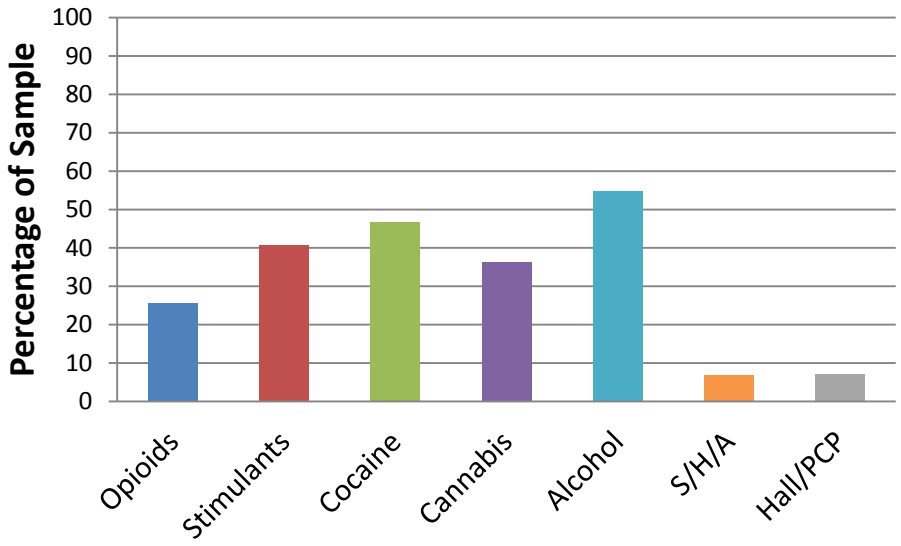

Figure 11. Percentage of sample meeting dependence diagnostic criteria by drug type.

In addition, to evaluate the extent and severity of substance use more generally, the total number of substances (out of alcohol, sedatives/hypnotics/anxiolytics, cannabis, stimulants, opioids, cocaine, hallucinogens/PCP) for which an individual met lifetime dependence criteria was calculated (scale: 0-7).

Exclusion criteria. A self-report screening form was used to collect each participant's age, the presence/absence of a first-degree relative with a psychotic disorder, MRI incompatibility, and past central nervous system disease. The adapted King et al. (1995) post-head injury symptoms questionnaire was used to assess the number of traumatic brain injuries and number and duration of loss of consciousness episodes. The WRAT3 (Wilkinson, 1993) was used to assess reading level. The SCID was used to assess past and current psychotic disorders.

External criterion analysis. Vocabulary and Matrix Reasoning subtests of the WAIS-III (Wechsler, 1997) were used to estimate full-scale IQ (Ryan et al., 1999). Impulsivity was assessed with the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995), a 30-item self-report questionnaire with three subscales (Attentional, Motor, and Nonplanning). Sensation seeking was assessed with the Sensation Seeking Scale (SSS; Zuckerman et al., 1978), a 40-item self-report questionnaire with four subscales: Thrill and Adventure Seeking (TAS), Disinhibition (DIS), Experience Seeking (ES), and Boredom Susceptibility (BS).

Cluster analysis. A two-step cluster analysis was performed in SPSS, v20. The two-step method is preferable with large data sets and with categorical data[21]. Additionally, the two-step procedure generates a predictor importance value (PIV) for

[21] Here, there were as many as 13,300 inputs (i.e., 35 variables x 380 cases; see descriptions of Strategies 1-6), and each DSM criterion is scored 1, 2, or 3.

each variable, which helps to determine the usefulness of each variable when the appropriate variables for inclusion are not definitively known, a priori. Finally, the correct number of clusters was also not known prior to performing the cluster analysis, and the two-step procedure is able to automatically determine the number of clusters that gives the best fit. Finally, because the final solution can depend on the order of the cases, the data were arranged in order of URSI (i.e., a randomly generated subject identifier), which is, in effect, random.

The first step in the two-step clustering procedure is to form preclusters, thereby reducing the number of cases that are used to create clusters. The second step is to perform a hierarchical clustering on the preclusters. The distance measure used was log-likelihood and Schwarz's Bayesian Criterion (BIC) was used as the clustering criterion. The number of clusters was allowed to be determined automatically, with a maximum of 15. All continuous variables were assumed to be standardized. Substance dependence criteria were used to form clusters of individuals; six different strategies were implemented regarding the sets of variables that were used for clustering:

1) All seven criteria from five substances (i.e., alcohol, cannabis, stimulants, opioids, and cocaine [after removing sedatives/hypnotics/anxiolytics and hallucinogens/PCP due to very low rates of endorsement]) were entered into the cluster analysis (seven criteria x five substances = 35 categorical variables).

2) After performing the cluster analysis from Strategy 1, substances with very low predictor importance values were removed (i.e., alcohol, cannabis), leaving seven criteria for each of stimulants, opioids, and cocaine (seven criteria x three substances = 21 categorical variables).

3) Two composite scores were created for each of the five substances used in Strategy 1: one score for the sum of the two physiological dependence symptoms (i.e., tolerance and withdrawal) and one score for the sum of the five compulsive use symptoms (two composite scores x five substances = 10 continuous variables).

4) Composite scores were created as described in Strategy 3 for the three substances with high predictor importance values (i.e., stimulants, opioids, and cocaine; two composite scores x three substances = six continuous variables).

5) Composite scores were created by summing all seven criteria for each substance (one composite score x five substances = five continuous variables).

6) Composite scores were created by summing all five substances (alcohol, cannabis, opioids, stimulants, and cocaine) for each criterion (one composite score x seven criteria = seven continuous variables).

***Internal criterion analysis*.** Internal criterion measures are used to assess the quality of the clusterings (i.e., clusters created with each strategy) using information from each clustering itself. One such measure is the silhouette measure of cohesion and separation (SMCS; Kaufman & Rousseeuw, 1990). The SMCS reflects the relatedness of objects within a cluster compared to the relatedness of objects between clusters; ideally, cohesion is high and separation is low. Numbers closer to one indicate better clustering quality.

***External criterion analysis*.** External criterion analyses use variables that were not used for clustering to determine the quality of the clustering solution. Here, age, IQ, psychopathy (PCL-R Total, two factors, and four facets), number of dependence diagnoses, impulsivity (BIS-11 Total and three factors), and sensation seeking (SSS

General and four factors) were used. One-way analysis of variance (ANOVA) tests, using a Bonferroni correction for multiple comparisons ($\alpha = .05/19 = .003$), were performed to test for differences among clusters for each external criterion.

Results

Descriptive statistics. Descriptive statistics for Study 3 variables (means, standard deviations, minima, maxima, and sample sizes) can be found in Table 4. Based on visual inspection of the normal probability plots and histograms, no variables were skewed enough to warrant transformation.

Table 4

Descriptive Statistics for Study 3

				Range	
	n	***M***	***SD***	**Actual**	**Potential**
Age	379	34.03	9.37	18-60	18-60
IQ[a]	377	95.58	12.95	72-137	45-155
Substance Use					
Number of Dependence Diagnoses	380	2.18	1.48	0-7	0-7
Psychopathy[b]					
Total	354	20.5	6.8	3.2-37.9	0-40
Factor 1	354	5.8	3.2	0.0-15.0	0-16
Facet 1	354	2.2	1.9	0.0-8.0	0-8
Facet 2	354	3.6	2.0	0.0-8.0	0-8
Factor 2	354	12.5	3.8	1.1-20.0	0-20
Facet 3	354	5.5	2.2	0.0-10.0	0-10
Facet 4	345	7.0	2.3	0.0-10.0	0-10
Impulsivity[c]					
Total*	319	69.97	10.71	39-106	30-120
Attentional	339	17.63	3.81	8-28	8-32
Motor	342	25.87	4.63	15-42	11-44
Nonplanning	340	26.66	5.00	13-41	11-44
Sensation Seeking[d]					
General	302	20.98	5.88	2-38	0-40
Thrill and Adventure Seeking	338	6.94	2.58	0-10	0-10
Experience Seeking	326	5.67	1.95	1-10	0-10
Disinhibition	319	5.54	2.47	0-10	0-10
Boredom Susceptibility	336	2.81	2.09	0-10	0-10

[a]From the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997); [b]From the Psychopathy Checklist-Revised (PCL-R; Hare, 2003); [c]From the Barratt Impulsiveness Scale v11 (BIS-11; Patton et al., 1995); [d]From the Sensation Seeking Scale (SSS; Zuckerman et al., 1978). *Patton et al. (1995) found a mean Total score of 76.30 (*SD* = 11.86) in a sample of male prison inmates (*n* = 73), a mean of 64.94 (*SD* = 10.19) in a sample of male undergraduates (*n* = 130), and a mean of 69.00 (*SD* = 10.21) in a sample of male substance abuse patients (*n* = 110).

