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# Influence of dorsolateral prefrontal cortex and ventral striatum on risk avoidance in addiction: A mediation analysis

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ABSTRACT

*Background:* Alterations in frontal and striatal function are hypothesized to underlie risky decision making in drug users, but how these regions interact to affect behavior is incompletely understood. We used mediation analysis to investigate how prefrontal cortex and ventral striatum together influence risk avoidance in abstinent drug users.
*Method:* Thirty-seven abstinent substance-dependent individuals (SDI) and 43 controls underwent fMRI while performing a decision-making task involving risk and reward. Analyses of *a priori* regions-of-interest tested whether activity in dorsolateral prefrontal cortex (DLPFC) and ventral striatum (VST) explained group differences in risk avoidance. Whole-brain analysis was conducted to identify brain regions influencing the negative VST-risk avoidance relationship.
*Results:* Right DLPFC (RDLPFC) positively mediated the group-risk avoidance relationship ($p < 0.05$); RDLPFC activity was higher in SDI and predicted higher risk avoidance across groups, controlling for SDI vs. controls. Conversely, VST activity negatively influenced risk avoidance ($p < 0.05$); it was higher in SDI, and predicted lower risk avoidance. Whole-brain analysis revealed that, across group, RDLPFC and left temporal-parietal junction positively ($p \leq 0.001$) while right thalamus and left middle frontal gyrus negatively ($p < 0.005$) mediated the VST activity-risk avoidance relationship.
*Conclusion:* RDLPFC activity mediated less risky decision making while VST mediated more risky decision making across drug users and controls. These results suggest a dual pathway underlying decision making, which, if imbalanced, may adversely influence choices involving risk. Modeling contributions of multiple brain systems to behavior through mediation analysis could lead to a better understanding of mechanisms of behavior and suggest neuromodulatory treatments for addiction.


## 1. Introduction

Risky decision making is a hallmark of substance use disorders. Individuals who abuse drugs also display impaired risk avoidance (i.e., exhibit risk-seeking behavior) on laboratory decision-making tasks that involve reward, punishment, and uncertainty (Bechara and Damasio, 2002; Grant et al., 2000). The neural circuitry of decision making is complex, but a large body of evidence supports the roles of prefrontal cortex, striatum, and limbic structures. The dorsolateral prefrontal cortex (DLPFC) is involved in cognitive control through choice selection, interference monitoring, and pre-potent response inhibition (Blasi et al., 2006). The right DLPFC (RDLPFC), in particular, is involved in decisions requiring response inhibition (Aron, 2011; Ernst et al., 2002; Nee et al., 2007) or when choices are ambiguous (Krain et al., 2006; Rodrigo et al., 2014). It has been suggested that RDLPFC causally inhibits risky decision making as previous work has shown that stimulation of RDLPFC increased risk avoidance (Fecteau et al., 2007) and reduced drug cravings in addicts (Camprodon et al., 2007; Fregni et al., 2008; Mishra et al., 2010) while suppression of RDLPFC activity was associated with riskier decision making (Knoch et al., 2006).

The striatum is also important for decision making under conditions of uncertainty and risk (Ernst et al., 2004; Matthews et al., 2004; Tom et al., 2007) and dopamine regulation in the striatum is a critical mechanism underlying this process. Higher dopamine D1 receptor mRNA expression in the ventral striatum (VST) has been associated with greater risk-taking in rats (Simon et al., 2011). In

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humans, VST activity is positively associated with decisions made under uncertainty (Linnet et al., 2011; Li et al., 2010) and risk (Matthews et al., 2004) and, in particular, with loss aversion during risky decisions (Tom et al., 2007).

Numerous lines of evidence indicate that frontal and striatal function is altered in drug users which may mediate increases in risky decision making. Decision-related activity in DLPFC is attenuated in drug users compared to healthy controls, suggesting impaired inhibitory cognitive control (Ersche et al., 2005; Paulus et al., 2002). Increased striatal activity has been found in substance-dependent individuals compared to controls during reward anticipation (Nestor et al., 2010; Yamamoto et al., 2014) or notification of reward outcome (Bjork et al., 2008; Jia et al., 2011; but see Hyatt et al., 2012) suggesting heightened striatal response during decision making is related to increased reward sensitivity in drug users.

Apart from possible independent contributions to decision-making deficits in drug users, striatum and DLPFC interact in ways that are likely important for drug related behavior. There is a close anatomical relationship between sectors of prefrontal cortex (e.g., ventral medial, dorsolateral, and orbital frontal cortex) and striatum (Haber and Knutson, 2010) and these regions appear to influence each other functionally (Staudinger et al., 2011). Lower dopamine D2 receptor binding in the striatum has been shown to correlate with lower frontal metabolism in stimulant abusers (Volkow et al., 2001, 1993) and is associated with craving (Volkow et al., 2006). In addition, impaired reward learning in alcoholic subjects has been associated with abnormal functional connectivity between VST and RDLPFC (Park et al., 2010). These previous studies reporting correlations between fronto–striatal function and behavior suggest that striatal dysregulation influences frontal function, manifesting as pathological motivation in substance dependent individuals to procure drugs despite known risks. However, the exact nature of the interactions between striatal and frontal activity, and between fMRI activity and risky behavior in substance dependent populations, remains incompletely understood.

