Available online at www.sciencedirect.com
ScienceDirect
Addictive Behaviors 33 (2008) 41–53
ADDICTIVE BEHAVIORS

The validity of cocaine dependence subtypes

Henry R. Kranzler [a,*], Marsha Wilcox [b], Roger D. Weiss [c], Kathleen Brady [d], Victor Hesselbrock [a], Bruce Rounsaville [e], Lindsay Farrer [b], Joel Gelernter [e]

[a] *Department of Psychiatry, University of Connecticut School of Medicine, Farmington, CT 06030-2103, United States*
[b] *Departments of Medicine (Genetics Program), Epidemiology, and Biostatistics, Boston University Schools of Medicine and Public Health, Boston, MA, United States*
[c] *Department of Psychiatry, Harvard Medical School, Boston, MA, and McLean Hospital, Belmont, MA, United States*
[d] *Department of Psychiatry, Medical University of South Carolina, Charleston, SC, United States*
[e] *Department of Psychiatry, Yale University School of Medicine, New Haven, CT and VA CT Healthcare Center, West Haven, CT, United States*

Abstract

Cocaine dependence (CD) is a multifactorial disorder, variable in its manifestations, and heritable. We examined the concurrent validity of homogeneous subgroups of CD as phenotypes for genetic analysis. We applied data reduction methods and an empirical cluster-analytic approach to measures of cocaine use, cocaine-related effects, and cocaine treatment history in 1393 subjects, from 660 small nuclear families. Four of the six clusters that were derived yielded heritability estimates in excess of 0.3. Linkage analysis showed genome-wide significant results for two of the clusters. Here we examine the concurrent validity of the six clusters using a variety of demographic and substance-related measures. In addition to being differentiated by a variety of cocaine-related measures, the clusters differed significantly on measures that were independent of those used to generate the clusters, i.e., demographic features and prevalence rates of co-morbid substance use and psychiatric disorders. These findings support the validity of the methods used to derive homogeneous subgroups of CD subjects and the resulting CD subtypes. Independent replication of these findings would provide further validation of this approach.

Keywords: Cocaine dependence; Subtyping; Cluster analysis; Heritability; Phenotype

* Corresponding author. Tel.: +1 860 679 4151; fax: +1 860 679 1316.
E-mail address: kranzler@psychiatry.uchc.edu (H.R. Kranzler).

0306-4603/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.addbeh.2007.05.011

1. Introduction

Cocaine use is widespread in the U.S., producing a variety of adverse medical and neuropsychiatric effects (Karch, 2005; Nnadi, Mimiko, McCurtis, & Cadet, 2005; Substance Abuse and Mental Health Services Administration, 2004; Wolff & O'Donnell, 2004). Cocaine dependence (CD), as a broad diagnostic entity, is a complex, heterogeneous, multifactorial disorder that includes cognitive, behavioral, and physiologic features. One way to reduce the heterogeneity of CD is the use of a typologic (or subtyping) approach (Babor & Dolinsky, 1988; Epstein, 2001). The validity of such an approach can be evaluated in terms of the utility of the subtypes for understanding etiology, presentation, natural history, or response to treatment of individuals with CD.

Vulnerability to the development of CD varies among individuals. Studies in animals and humans have examined the relative contributions of environmental and genetic factors in the etiology of substance dependence (Uhl, Elmer, LaBuda, & Pickens, 1995). Elucidating the genetic basis of CD would represent major progress in understanding the etiology of the disorder and could contribute substantially to the effort to develop efficacious medications to treat the disorder. This effort has, to date, been largely unsuccessful (Kosten & Ciraulo, 2005). The failure to identify efficacious medications to treat cocaine dependence may reflect an inadequate understanding of the heterogeneity of the disorder or an incomplete understanding of the pathophysiology of the disorder, with inadequate specification of potential medication-responsive dimensions.

Twin studies have shown that cocaine and other stimulant dependence is genetically influenced (Kendler, Jacobson, Prescott, & Neale, 2003; Kendler & Prescott, 1998; Tsuang et al., 1996). Although

Table 1
Lifetime prevalence of substance use and psychiatric disorders by sex [*N* (%) [a]]

Diagnosis	Total (*N*=1393)	Male (*N*=687)	Female (*N*=706)	χ^2 (1 *df*)	*P*-value
Substance use disorders					
Cocaine dependence	1229 (88.2)	606 (87.8)	623 (88.2)	0.21	0.65
Nicotine dependence	948 (68.1)	458 (66.7)	490 (69.4)	1.77	0.18
Alcohol dependence	628 (45.1)	339 (49.3)	289 (41.0)	9.05	0.003
Opioid dependence	626 (44.9)	347 (50.5)	279 (39.5)	15.82	<0.001
Cannabis dependence	383 (28.3)	240 (34.9)	143 (20.3)	39.03	<0.001
Sedative dependence	99 (7.1)	57 (8.3)	42 (5.9)	2.76	0.096
Stimulant dependence	97 (7.0)	56 (8.2)	41 (5.8)	2.80	0.094
Other substance dependence	237 (17.0)	139 (20.2)	98 (13.9)	9.49	0.002
Psychiatric disorders					
MDE	198 (14.6)	69 (10.0)	129 (18.8)	18.98	<0.001
ASPD	173 (12.4)	126 (18.3)	47 (6.8)	45.93	<0.001
PTSD	133 (9.6)	44 (6.4)	89 (13.1)	16.66	<0.001
Compulsive gambling	127 (9.1)	93 (13.5)	34 (4.9)	32.5	<0.001
Panic disorder	93 (6.7)	33 (4.8)	60 (8.8)	8.29	0.004
Agoraphobia	59 (4.2)	14 (2.0)	45 (6.7)	17.27	<0.001

Other substance dependence includes dependence on phencyclidine, hallucinogens, inhalants, solvents, or a combination of opioids and cocaine (i.e., "speedballs"); MDE: Major Depressive Episode; ASPD: Antisocial Personality Disorder; PTSD: Posttraumatic Stress Disorder.

[a] In some cases, percentage is increased due to missing data.