Relationships among psychopathy and substance use variables. Zero-order and partial correlations were computed to examine the relationships among psychopathy and substance use variables.

Number of dependence diagnoses. Consistent with hypotheses, PCL-R Total score was significantly positively related to the number of dependence diagnoses, $r = .20$, $p < .001$. Using partial correlations, Factor 1 was significantly negatively related to the number of dependence diagnoses, $r = -.12$, $p = .020$, whereas Factor 2 was significantly positively related to the number of dependence diagnoses, $r = .32$, $p < .001$. Also as predicted, Facet 2 was significantly negatively related to the number of dependence diagnoses, $r = -.12$, $p = .031$. Facets 3 and 4 were positively related to the number of dependence diagnoses, $r = .16$, $p = .003$ and $r = .21$, $p < .001$, respectively. Facet 1 was not significantly related to the number of dependence diagnoses.

Compulsive use versus physiological dependence. Using partial correlations, PCL-R Total score was significantly positively related to a composite score of the five compulsive use criteria across seven substances (range: 35-105), when controlling for a composite score of the two physiological dependence criteria (range: 14-42), $r = .15$, $p = .006$. However, PCL-R Total score was unrelated to physiological dependence when controlling for compulsive use, $r = -.03$, $p = .537$. Factor 1, when controlling for Factor 2 and physiological dependence, was not significantly related to compulsive use, $r = .01$, $p = .845$; however Factor 1 was significantly negatively related to physiological dependence, when controlling for Factor 2 and compulsive use, $r = -.11$, $p = .044$. Factor 2, when controlling for Factor 1 and physiological dependence, was significantly positively related to compulsive use, $r = .14$, $p = .008$; Factor 2 was not related to

physiological dependence, when controlling for Factor 1 and compulsive use, $r = .07$, $p = .219$. The only significant facet-level partial correlation was between Facet 3 and compulsive use, controlling for physiological dependence and the other three facets, $r = .12$, $p = .028$. Correlations among all study variables can be found in Tables 5-10.

Table 5

Psychopathy Checklist-Revised Scores and Correlations with Study Variables

	Total[a]	**Factor 1**[a]	**Factor 2**[a]	**Facet 1**[a]	**Facet 2**[a]	**Facet 3**[a]	**Facet 4**[a]
Age	-.16**	-.03 (.11*)	-.26** (-.28**)	.05 (.16**)	-.10 (-.05)	-.16** (-.10)	-.30** (-.25**)
IQ[b]	.12*	.12* (.12*)	.05 (-.01)	.22** (.22**)	-.01 (-.09)	.09 (.01)	.01 (-.02)
Number of Dependence Diagnoses	.20**	.04 (-.12*)	.30** (.32**)	.07 (-.02)	-.01 (-.12*)	.24** (.16**)	.27** (.21**)
Impulsivity Total[c]	.16**	.04 (-.09)	.24** (.25**)	-.00 (-.15**)	.06 (.01)	.29** (.30**)	.12* (-.00)
Attentional Impulsivity[c]	.08	-.02 (-.11*)	.16** (.20**)	-.02 (-.10)	-.02 (-.06)	.19** (.21**)	.09 (.02)
Motor Impulsivity[c]	.20**	.10 (-.02)	.24** (.23**)	.07 (-.08)	.10 (.02)	.31** (.29**)	.11 (-.03)
Nonplanning Impulsivity[c]	.09	-.02 (-.12*)	.18** (.21**)	-.05 (-.16**)	.02 (-.01)	.22** (.24**)	.10 (.02)
Sensation Seeking (General)[d]	.31**	.19** (.04)	.34** (.29**)	.15* (.00)	.17** (.06)	.28** (.14*)	.30** (.19**)
TAS[d]	.10	.09 (.06)	.09 (.06)	.10 (.07)	.05 (-.00)	.09 (.03)	.07 (.03)
ES[d]	.18**	.10 (.02)	.19** (.16**)	.16** (.11)	.01 (-.09)	.17** (.09)	.15** (.10)
DIS[d]	.21**	.10 (-.02)	.26** (.24**)	.04 (-.07)	.13* (.06)	.19** (.10)	.25** (.18**)
BS[d]	.25**	.15** (.03)	.28** (.24**)	.07 (-.08)	.18** (.10)	.24** (.15**)	.24** (.14*)

Note. Zero-order correlations are given (with partial correlations with each PCL-R factor/facet, controlling for the other factor/facets, are in parentheses).

[a]From the Psychopathy Checklist-Revised (PCL-R; Hare, 2003); [b]From the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997); [c]From the Barratt Impulsiveness Scale v11 (BIS-11; Patton et al., 1995); [d]From the Sensation Seeking Scale (SSS; Zuckerman et al., 1978).

** Correlation is significant at the .01 level (2-tailed).

* Correlation is significant at the .05 level (2-tailed).

Table 6

Psychopathy Checklist-Revised Correlations

	PCL-R Total	Factor 1	Factor 2	Facet 1	Facet 2	Facet 3	Facet 4
PCL-R Total	–						
Factor 1	.81**	–					
Factor 2	.87**	.47**	–				
Facet 1	.68**	.81**	.40**	–			
Facet 2	.66**	.84**	.37**	.36**	–		
Facet 3	.77**	.46**	.85**	.45**	.32**	–	
Facet 4	.70**	.31**	.84**	.22**	.29**	.43**	–

Note. PCL-R = Psychopathy Checklist-Revised (Hare, 2003)

** Correlation is significant at the .01 level (2-tailed).

Table 7

Barratt Impulsiveness Scale-11 Scores and Correlations with Study Variables

	Impulsivity Total[a]	**Attentional Impulsivity[a]**	**Motor Impulsivity[a]**	**Nonplanning Impulsivity[a]**
Age	-.12*	-.10 (-.06)	-.06 (.01)	-.09 (-.05)
IQ[b]	-.06	-.07 (-.05)	-.01 (.05)	-.08 (-.07)
Number of Dependence Diagnoses	.25**	.22** (.09)	.21** (.08)	.23** (.14*)
PCL-R Total[c]	.16**	.08 (-.04)	.20** (.17**)	.09 (.03)
Factor 1[c]	.04	-.02 (-.07)	.10 (.14*)	-.02 (-.04)
Factor 2[c]	.24**	.16** (.02)	.24** (.17**)	.18** (.08)
Facet 1[c]	-.00	-.02 (-.03)	.07 (.10)	-.05 (-.08)
Facet 2[c]	.06	-.02 (-.10)	.10 (.16**)	.02 (.01)
Facet 3[c]	.29**	.19** (.03)	.31** (.20**)	.22** (.09)
Facet 4[c]	.12*	.09 (.02)	.11 (.06)	.10 (.04)
Sensation Seeking (General)[d]	.24**	.14* (-.03)	.29** (.25**)	.14* (.03)
TAS[d]	-.03	-.05 (-.07)	.08 (.16**)	-.11 (-.13*)
ES[d]	.06	.04 (-.01)	.09 (.09)	.03 (-.00)
DIS[d]	.27**	.17** (.02)	.26** (.18**)	.20** (.09)
BS[d]	.40**	.26** (.03)	.38** (.26**)	.29** (.15**)

Note. Zero-order correlations are given (with partial correlations with each BIS-11 factor, controlling for the other two factors, are in parentheses).

[a]From the Barratt Impulsiveness Scale v11 (BIS-11; Patton et al., 1995); [b]From the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997); [c]From the Psychopathy Checklist-Revised (PCL-R; Hare, 2003); [d]From the Sensation Seeking Scale (SSS; Zuckerman et al., 1978).

