Distinctive Personality Traits and Neural Correlates Associated with Stimulant Drug Use Versus Familial Risk of Stimulant Dependence

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Background: Stimulant drugs such as cocaine and amphetamine have a high abuse liability, but not everyone who uses them develops dependence. However, the risk for dependence is increased for individuals with a family history of addiction. We hypothesized that individuals without a family history of dependence who have been using cocaine recreationally for several years but have not made the transition to dependence will differ in terms of personality traits and brain structure from individuals who are either dependent on stimulants or at risk for dependence.

Methods: We compared 27 individuals without a familial risk of dependence who had been using cocaine recreationally with 50 adults with stimulant dependence, their nondependent siblings ($n = 50$), and unrelated healthy volunteers ($n = 52$) who had neither a personal nor a family history of dependence. All participants underwent a magnetic resonance imaging brain scan and completed a selection of personality measures that have been associated with substance abuse.

Results: Increased sensation-seeking traits and abnormal orbitofrontal and parahippocampal volume were shared by individuals who were dependent on stimulant drugs or used cocaine recreationally. By contrast, increased levels of impulsive and compulsive personality traits and limbic-striatal enlargement were shared by stimulant-dependent individuals and their unaffected siblings.

Conclusions: We provide evidence for distinct neurobiological phenotypes that are either associated with familial vulnerability for dependence or with regular stimulant drug use. Our findings further suggest that some individuals with high sensation-seeking traits but no familial vulnerability for dependence are likely to use cocaine but may have relatively low risk for developing dependence.

Key Words: Cocaine, compulsivity, familial vulnerability, impulsivity, resilience, sensation-seeking

According to estimates by the United Nations, approximately 21 million people worldwide are using cocaine (1), but only one in six cocaine users appears to make the transition from occasional cocaine use to cocaine dependence (2). Although the likelihood of becoming dependent on cocaine is increased in people with a family history of drug/alcohol dependence (3), this risk is not reflected in contemporary categorizations of cocaine users. Recreational users are usually described as socially integrated people who use cocaine infrequently, in small amounts at social occasions, without experiencing psychological or physiological signs associated with cocaine abuse (4–6). Problem or dependent cocaine users, however, use cocaine in a more habitual manner that is associated with physical, social, and psychological problems, for which the user seeks help (4,5). Generally, these individuals satisfy the criteria for a clinical diagnosis of cocaine dependence stipulated by the American Psychiatric Association (7), but for recreational users, no such criteria are available. Whether recreational and dependent cocaine users reflect different neurobiological phenotypes or are expressing variable degrees of impairment on the same phenotype along a trajectory to dependence warrants investigation.

Preclinical evidence supports the notion that different cocaine user types can be distinguished by traits of sensation-seeking (predicting the initiation of cocaine intake) and impulsivity (predicting the development of compulsive cocaine seeking and dependence) (8). Analogously, impulsive traits and ritualistic behavior tendencies in human cocaine users have been associated with a familial risk for developing dependence (9–11) and sensation-seeking traits have been associated with a risk of initiating drug use during adolescence (12,13). We sought to illuminate the neurobiological basis of recreational cocaine use further by comparing four groups of individuals who differed with regard to two factors: familial risk for addiction and stimulant drug exposure. Specifically, we compared 27 individuals without a familial risk of dependence who had been using cocaine for an average of 8 years ($\pm$5.9 SD) but had not made the transition to dependence with a previously published sample of 1) 50 individuals who satisfied the DSM-IV criteria for dependence on stimulant drugs; 2) 50 unaffected siblings of the stimulant-dependent individuals; and 3) 52 unrelated healthy volunteers who had neither a family nor a personal history of dependence. We compared these four groups in terms of sensation-seeking traits, impulsivity, ritualistic behavior (a possible marker of compulsive traits), and brain structure.

Abnormalities in corticostriatal pathways, such as a relative reduction in prefrontal cortex gray matter and an increase in striatal volume, have been associated with impulsive and compulsive traits and have frequently been reported in stimulant-dependent individuals (14–19). First-degree relatives share with their

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Table 1. Demographic Information About the Four Groups

