RESEARCH ARTICLE

Relationship between drug use and prefrontal-associated traits

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Abstract
The prefrontal cortex plays an important role in the strategic and emotional regulation of behavior. Both cognitive and neuroimaging studies have implicated prefrontal cortex in processes of reward and addiction. Prefrontal-associated neurobehavioral traits may be measured psychometrically with the Frontal Systems Behavior Scale (FrSBe), so it was hypothesized that self-ratings on this instrument would correlate with parameters of psychoactive drug use in a community sample. Modest but significant correlations were found for various parameters of tobacco use, even after controlling for demographic variables. Significant differences were noted in the mean scores when non-users were compared with users of cannabis, major stimulants (e.g. cocaine, amphetamine), and dissociative hallucinogens (e.g. phencyclidine, ketamine) and polysubstance use, particularly with the Disinhibition subscale. Smokers rated greater dysfunction than non-smokers on all three subscales, with ex-smokers showing intermediate ratings between the two. Polysubstance users showed greater dysfunction on the Disinhibition subscale compared to non-polysubstance users. In summary, this study further supports a role a relationship between prefrontal dysfunction and drug use in normal individuals, convergently with other methodologies for studying addiction.

Introduction
The human prefrontal cortex plays a pivotal role in directing behavior. It has reciprocal connections with a number of other brain structures, taking in a variety of influences to guide behavior at an executive level. Inputs from structures mediating higher order sensory perception, emotion, memory and other forms of cognition are integrated in the prefrontal cortex to yield behavior that is strategically guided and goal-oriented rather than reactive to immediate environmental demands. Since drug addiction involves maladaptive behaviors and coping strategies, prefrontal cortex is a logical structure to research in this context.

There is mounting anatomical and physiological evidence that implicates prefrontal dysfunction in various forms of addiction. Human polysubstance abusers have a smaller volume of prefrontal gray matter than controls. Similarly, cocaine abusers have decreased gray matter in ventromedial orbitofrontal, anterior cingulate and anteroventral insular cortex. Concordantly, functional neuroimaging studies show alterations in prefrontal activity in association with addiction. Long-term opioid addiction is associated with changes in regional cerebral blood flow.
(rCBF) to multiple brain areas, but particularly in prefrontal cortex. People with either opioid or nicotine addiction show altered patterns of rCBF in response to monetary and non-monetary rewards. Specifically, alterations are evident in targets of mesotelencephalic dopamine projections, including orbitofrontal cortex.

Support for a prefrontal role in addiction also comes from studies of people with traumatic brain injury (TBI). TBI causes cognitive, emotional and behavioral deficits related largely to prefrontal dysfunction. Longitudinal studies of people with TBI suggest an increase in substance abuse after brain injury. One study has shown that 20% of individuals who abstained from alcohol or were light drinkers before their injury progressed to high volume consumption after their injury. Another longitudinal study similarly showed that 15% of patients developed alcohol dependence problems within 2 years of their brain injury. These changes could indirectly be reactions to psychosocial stressors resulting from TBI sequelae, as well as due directly to prefrontal dysfunction and resultant changes in emotional regulation and impulse control.

Several lines of evidence implicate orbitofrontal cortex in various processes of reward and punishment. Orbitofrontal activity represents the specific motivational significance of rewards. It represents the incentive value of both primary rewards and conditioned reward associations, as well as the anticipation and delivery of rewards. Humans with orbitofrontal damage show impairments in both the learning and reversal of reward associations. There appears to be anatomical segregation of reward and punishment representations within orbitofrontal cortex: lateral regions represent punishing outcomes, while medial regions represent rewarding outcomes. Accordingly, orbitofrontal cortex has especially been implicated in addiction. For example, increased rCBF in orbitofrontal cortex correlates with self-reports of ‘urge to use’ among opiate addicts. Similarly, activation of orbitofrontal cortex occurs in conjunction with cocaine cravings induced by the psychostimulant methylphenidate.

Psychometric evidence has complemented the neuroimaging and neurophysiological data to implicate orbitofrontal cortex in addiction. Denial of addiction has been associated with performance on prefrontal-associated measures of executive functions. Other studies have more specifically targeted orbitofrontal cortex. For example, parameters of tobacco smoking (smoking status and packs smoked per day) correlated with impairment on putative measures of orbitofrontal dysfunction (go/no-go, antisaccades, delayed alternation, and impulsivity self-ratings) in tobacco smokers. Both substance abusers and pathological gamblers show evidence of impairment in the Iowa Gambling Task, which is sensitive to ventromedial prefrontal dysfunction. Differential patterns of orbitofrontal activation were observed between substance abusers and controls while performing the Stroop task, a measure of response inhibition. Anti-saccades, another response inhibition task, was impaired in abstinent tobacco smokers, while other prefrontal-sensitive measures (digit span backwards, verbal fluency) were unaffected, suggesting that certain prefrontal areas may be more relevant to addiction than others.