** Correlation is significant at the .01 level (2-tailed).

* Correlation is significant at the .05 level (2-tailed).

Table 8

Barratt Impulsiveness Scale-11 (BIS-11; Patton et al., 1995) Correlations

	Impulsivity Total	**ATT**	**MOT**	**NP**
Impulsivity Total	–			
Attentional Impulsivity	.79**	–		
Motor Impulsivity	.81**	.52**	–	
Nonplanning Impulsivity	.81**	.44**	.41**	–

Note. ATT = Attentional impulsivity; MOT = Motor impulsivity; NP = Nonplanning impulsivity.

** Correlation is significant at the .01 level (2-tailed).

Table 9

Sensation Seeking Scale Scores and Correlations with Study Variables

	Sensation Seeking (General)[a]	Thrill and Adventure Seeking[a]	Experience Seeking[a]	Disinhibition[a]	Boredom Susceptibility[a]
Age	-.23**	-.05 (-.01)	.02 (.12*)	-.34** (-.30**)	-.19** (-.08)
IQ[b]	.20**	.20** (.14*)	.30** (.27**)	-.01 (-.14*)	.05 (.07)
Number of Dependence Diagnoses	.18**	.10 (.05)	.14* (.09)	.14* (.09)	.08 (.03)
PCL-R Total [c]	.31**	.10 (.04)	.18** (.12*)	.21** (.08)	.25** (.19**)
Factor 1[c]	.19**	.09 (.07)	.10 (.06)	.10 (.02)	.15** (.13*)
Factor 2[c]	.34**	.09 (.03)	.19** (.11)	.26** (.13*)	.28** (.20**)
Facet 1[c]	.15*	.10 (.05)	.16** (.12*)	.04 (-.03)	.07 (.10)
Facet 2[c]	.17**	.05 (.06)	.01 (-.01)	.13* (.06)	.18** (.15*)
Facet 3[c]	.28**	.09 (.03)	.17** (.13*)	.19** (.07)	.24** (.20**)
Facet 4[c]	.30**	.07 (.03)	.15** (.10)	.25** (.16**)	.24** (.15*)
Impulsivity Total[d]	.24**	-.03 (-.06)	.06 (-.01)	.27** (.15*)	.40** (.32**)
Attentional Impulsivity[d]	.14*	-.05 (-.07)	.04 (.00)	.17** (.10)	.26** (.20**)
Motor Impulsivity[d]	.29**	.08 (.06)	.09 (.00)	.26** (.11)	.38** (.36**)
Nonplanning Impulsivity[d]	.14*	-.11 (-.14*)	.03 (.01)	.20** (.12*)	.29** (.23**)

Note. Zero-order correlations are given (with partial correlations with each SSS factor, controlling for the other three factors, are in parentheses).

[a]From the Sensation Seeking Scale (SSS; Zuckerman et al., 1978); [b]From the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997); [c]From the Psychopathy Checklist-Revised (PCL-R; Hare, 2003); [d]From the Barratt Impulsiveness Scale v11 (BIS-11; Patton et al., 1995).

** Correlation is significant at the .01 level (2-tailed).

* Correlation is significant at the .05 level (2-tailed).

Table 10

Sensation Seeking Scale (SSS; Zuckerman et al., 1978) Correlations

	Sensation Seeking (General)	**TAS**	**ES**	**DIS**	**BS**
Sensation Seeking (General)	–				
Thrill and Adventure Seeking	.62**	–			
Experience Seeking	.62**	.30**	–		
Disinhibition	.75**	.22**	.27**	–	
Boredom Susceptibility	.58**	.01	.14*	.39**	–

Note. TAS = Thrill and Adventure Seeking; ES = Experience Seeking; DIS = Disinhibition; BS = Boredom Susceptibility.

** Correlation is significant at the .01 level (2-tailed).

* Correlation is significant at the .05 level (2-tailed).

Cluster analysis. (1) Cluster analysis using Strategy 1 (35 variables) resulted in six clusters, ranging in size from 9.5% to 25.3% of the sample. The average SMCS was .2, indicating "fair"[22] fit. PIVs ranged from 1.00 (opioids: great deal of time) to .00 (alcohol: persistent desire or unsuccessful efforts).

(2) Cluster analysis using Strategy 2 (21 variables) resulted in seven clusters, ranging in size from 6.6% to 24.5% of the sample. The average SMCS was .5, indicating "fair" fit. PIVs ranged from 1.00 (opioids: great deal of time) to .45 (cocaine: physical or psychological problem).

(3) Cluster analysis using Strategy 3 (10 variables) resulted in four clusters, ranging in size from 17.6% to 29.7% of the sample. The average SMCS was .4, indicating "fair" fit. PIVs ranged from 1.00 (opioids: physiological dependence) to .01 (alcohol: physiological dependence).

(4) Cluster analysis using Strategy 4 (six variables; Figures 12-14) resulted in six clusters, ranging in size from 11.3% to 26.8% of the sample. The average SMCS was .6, indicating "good" fit. PIVs ranged from 1.00 (opioids: physiological dependence) to .36 (cocaine: physiological dependence).

[22] Classifications of "poor," "fair," and "good" were given by SPSS.

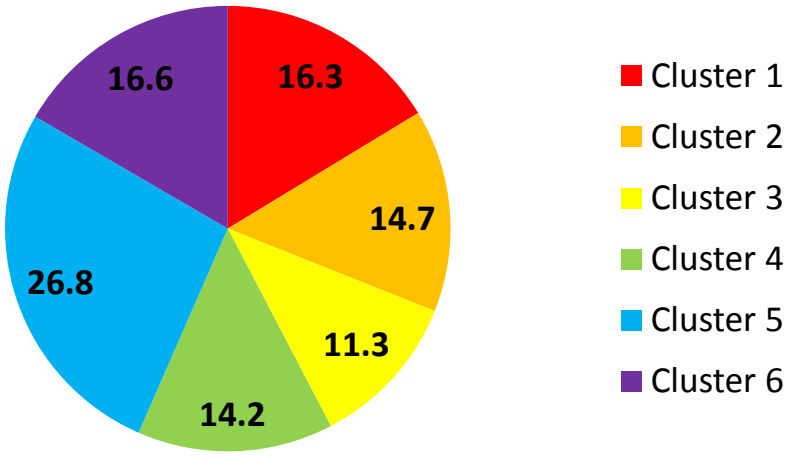

Figure 12. Percentage of total sample in each cluster using Strategy 4.