Demographics	Healthy Control Volunteers ($n = 52$) Mean (±SD)	Recreational Cocaine Users ($n = 27$) Mean (±SD)	Unaffected Siblings ($n = 50$) Mean (±SD)	Stimulant-Dependent Siblings ($n = 50$) Mean (±SD)	Group Comparisons		
					F, t, or χ^2	p	Post Hoc Tests[a]
Gender (% Male)	64%	52%	50%	88%	18.6	<.001	D > C, R, S
Age (Years)	32.5 (±8.9)	29.1 (±7.6)	32.9 (±8.4)	34.3 (±7.2)	2.4	.073	
Verbal Intelligence (NART)	112.6 (±8.2)	115.6 (±5.4)	109.2 (±9.1)	110.6 (±7.5)	4.1	.008	R > D
Duration of Formal Education (Years)	12.7 (±1.9)	13.4 (±1.7)	12.3 (±2.3)	11.6 (±1.7)	5.8	.001	R > D and C > D
Disposable Income (£ per Month)	629 (±911)	839 (±1208)	421 (±414)	370 (±622)	3.0	.032	R > D
Childhood Maltreatment (CTQ)[b]	17.8 (±5.5)	18.8 (±3.8)	24.3 (±10.7)	28.5 (±14.4)	12.3	<.001	D = S > R = C
Alcohol Consumption (AUDIT)	3.3 (±2.2)	5.7 (±1.5)	3.8 (±4.5)	11.1 (±11.1)	11.8	<.001	D > R = S = C
Drug-Taking Experiences (DAST-20)	.0 (±.0)	2.4 (±1.0)	.5 (±1.1)	not administered	81.5	<.001	R > S > C
Duration of Stimulant Use (Years)[c]		7.9 (±5.8)		16.1 (±6.4)	−5.5	<.001	
Age of Onset Stimulant Use (Years)[c]		20.2 (±4.8)		16.4 (±2.8)	4.4	<.001	
Age of Onset Cannabis Smoking (Years)	17.6 (±4.0) $n = 11$	17.9 (±6.8) $n = 26$	17.7 (±4.2) $n = 35$	14.5 (±3.2) $n = 50$	5.3	.002	D > R = S = C
Age of Onset Tobacco Smoking (Years)	16.0 (±2.8) $n = 8$	16.1 (±4.0) $n = 24$	14.5 (±2.0) $n = 46$	12.5 (±3.3) $n = 49$	12.2	<.001	D > R = S = C
Cigarette Consumption (Number/Day)[d]	7.1 (±5.5)	7.0 (±5.6)	5.0 (±7.8)	15.7 (±12.5)	5.2	.001	D > R = S = C

AUDIT, Alcohol Use Identification Test (cutoff score for harmful alcohol use: >8), Saunders *et al.* (24); CTQ, Childhood Trauma Questionnaire, Bernstein *et al.* (28); DAST-20, Drug Abuse Screening Test (cutoff score for harmful use: >5), Skinner (23); NART, National Adult Reading Test, Nelson (27).

[a]Abbreviations of the groups in the post hoc tests: C, control; R, recreational; S, sibling; D, dependent.

[b]Composite score of the subscales: emotional abuse, physical abuse, sexual abuse.

[c]Stimulant use includes the duration/onset of amphetamine, cocaine, and crack-cocaine use.

[d]Cigarette consumption refers to the numbers of cigarettes smoked by those individuals in the group who were smokers.

dependent family member the striatal enlargement (in the putamen) but not the gray matter deficits in the prefrontal cortex (20), indicating that the reduced prefrontal volume is not a candidate endophenotype predisposing stimulant dependence but may be a consequence of chronic stimulant abuse. If recreational cocaine users constitute a different neurobiological phenotype from dependent stimulant users or their at-risk first-degree relatives, we would expect their levels of impulsivity and obsessive-compulsive behaviors, as well as their striatal structure, to be normal. However, if recreational cocaine users exhibit a trajectory toward dependence, we would expect to identify abnormalities, specifically in the prefrontal cortex, that are typically seen in stimulant-dependent individuals, albeit to a lesser degree.

Methods and Materials

Study Sample and Procedures

We recruited 27 individuals by advertisements in the local community who fulfilled the following criteria: 1) no personal or family history of substance dependence (including alcohol but excluding nicotine); 2) repeated use of cocaine for at least 2 years without experiencing physiological or psychological symptoms of dependence, as described in the DSM-IV; and 3) no use of stimulant drugs for medical reasons. Exclusion criteria were a lifetime history of a psychiatric or neurological disorder, neurodevelopmental disorder, or a traumatic head injury. These individuals were recruited in addition to a previous sample of participants (20) consisting of 50 biological sibling pairs (within each pair, one sibling satisfied the DSM-IV text revision [DSM-IV-TR] criteria for dependence on stimulant drugs and the other had no history of drug or alcohol dependence) and 52 unrelated healthy volunteers with no personal or family history of drug/alcohol dependence. Tobacco smokers were not excluded from the study to ensure variation of smoking habits across groups.

The recreational cocaine users started using cocaine at the age of 21 years (±5.1 SD) and had used it in relatively small amounts (mean .6 g ± .3 g SD illicit drug dose) infrequently ever since. They exclusively used cocaine in powdered form in social settings with friends and never developed patterns of compulsive use, which was reflected by their low scores (mean 1.2 ± 1.6 SD) on the Obsessive-Compulsive Drug Use Scale (21). Almost all recreational cocaine users (96%) had a lifetime history of sporadic experimentation with other illicit drugs than cocaine but never fulfilled the DSM-IV-TR criteria of substance dependence or ever considered seeking treatment for drug or alcohol use. Accordingly, their scores on the Drug Abuse Screening Test (DAST-20) (22) and the Alcohol Use Identification Test (AUDIT) (23) were low (Table 1).

All drug-dependent individuals met the DSM-IV-TR criteria for stimulant dependence (94% cocaine, 6% amphetamines). The majority was recruited from treatment services (76%) and all except five were actively using stimulant drugs by nasal, oral, or intravenous routes. They started using stimulants at the age of 16 years (±2.8 SD) and had been using them in varying amounts for an average of 16 years (±6.4 SD). Their Obsessive-Compulsive Drug Use Scale scores indicated moderate levels of stimulant-related compulsivity (mean score: 23.7 ± 9.5 SD). All stimulant-dependent individuals were regularly using other substances alongside stimulants; 54% of the sample met the DSM-IV-TR criteria for dependence on opiates, 24% met the criteria for dependence on alcohol, and 8% met the criteria for dependence