The Frontal Systems Behavior Scale (FrSBe) is an instrument that measures neurobehavioral traits associated with regions of the prefrontal cortex. Items cover a variety of traits, including ones in social, behavioral, emotional and cognitive domains. Subjects rate themselves on 46 items, which yield scores for three scales of dysfunction: apathy (A), disinhibition (D) and executive dysfunction (E). Based on the neurobehavioral syndromes produced by prefrontal lesions, these scales were designed to measure neurobehavioral syndromes associated with medial prefrontal, orbitofrontal and dorsolateral prefrontal cortex, respectively.

Given the evidence for prefrontal dysfunction in addiction and the sensitivity of the FrSBe to prefrontal functioning, it was hypothesized that subjects’ self-ratings on the FrSBe would correlate with parameters of psychoactive drug use. More specifically, it was proposed that the D scale would show particular relevance to the use of psychoactive drugs, reflecting the important role of orbitofrontal cortex in reinforced behaviors.

Methods

Subjects
Subjects (n = 90) were a convenience sample of community-dwelling adults who were recruited by student volunteer research assistants. No financial compensation was given for participation. There were no specific selection criteria given to the research assistants other than to find healthy adults of either sex. The study was
approved by an institutional review board and all subjects read and signed an appropriate informed consent, in accordance with the Declaration of Helsinki. The subjects (54 females, 36 males) ranged in age from 17 to 56 years of age (mean 26.92 ± 9.55 years) and had a mean of 13.87 ± 1.88 years of education.

**Frontal Systems Behavior Scale (FrSBe)**
An adaptation of the FrSBe was used to measure prefrontal-associated traits. The original form asks for pre- and post-injury ratings from the subject, but since this study was conducted in a community sample, subjects were asked for only one overall rating for themselves. Reliability studies of the FrSBe have shown high intrascale reliability in normal and clinical samples.²⁷ Factor analytic data have supported the validity of these scales. The normative data indicate that all scales of the FrSBe have been noted to vary with age, sex, and level of education.

The FrSBe was designed for neurological patients, with pre-illness/injury and post-illness/injury ratings taken from both the patient and family members or caretakers. A modified version was used for this study because pre-/post-illness ratings would not apply to a normal population. Rather, long-standing neurobehavioral traits are of interest for this study.

Scores were computed for the A, D and E scales. The A scale focuses on the initiation and persistence behaviors (e.g. ‘I sit around doing nothing’ and ‘I start things but fail to finish them, “peter out”’). The D scale items address behavioral self-regulation (e.g. ‘I do things impulsively’ and ‘I do risky things just for the heck of it’), while the E items focus on mental flexibility and sequencing (e.g. ‘I repeat certain actions or get stuck on certain ideas’ and ‘I use strategies to remember important things’) The Likert-scale scoring is arranged to produce a higher score with greater degrees of impairment.

**Drug use questionnaire**
The informed consent form was detached from the actual FrSBe and drug use questionnaire forms to ensure anonymity. Further, subjects were instructed to only provide their demographic information, and to seal their form (separate from the informed consent) in an envelope to ensure their confidentiality and privacy, and to encourage honesty in responses. Regarding tobacco use, subjects were asked to supply the number of packs of cigarettes per day currently smoked, the maximum packs per day they ever smoked, the number of cigars smoked per week and how many attempts they made to quit. From data provided, the proportion of their life smoked (years smoking/age) and pack-years were calculated. The user status (user vs. non-user) and frequency of use (number of days using the drug in an average month) were obtained for cannabis (marijuana, hashish), opioids (e.g. heroin, morphine, oxycodone), major stimulants (e.g. cocaine, crack, methamphetamine), ecstasy (MDMA) or dissociative hallucinogens (NMDA antagonists such as PCP, ketamine or dextromethorphan). Those reporting habitual use of more than one psychoactive drug, other than tobacco, were counted as polysubstance users. Those reporting use of one or no psychoactive drugs, other than tobacco, were classified as non-polysubstance users.

**Results**
Due to the relevance of demographic factors to both FrSBe scores and drug use patterns, two-tailed partial correlations were performed between the three FrSBe subscales and parameters of tobacco and drug use. Table 1 shows positive correlations between all parameters of tobacco use and several FrSBe scales. The D scale is the consistently correlates with all parameters of tobacco use. However, none of the correlations between FrSBe scales and frequency of use for cannabis, opioids, stimulants, ecstasy or dissociative hallucinogens reached significance after controlling for demographic variables.