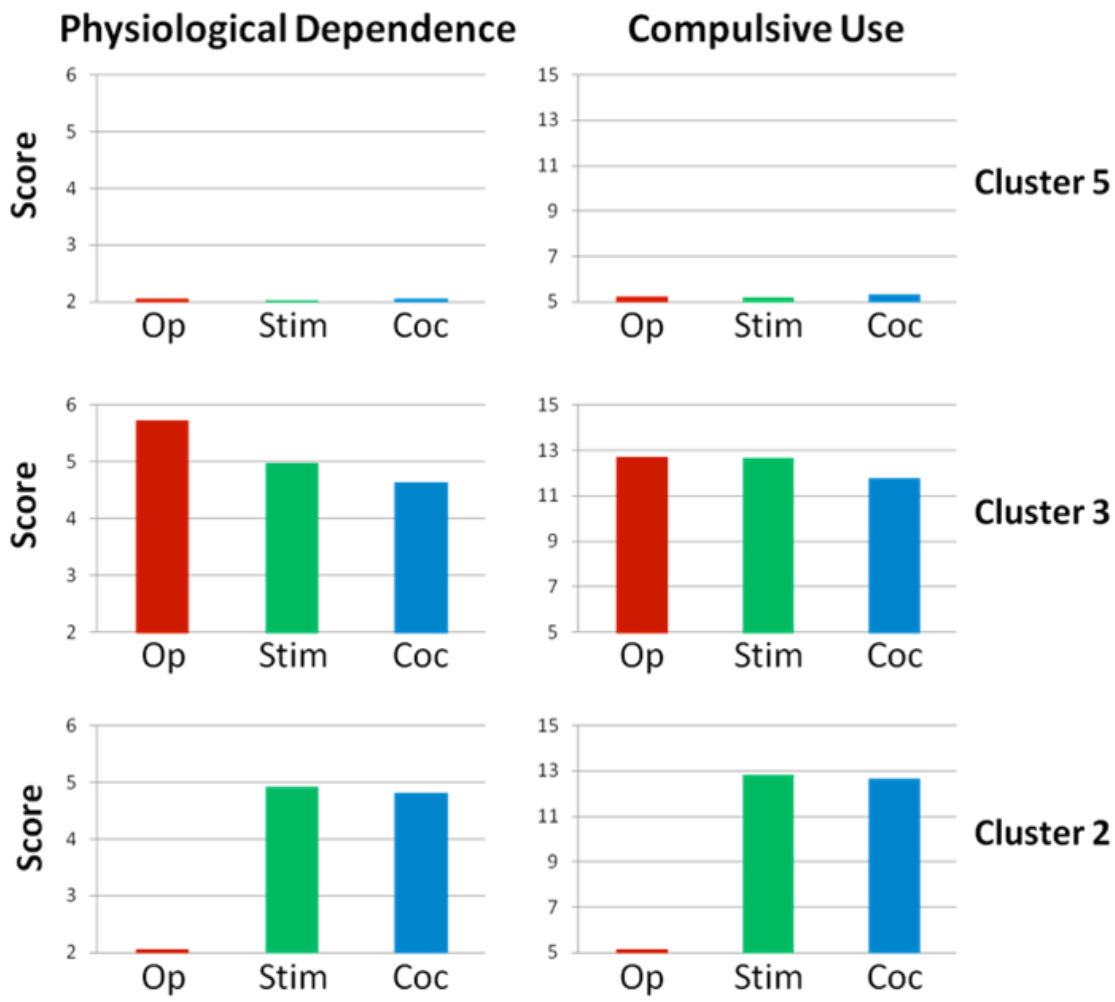

Figure 13. Clusters 5, 3, and 2 (derived from Strategy 4) and their means for each of the six variables.

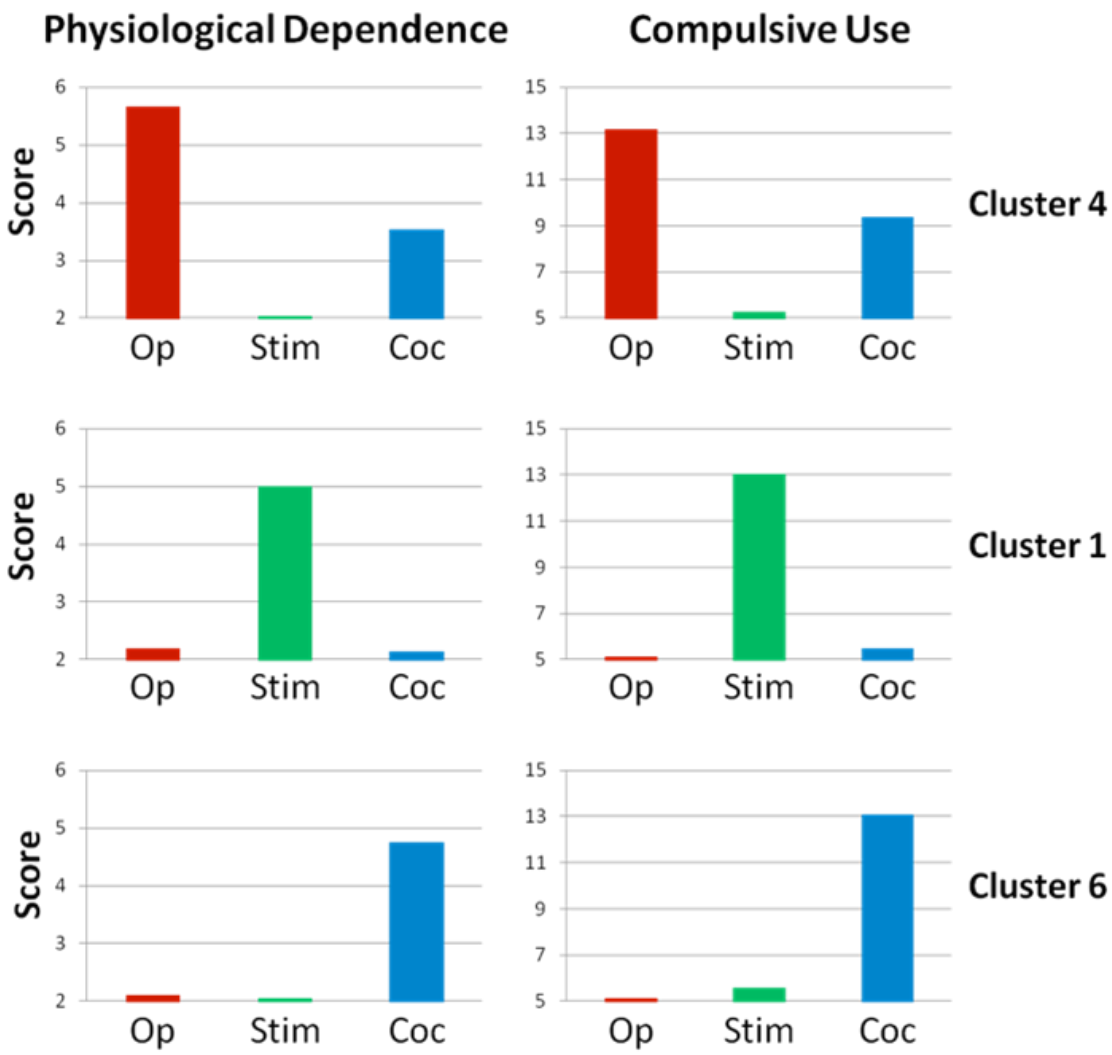

Figure 14. Clusters 4, 1, and 6 (derived from Strategy 4) and their means for each of the six variables.

(5) Cluster analysis using Strategy 5 (five variables) resulted in four clusters, ranging in size from 16.3% to 30.8% of the sample. The average SMCS was .4, indicating "fair" fit. PIVs ranged from 1.00 (opioids) to .01 (alcohol).

(6) Cluster analysis using Strategy 6 (seven variables) resulted in three clusters, ranging in size from 25.5% to 37.9% of the sample. The average SMCS was .4, indicating "fair" fit. PIVs ranged from 1.00 (great deal of time) to .51 (persistent desire).

External criterion analyses. Strategy 4, with the highest average SMCS and high PIVs, was chosen as the "best" model and the one to use for tests of external criteria. The decision to use Strategy 4 for the remaining analyses was also based on an attempt to maximize both model fit and interpretability/generalizability. The clusters derived from this strategy were tested for differences in age, IQ, psychopathy (PCL-R Total, two factor scores, and four facet scores), number of dependence diagnoses, impulsivity (BIS-11 Total and three factor scores), and sensation seeking (SSS General and four factor scores) using one-way ANOVAs with a Bonferroni correction for multiple comparisons (α = .05/19 = .003).

Five dependent variables showed evidence of heterogeneity of variance based on a significant Levene statistic: number of dependence diagnoses, $F(5, 374) = 3.24$, $p = .007$; PCL-R Factor 2, $F(5, 348) = 2.38$, $p = .038$; PCL-R Facet 4, $F(5, 339) = 4.91$, $p < .001$; Thrill and Adventure Seeking, $F(5, 332) = 3.27$, $p = .007$; Disinhibition, $F(5, 313) = 2.64$, $p = .024$; because sample sizes here were also unequal (*n*s were between 43 and 102), Welch's *F*-statistic was used for these five variables. For the remaining 14 variables, the traditional *F*-statistic was used. A Games-Howell post hoc procedure was used to identify significant group comparisons after significant omnibus *F*-tests (Field,

2009). Results showed that age, IQ, PCL-R Facet 1, Attentional impulsivity, and Disinhibition were significantly different in at least two clusters at the $p < .05$ level. At the more stringent Bonferroni corrected level of $p < .003$, number of dependence diagnoses, PCL-R Total, PCL-R Factor 2, PCL-R Facet 3, PCL-R Facet 4, Total BIS-11, Motor impulsivity, Nonplanning impulsivity, General SSS, and Thrill and Adventure Seeking were significantly different in at least two clusters. The full results of these one-way ANOVAs and post hoc tests can be found in Table 11 and Figures 15-20.

Table 11

Cluster Differences using Clusters Derived from Strategy 4

	***F*-statistic**	***df***	***p*-value**
Age	3.417	373	**.005**
IQ[a]	3.498	371	**.004**
Number of Dependence Diagnoses*	109.784	154.3	**< 1.0e-07^**
Psychopathy[b]			
Total	3.828	348	**.002^**
Factor 1	1.029	348	.400
Factor 2*	6.739	149.9	**1.1e-05^**
Facet 1	2.665	348	**.022**
Facet 2	1.162	348	.327
Facet 3	4.709	348	**3.6e-04^**
Facet 4*	5.912	149.0	**5.1e-05^**
Impulsivity[c]			
Total	4.922	313	**2.4e-04^**
Attentional	2.826	333	**.016**
Motor	3.851	336	**.002^**
Nonplanning	5.167	334	**1.4e-04^**
Sensation Seeking[d]			
General	4.275	296	**.001^**
Thrill and Adventure Seeking*	4.775	140.1	**4.6e-04^**
Experience Seeking	1.845	320	.104
Disinhibition*	2.802	131.8	**.019**
Boredom Susceptibility	2.056	330	.071

[a]From the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997); [b]From the Psychopathy Checklist-Revised (PCL-R; Hare, 2003); [c]From the Barratt Impulsiveness Scale v11 (BIS-11; Patton et al., 1995); [d]From the Sensation Seeking Scale (SSS; Zuckerman et al., 1978); *Welch's *F*-statistic was used due to inhomogeneity of variance.

Significant *p*-values are in bold print ($p < .05$). With Bonferroni correction (.05/19 = .003), significant *p*-values are marked with a ^.

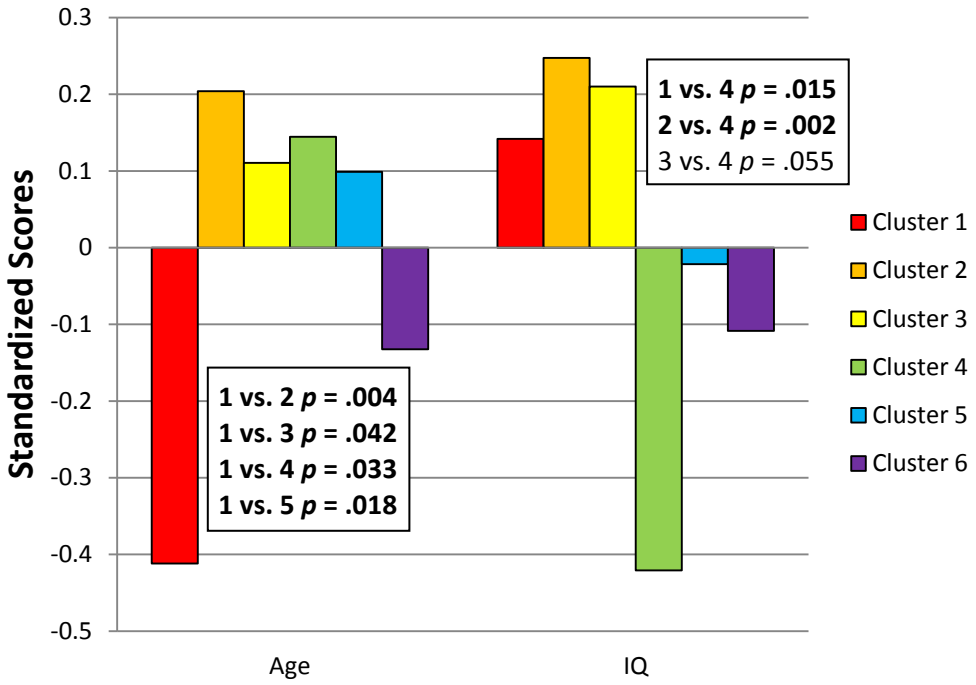

Figure 15. Bar graph depicting cluster differences on age and IQ. Significant between-cluster differences are indicated in bold print ($p < .05$). Trends ($p < .07$) are also given.

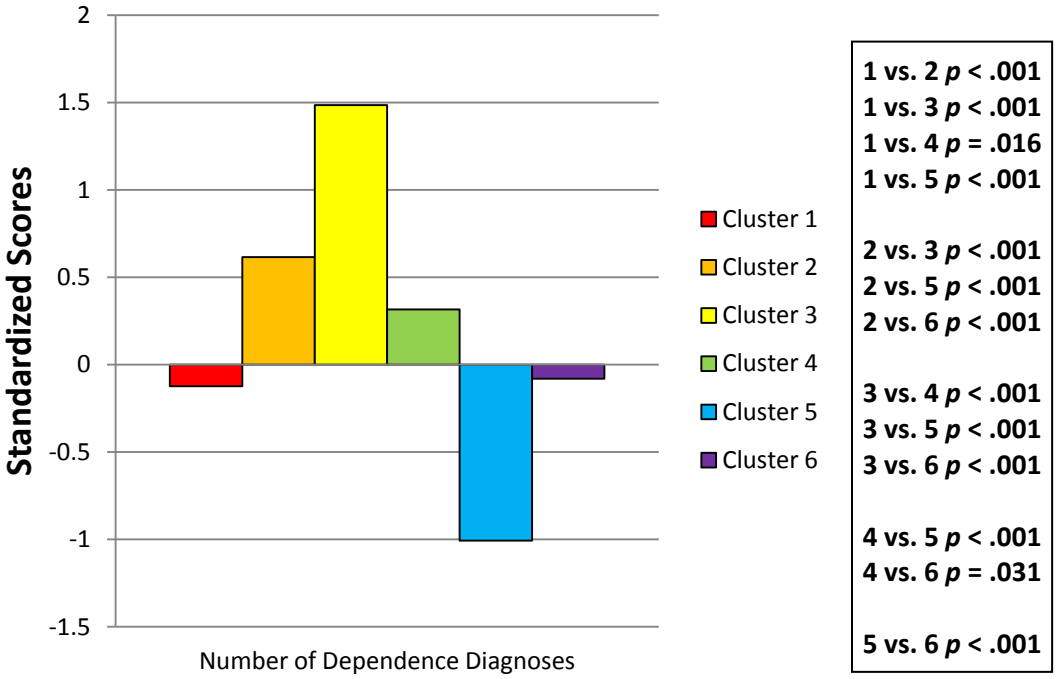

Figure 16. Bar graph depicting cluster differences on the number of dependence diagnoses. Significant between-cluster differences are indicated in bold print ($p < .05$).