In addition to determining a relationship between drug use frequency and FrSBe scores, comparisons were made for each drug to determine whether users differed from non-users. For each non-tobacco drug independent t-tests were performed, comparing non-users vs. users (Table 2). Mean scores for non-users were uniformly lower than those of users in each category, as predicted. Significant differences were noted on the D and/or total score for cannabis, stimulants, dissociative hallucinogens and polysubstance use (Fig. 1).

Regarding tobacco, scores on the FrSBe scales were compared between current smo-
Non-smokers (i.e. people who have never smoked tobacco) and ex-smokers (i.e. people who have smoked tobacco but do not currently). Current smokers ($n=26$) had mean scores of 39.3 (A), 37.7 (D), 40.1 (E) and 117.1 (total). Ex-smokers ($n=16$) had mean scores of 39.2 (A), 35.0 (D), 35.1 (E) and 109.3 (total). Non-smokers ($n=48$) had scores...
of 34.2 (A), 29.6 (D), 33.0 (E) and 96.8 (total). Thus, a consistent pattern of scores for all three subscales was seen, with non-smokers having the lowest scores, ex-smokers having intermediate scores and current smokers having the highest scores, indicating the greatest level of dysfunction. One way analyses of variance revealed significant differences among these three groups on all three subscales: A [$F(2, 87) = 4.51, p = 0.01$], D [$F(2,87) = 10.79$, n.s.], E [$F(2,87) = 4.51, p = 0.01$].

Figure 1. Mean FrSBe subscale scores according to tobacco use (see Results for significant differences).

Figure 2. Mean FrSBe subscale scores in polysubstance users vs. non-polysubstance users. Significant differences are present on the D scale ($p = 0.01$) and total score ($p = 0.05$, not shown).
Independent t-test comparisons revealed that current- and ex-smokers differed on the E scale $t(40) = -2.26$, $p = 0.03$. Ex- and non-smokers differed on the A $t(63) = -2.19$, $p = 0.03$, D $t(62) = -2.57$, $p = 0.01$, and total $t(62) = -2.46$, $p = 0.02$ scores. Non- and current smokers differed significantly on all scales: A $t(72) = -2.58$, $p = 0.012$, D $t(72) = -4.44$, $p < 0.001$, E $t(72) = -4.26$, $p < 0.001$ and total $t(62) = -4.60$, $p < 0.001$ scores.

The mean score of the FrSBe scales were compared between polysubstance users and non-polysubstance users. Non-polysubstance users ($n = 77$) had mean scores of 36.3 (A), 32.0 (D), 34.9 (E) and 103.2 (total), while polysubstance users ($n = 13$) had higher mean scores of 37.8 (A), 38.4 (D), 38.5 (E) and 114.7 (total). Independent t-tests revealed significant a difference on the D scale $t(88) = -2.70$, $p = 0.008$ and a marginally significant difference on the total score $t(88) = -1.95$, $p = 0.054$ (see Fig. 2).

Discussion

The results indicate that prefrontal-associated personality traits relate to parameters of psychoactive drug use. While all three subscales of the FrSBe correlate with current and maximum cigarette smoking, the remainder of tobacco use parameters suggest a predominant relationship with the D subscale, even after adjustment for demographic variables (age, sex, and education). The correlations between frequency of use and FrSBe subscales fell below significance, but this may be due to the size of this sample and the small number of respondents reporting use of illegal drugs. However, comparisons of users vs. non-users for each illegal drug indicated that non-users had consistently lower scores than users (indicating greater impairment in users), reaching significance for cannabis, stimulants, dissociative hallucinogens and polysubstance use. The D scale was consistently the most relevant of the three subscales in all analyses.

Further, a comparison of means between polysubstance users vs. non-polysubstance users suggested that these two groups differed significantly by their D subscale results. This difference was considerable, with polysubstance users scoring nearly a standard deviation worse than non-polysubstance users. This latter finding is particularly interesting in light of the findings of Liu and colleagues suggesting smaller prefrontal volume in polysubstance users. The relevance of the D scale to parameters of psychoactive drug use support the role of orbitofrontal systems in drug use and addiction. A tendency to use psychoactive drugs related to a greater tendency to endorse items that characterize orbitofrontal function in this study. This is consistent with neuroimaging and neuropsychological studies that implicate orbitofrontal dysfunction in drug abuse and the role orbitofrontal cortex plays in reward and reinforcement in general. The behavioral syndrome produced by orbitofrontal damage (altered personality and social conduct, verbal and behavioral disinhibition, jocularity, lack of concern) is explainable largely by an underlying change in responsiveness to reward contingencies.