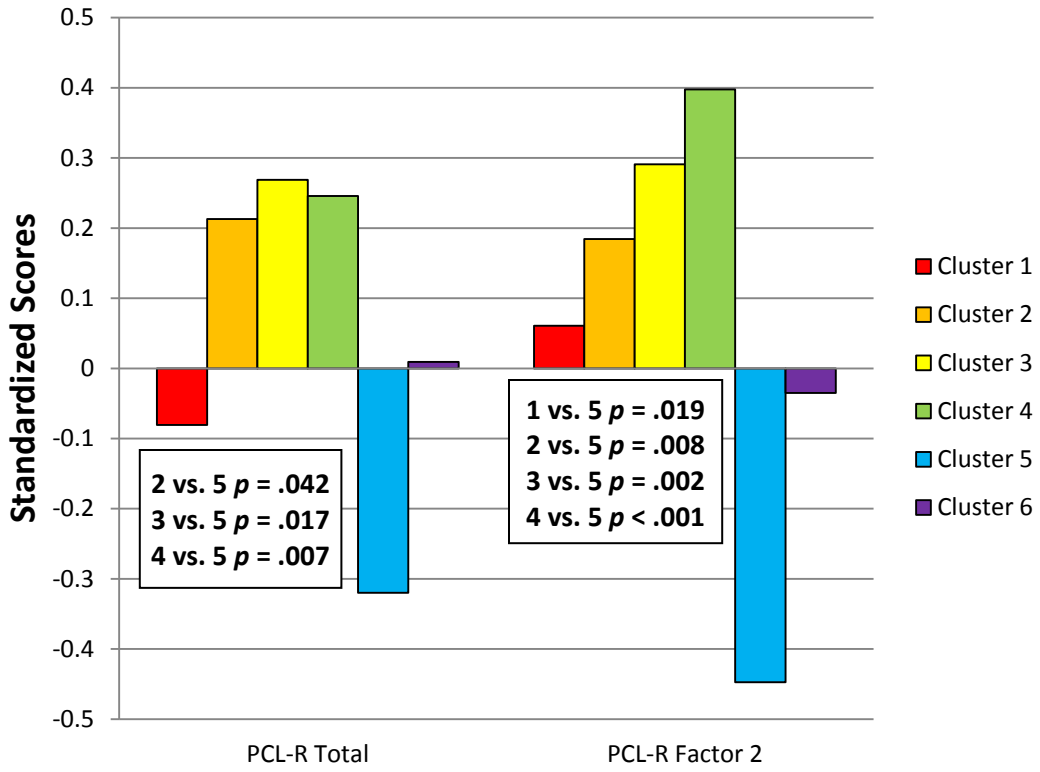

Figure 17. Bar graph depicting cluster differences on psychopathy (PCL-R) scores (Total and Factor 2). Significant between-cluster differences are indicated in bold print ($p < .05$).

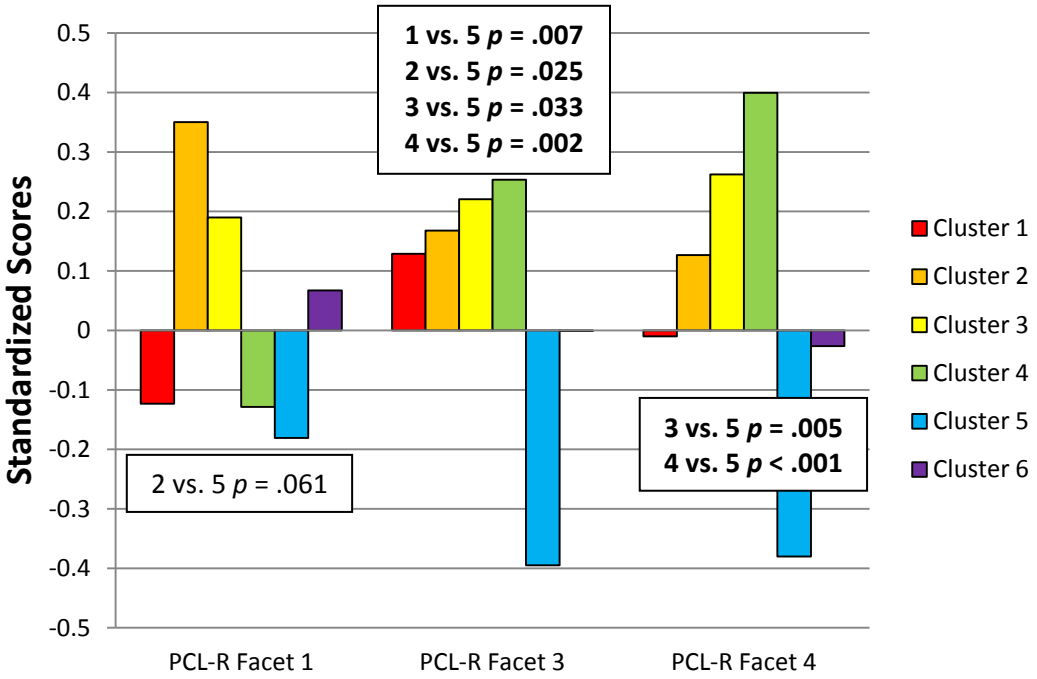

Figure 18. Bar graph depicting cluster differences on psychopathy (PCL-R) scores (Facets 1, 3, and 4). Significant between-cluster differences are indicated in bold print ($p < .05$). Trends ($p < .07$) are also given.

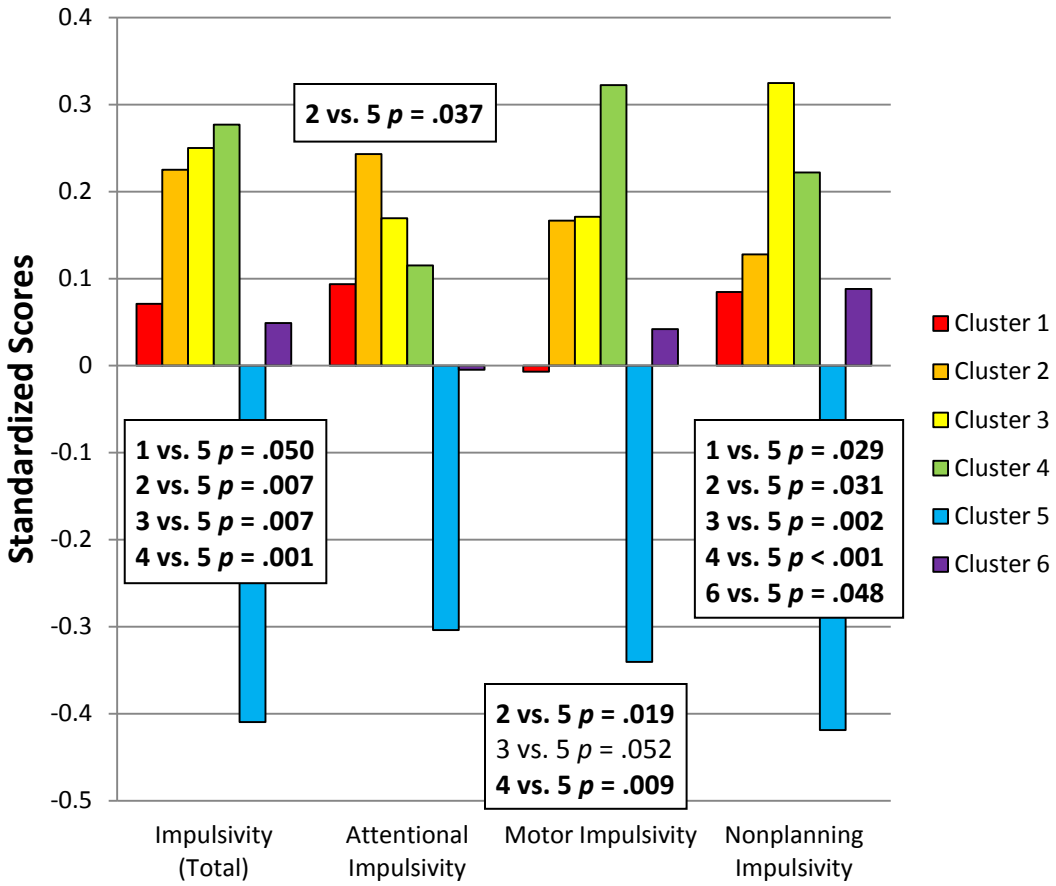

Figure 19. Bar graph depicting cluster differences on impulsivity (BIS-11) scores. Significant between-cluster differences are indicated in bold print ($p < .05$). Trends ($p < .07$) are also given.

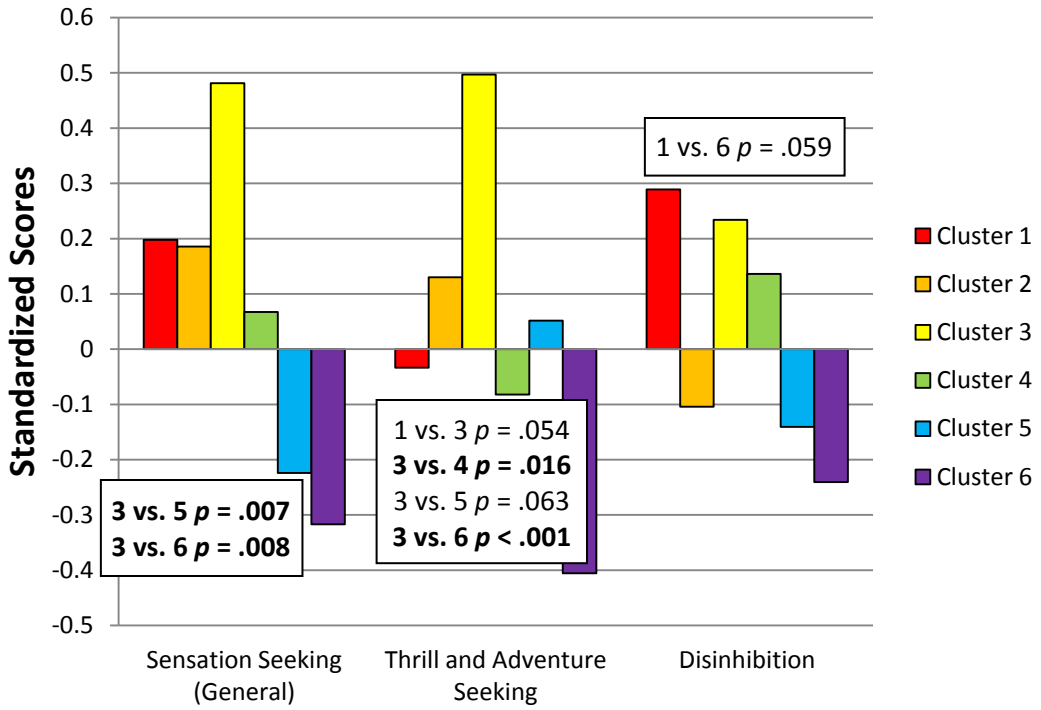

Figure 20. Bar graph depicting cluster differences on sensation seeking (SSS) scores. Significant between-cluster differences are indicated in bold print ($p < .05$). Trends ($p < .07$) are also given.

Discussion

This study utilized cluster analysis and personality assessment to evaluate associations among personality (impulsivity, sensation seeking, and psychopathy) and individual differences variables (age and IQ) and drug dependence criteria in a large sample of adult male inmates. Cluster analyses revealed that the structure of substance dependence is consistent with there being both subtypes and a dimension of severity.

Review of findings. Consistent with hypotheses and with previous work (Walsh et al., 2007), psychopathy scores (i.e., PCL-R Total, Factor 2, and Facets 3 and 4) were positively correlated with substance dependence (i.e., number of substance dependence diagnoses). Additionally, the interpersonal and affective component of psychopathy, Factor 1, and the affective facet, Facet 2, were significantly negatively correlated with the number of substance dependence diagnoses. Both impulsivity/disinhibition and negative affect (e.g., depression, anxiety) have been frequently linked to alcohol and other drug use (Trull et al., 2004). Thus it makes sense that Factor 2 (i.e., the impulsive, disinhibition factor) would be positively related to drug use, whereas Factor 1 (i.e., the deficient affect factor) and Facet 2 in particular would be negatively related to drug use. One interpretation of this effect is that some individuals use drugs to self-medicate their negative affect, whereas trait disinhibition leads others to develop substance abuse/dependence. The correlations with the PCL-R factors fit this pattern: Psychopaths typically do not ruminate about problems or experience long-term anxiety or depression (Cleckley, 1976; Hare, 2003), thus individuals who score high on Factor 1 are less likely to experience negative affect, and are less likely to use drugs for that reason. Given differential correlations with the factors/facets, these findings highlight the need to

examine the PCL-R factors separately whenever the PCL-R is used, rather than treating psychopathy as a single unified construct. They also point to the importance of controlling for the other factor (or facets) with partial correlations.

In line with evolutionary theories of psychopathy, recent imaging work suggests that psychopaths do not experience craving to the same extent as nonpsychopaths (Cope et al., 2013b). Following this line of thinking, psychopathy scores were correlated with two sets of composite scores: one set of scores from the five compulsive use criteria and one set of scores from the two physiological dependence criteria (i.e., tolerance and withdrawal). Using partial correlations, PCL-R Total score was significantly positively related to a composite score of the five compulsive use criteria across seven substances when controlling for a composite score of the two physiological dependence criteria. However, PCL-R Total score was unrelated to physiological dependence when controlling for compulsive use. This avenue should be pursued further after the DSM-V is released and drug craving is included as a substance use disorder criterion.

For the cluster analysis, two composite scores were created for each of cocaine, stimulants, and opioids: one for compulsive use and one for physiological dependence. Using these six variables and the two-step cluster procedure, individuals were meaningfully classified into six mutually exclusive groups that support the presence of both a severity spectrum and subgroups. Whereas members of Cluster 5 had no substantial problems with any drug, members of Cluster 3 had problems with all three types of drugs. Members of Clusters 1 (stimulants) and 6 (cocaine) both had problems with one drug, while members of Clusters 2 (stimulants and cocaine) and 4 (opioids and, to a lesser extent, cocaine) had problems with two. Thus, the clusters formed a dimension

in terms of the number of problematic substances, but also formed subgroups based on drug of choice. This finding of there being both severity dimensions and subgroups is consistent with at least one prior study using latent class analysis and multinomial logistic regression (Ghandour et al., 2008). This work extends the findings of prior studies where criteria for only one drug type were examined, and may be more representative of the typical treatment seeker (U.S. HHS, 2011).

In the present analysis, the clustering procedure did not form groups based on differences between compulsive use and physiological dependence, despite there being evidence for individual differences in craving (Cope et al., 2013b). One potential reason for this finding is that many prisoners – many of whom are nonpsychopaths – experience many, if not all, of the symptoms of drug dependence for each problematic substance (e.g., for each of alcohol, stimulants, opioids, and cocaine, approximately 10% of participants met all seven criteria [but not necessarily the same individuals for each drug type], with a much greater percentage meeting at least 5 criteria). So, even if psychopaths do tend to experience physiological dependence symptoms less than nonpsychopaths, this effect might have been washed out because of the number of individuals scoring above the diagnostic cut-off (i.e., 30) was low (36 out of 354 or 10.2%).

These findings are relevant to the field's ongoing debate regarding whether psychopathy is best represented by a dimension or a taxon. Early work by Harris, Rice, and Quinsey (1994) led to the assertion that that psychopathy represents a distinct taxon, though these results were limited to PCL-R Factor 2 and have been called into question because of inappropriate methods (Edens et al., 2006). Recent evidence has instead supported psychopathy as a dimension (Edens et al., 2006; Walters, Duncan, & Mitchell-

Perez, 2007). Given the uncertainty and the fact that many researchers consider both approaches to be valid, both group comparisons and multiple regression analyses are often performed within the same study (e.g., de Oliveira-Souza et al., 2008; Glenn, Raine, Yaralian, & Yang, 2010). If psychopathy is truly taxonomic, however, this could be one potential reason for the present findings: Under this assumption, the 138 individuals who scored in the "middle" range of the PCL-R (20-30 exclusive) do not have the same neurobiological abnormalities that are present in individuals with the highest scores on the PCL-R. Future work should attempt to investigate this further by sampling more high-scorers.

Despite this lack of a finding for compulsive use versus physiological dependence in the cluster analysis, however, the subgroups found here are potentially interesting, given the differences among the clusters on personality variables. Using a conservative Bonferroni-corrected threshold of $p < .003$, groups were significantly different on the number of dependence diagnoses (not surprisingly), PCL-R Total, Factor 2, Facet 3, and Facet 4 (psychopathy), BIS-11 Total, Motor, and Nonplanning (impulsivity), and SSS General and Thrill and Adventure Seeking (sensation seeking). Additionally, age, IQ, PCL-R Facet 1, Attentional impulsivity, and Disinhibition reached significance at a more liberal threshold of $p < .05$, and should be investigated further in future work.