Of course, this study cannot definitively localize the drug abuse-related dysfunction to orbitofrontal cortex, but rather suggests involvement of interrelated neuroanatomical systems. Processing of reward information is not limited to orbitofrontal cortex, but rather involves a circuit including medial and orbitofrontal cortex, the striatum and nucleus accumbens, ventral pallidum and mediodorsal thalamus. Also incorporated in this circuit are inputs from limbic structures such as the amygdala and brainstem nuclei, such as the ventral segmental nucleus. None the less, the constellation of neuro-behavioral traits listed in these scales, in toto, best relate to function the prefrontal–striatal–thalamic circuits.

Prefrontal dysfunction are not necessarily be limited to orbitofrontal regions. Correlations also were found between current and maximum cigarette use and differences were found between non-smoker, ex-smoker and current smoker populations across all three subscales, suggesting more widespread prefrontal impairment. While orbitofrontal regions are is not the only prefrontal region related to drug use, it may play a more important role in the motivational and impulse control aspects of the condition. As nicotine has cognitive enhancing effects, higher tobacco use in association with scores in all three FrSBe scales may represent an attempt to ‘self-medicate’ prefrontal-based cognitive dysfunction. Involvement of medial prefrontal cortex, as indicated by responses on the A scale, did not correspond to drug use in most of the indices of drug use measured. However, medial prefrontal
cortex has been implicated in reward processes, including both drug and monetary reward.\textsuperscript{32–34} It is possible that the A scale is not sensitive enough to medial prefrontal-associated traits in a normal population, but this scale is highly consistent as identified by factor analysis.\textsuperscript{27} Medial prefrontal activation often indicates initiation and behavioral drive within a situational context, so it is possible, alternatively, that the overall trait-oriented nature of this measure is not able to capture the context-sensitive activation that occurs in medial prefrontal cortex.

The correlational nature of this study means that definitive statements about causal relationships between prefrontal cortex and drug use cannot be made, which is also true with many neuroimaging studies of addiction. It is possible that psychoactive drug use directly (e.g. pharmacologically) or indirectly (e.g. behaviorally or emotionally) alters functioning in prefrontal structures. In support of this, metabolic mapping studies in animal models of addiction show altered patterns of activity within prefrontal cortex corresponding to the duration of drug exposure.\textsuperscript{35} On the other hand, the lack of impulse control and self-regulation seen in people with diminished prefrontal function could easily put one at greater risk for substance abuse. These two possibilities are not mutually exclusive, but rather, may have simultaneous and reciprocal effects on behavior.

The reasons for prefrontal dysfunction in substance use and abuse populations remain unclear. Aside from those with frank brain injuries, it is possible that subtle and insidious insults to prefrontal cortex may alter its function and thus predispose individuals to more impulsive coping strategies. In addition to subtle pathology, there are normal variations in the morphological development of neuroanatomical structures across individuals and across the life span that could also contribute to the development of this behavior.\textsuperscript{36}

The differences observed in FrSBe subscales between non-smokers, ex-smokers and current smokers have potential implications for treatment and rehabilitation. Current smokers showed the greatest degree of prefrontal dysfunction, ex-smokers showed an intermediate degree and non-smokers showed the least prefrontal dysfunction. Similarly, greater D scores related to the number of attempts needed to quit smoking tobacco. Although it is uncertain whether this pattern is cause or effect, it does suggest that altered prefrontal function may accompany the quitting and recovery process. Thus, addiction treatment programs may benefit from treatments that incorporate executive strategies.

This study is limited by its sample size. As the sample was taken from a normal community population, relatively few respondents reported use of illicit drugs. It would be worthwhile to replicate these results in a larger population, or in a more targeted population such as a substance abuse treatment sample. Another potential limitation of this study is the self-report nature of the FrSBe, which may underestimate the relationship between drug abuse and prefrontal-associated traits. People with prefrontal injuries, particularly orbitofrontal insults, are notorious for underestimating their own deficits and shortcomings, due to an impairment of self-monitoring and self-awareness.\textsuperscript{37} However, rather than being all-or-none phenomena, self-awareness and self-monitoring are probably graded phenomena.\textsuperscript{38} If so, those with greater dysfunction may progressively underestimate their own characteristics, which would restrict the reporting of traits most relevant to drug abuse. Despite this possibility, modest correlations between D and drug use were still evident.

In conclusion, thus this study confirms the role of prefrontal cortex in addiction, in concordance with previous studies employing neuroimaging and cognitive methods. Although psychometric in nature, it suggests that traits associated with various regions of prefrontal functioning bear a reliable relationship to patterns of drug use, and adds a new form of methodology with which to studying such disorders.

\textbf{References}


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