Starting with PCL-R Total score, Cluster 5 (no substantial drug problems) was significantly lower than Cluster 2 (stimulants and cocaine), Cluster 3 (opioids, stimulants, and cocaine), and Cluster 4 (opioids [primary] and cocaine [mild]), but not Cluster 1 (stimulants), or Cluster 6 (cocaine). The results were similar for Factor 2, with the addition of Cluster 1 (stimulants) being significantly higher than Cluster 5 (no substantial

drug problems). Regarding the facets, Cluster 5 was significantly lower than Clusters 1, 2, 3, and 4 on Facet 3 (Behavioral Lifestyle), and Cluster 5 was significantly lower than Clusters 3 and 4 on Facet 4 (Antisocial). The pattern that emerged from these comparisons is that the clusters with two or three drugs were higher on psychopathy (i.e., PCL-R Total, Factor 2, Facet 3, and Facet 4) scores than the clusters with one or no drugs. This supports the assertion that psychopathy is highly comorbid with substance use disorders, above and beyond the already high rate of substance abuse in prison samples. It should be noted that although individuals' drug use is taken into account by at least one of the PCL-R items (need for stimulation/proneness to boredom), this accounts for a very small portion of the overall score.

As expected, Cluster 5 (no substantial drug problems) was again the lowest on the three significant impulsivity domains. Cluster 5 was significantly lower than Clusters 1, 2, 3, and 4 on BIS-11 Total score, Clusters 2, 3, and 4 on Motor Impulsivity, and all five clusters on Nonplanning Impulsivity. One question that arises from these findings is whether the observed differences in impulsivity are a cause or consequence of the substance dependence. Although the current study cannot speak to this issue, work by Bauer (2001) found that at least one cognitive function, time estimation, is related to personality (specifically, APD) and neural processes that predate the onset of substance dependence.

Regarding differences on sensation seeking, Cluster 3 emerged with the highest scores compared to Clusters 5 and 6 on General Sensation Seeking score, and Clusters 1, 4, 5, and 6 on Thrill and Adventure Seeking. Not surprisingly, Cluster 3 is the group with problems with all three drug types.

Four variables were not significantly different among the six clusters: PCL-R Factor 1, PCL-R Facet 2, Experience Seeking, and Boredom Susceptibility. The latter two findings may seem particularly surprising at first, but these two variables were not significantly correlated with the number of dependence diagnoses either. The lack of findings for PCL-R Factor 1 and Facet 2 are also not unexpected, given past work that found stronger relationships between drug use and Factor 2, than between drug use and Factor 1 (Hart & Hare, 1989; Mailloux et al., 1997).

Strengths and limitations. This study represented a novel approach to the study of substance dependence and personality. For instance, this is one of the first studies to examine dependence criteria for multiple drugs using a cluster analytic approach and using prisoners as participants. Procedures such as this have the potential to help identify subgroups of drug users with different characteristics (e.g., age, IQ, personality) so that treatment can be tailored to individuals' needs.

The results of this study should be interpreted with several limitations in mind. The first involves the manner in which the substance dependence criteria were assessed. For individuals who used more than one drug, it is possible that they attributed symptoms that were the result of one drug to a different drug, especially if they were using multiple drugs at one time. This is a potential problem in any study that examines substance abuse and/or dependence *symptoms*, but especially so in this study where 41% of the sample met lifetime dependence criteria on three or more substances.

Another limitation involves the complexity of the clustering procedure. On the one hand, polydrug use is more common than single drug use, at least among treatment seekers (U.S. HHS, 2011); thus it may be more realistic and generalizable to include

users of multiple drugs in order to characterize the typical drug user. However, perhaps heterogeneity in the drugs' effects and typical symptom profiles (e.g., the degree to which tolerance develops, the lack of withdrawal syndrome for drugs like cannabis and hallucinogens; though see Stone, Storr, & Anthony, 2006) reduced the chances of finding meaningful results. Many previous studies sampled from users of multiple drugs, but focused on one drug type for the clustering or latent class analysis (Ghandour et al., 2008; Shand et al., 2010 [both opioids]). This approach could be employed in the present data set, focusing on each drug of interest individually.

Finally, cluster analysis was but one of a number of appropriate statistical methods that could have been employed here. Other potential methods are multinomial regression (Ghandour et al., 2008), factor mixture modeling (Shand et al., 2010), and/or latent class analysis (Ghandour et al., 2008; Grant et al., 2006).

CHAPTER 3

GENERAL DISCUSSION

Across structural and functional neuroimaging and a cluster analysis of drug dependence criteria, the well-described but still poorly understood interaction of psychopathy and substance use disorders was investigated.

In male and female adults and adolescents, structural differences related to psychopathic traits were largely consistent, lending support to the idea that a network of regions across the paralimbic system is abnormal, at least structurally. Abnormalities in gray matter were observed in adolescents as young as 14, but future work should determine if these differences can be seen in children even younger. Based on studies of children with callous/unemotional traits (e.g., Frick, Cornell, Barry, Bodin, & Dane, 2003), it is likely that they will. These results thus support a neurodevelopmental model of psychopathy (see Blair et al., 2006), though the wide extent of structural differences gives more credence to the comprehensive paralimbic dysfunction model (Kiehl, 2006) than to Blair's OFC/amygdala dysfunction model (Blair, 2008). Regarding the two adolescent studies, it is important to note that these findings do not inevitably support preemptive incarceration or similar measures. Rather, we believe that early identification and intensive treatment of at-risk youth is crucial, in line with recent studies showing positive treatment outcomes for some of the most severe adolescent offenders (Caldwell, Skeem, Salekin, & Van Rybroek, 2006).

Several of the regions identified in the structural studies were also hypoactive during the viewing of drug cues in an fMRI study of craving, suggesting a close link between structural and functional abnormalities. Finally, cluster analysis was used to

identify typologies of substance users, and differential correlations with personality and individual differences variables were found. This cluster analysis study represents a first look at the associations among intelligence, substance dependence, psychopathy, impulsivity, and sensation seeking by drug type in a large sample of incarcerated adult males. In line with Ghandour et al. (2008), these results suggest that substance users are actually a heterogeneous group in terms of severity, drugs of choice, and personality correlates. Like the findings from the study of cue-elicited drug craving and psychopathy, this heterogeneity suggests that individual differences should be taken into account when designing substance use treatment strategies. Analogous to the notion of personalized medicine, this philosophy could be at once both more effective and more efficient when applied to substance use treatment.

Future Directions

In addition to the ideas for future projects that have already been mentioned, there are several additional analyses that should be done to further investigate the complicated relationships among personality dimensions like psychopathy and impulsivity and motivations for and consequences of drug use. For instance, one question that should be addressed is whether psychopaths are more likely to use certain kinds of drugs (e.g., stimulants versus depressants), given different drugs' variability in euphorigenic properties and likelihood of causing withdrawal and physiological dependence. Additionally, the neurobiological craving aspect should be considered further; it will be important to characterize how changes to the DSM-V (where craving will be a criterion for substance use disorder) impact this area of study.

Another avenue that should be explored further is an empirical study of psychopaths' reported lack of craving and withdrawal upon becoming incarcerated. This could be achieved by collecting both quantitative and qualitative data on craving and withdrawal at jails and/or prisons in individuals who have very recently become incarcerated (i.e., within approximately one to two weeks).

Incentive sensitization theory posits that the attribution of incentive salience is the one and only process (of the three) that is mediated by the mesolimbic and neostriatal dopamine systems (Berridge & Robinson, 1998)[23]. According to this theory, "wanting" can be altered by dopamine manipulations, and it is this fact that could be used to test the explanation that psychopaths' reduced cue-elicited craving is due to a failure of incentive salience attribution and malfunctioning of the mesolimbic dopamine system. That is, in line with the Haney et al. (1998) study that found administration of a dopamine agonist prior to cocaine administration increased subjective ratings of "I want cocaine" but not "I like [cocaine]," a similar procedure could be done with psychopaths and nonpsychopaths, though ethical concerns might make such a paradigm difficult. Regardless, this avenue should be pursued further.

Conclusions

In conclusion, these studies highlight the presence of structural differences related to personality, and individual variability in motivations for – and consequences of – drug use. They emphasize the need for individual considerations when designing treatment strategies in an effort to reduce the immense burden of substance-related crime, and for continuing work addressing the structural and functional correlates of psychopathy.

[23] In contrast, the hedonic value of a stimulus is mediated by γ-aminobutyric acid (GABA), benzodiazepines, and/or opioids, according to Berridge and Robinson (1998).

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