Mediation is a statistical method that can inform our understanding of how brain regions interact to result in behavior. Mediation tests whether the relationship between an independent and a dependent variable can be explained by a third variable (Fig. 1) and has been used extensively in psychology research to test relational pathways among correlated variables (Baron and Kenny, 1986; MacKinnon et al., 2007). Though it has often been used to infer causality from observational data, which has been controversial (Green et al., 2010), it need not imply causal effects to provide useful models of statistical multivariate relationships. Applied to neuroimaging, studies have shown that the relationship between DLPFC activity and cognitive control of tobacco craving was mediated by decreased VST activity (Kober et al., 2010). In other words, the mediation model suggests that increases in DLPFC activity are associated with control of craving through reductions in VST activity. We use mediation analysis to investigate how DLPFC and VST activity during decision-making influence risk avoidance in long-term abstinent substance dependent individuals and controls. Because of its known contribution to addiction, impulsivity was tested as a trait mediator of risk avoidance. To our knowledge, the influence of regional and whole brain activity on risk avoidance has not been performed using these methods in drug dependence.

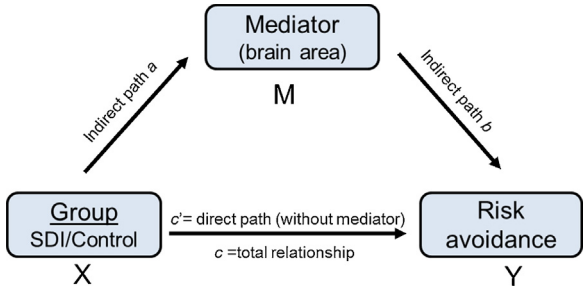


**Fig. 1.** Single-level mediation model. Path *a* represents the relationship of X to M. Path *b* represents the relationship of M to Y while controlling for X, *c'* represents the relationship of X to Y controlling for M, and *c* represents the indirect relationship of X to Y (not adjusted for any other factors).

## 2. Methods

In a prior study, we reported increased striatal activity and impaired risk avoidance in substance dependent individuals (SDI) compared to controls and a negative VST-risk avoidance relationship. The data collection has already been described and is briefly repeated here for ease of understanding. Notably, this study uses a completely different analysis technique to determine if DLPFC and VST activity have different mediation effects on increased risky behavior in long-term abstinent SDI.

### 2.1. Subjects

The sample population included 80 subjects: 37 SDI (18 M/19F) and 43 controls (23 M/20F). SDI with lifetime DSM-IV stimulant dependence were recruited from a residential treatment program at the University of Colorado Denver Addiction Research and Treatment Service (ARTS). SDI were abstinent from drugs and alcohol an average of 14 months (range = 2–65, standard deviation = 14.33). Most SDI were referred to ARTS from the criminal justice system where they were abstinent from drugs, alcohol, and tobacco. SDI were recruited to this study 2–4 months after admission to ARTS, where abstinence from drugs, alcohol and tobacco is monitored by direct supervision and random drug screening. These factors contributed to the long abstinence duration. Controls were recruited from the community and excluded if they met DSM-IV criteria for lifetime abuse or dependence on drugs or alcohol. Exclusions for all subjects included neurological illness, schizophrenia, bipolar disorder, major depression within the last 2 months, head trauma resulting in >15 min loss of consciousness, or IQ ≤ 80. All subjects provided written informed consent approved by the Colorado Multiple Institutional Review Board.

### 2.2. Behavioral measures

Screening assessment: All subjects received structured interviews and behavioral measures administered by trained lay professionals. Drug dependence was assessed using the computerized Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM; Cottler et al., 1989). DSM-IV dependence diagnoses are listed in Table 1. The Computerized Diagnostic Interview Schedule–Version IV (C-DIS-IV) was administered to exclude schizophrenia, bipolar disorder, and current major depression (within 2 months). IQ was assessed with matrix and verbal reasoning Wechsler Abbreviated Scale of Intelligence subtests (WASI; Psychological Corporation, 1999). Impulsivity was measured using the Barratt impulsiveness scale (BIS-11), a 30-item self-report questionnaire (Patton et al., 1995).

Decision-making test of risk avoidance: Subjects played a modified version of the computerized Iowa Gambling Task (IGT) during fMRI scanning. This decision-making task is sensitive to differences in risk avoidance (Thompson et al., 2012) and loss sensitivity (Tanabe et al., 2013) in SDI compared to healthy controls. Subjects were presented four decks of cards and instructed to earn as much pretend money as possible by choosing to either play or pass on a given deck. A "Play" response resulted in a single positive or negative monetary value, along with the running total. "Pass" response resulted in no change. To perform well, subjects had to learn to "Pass" on the two bad decks that resulted in net loss and "Play" on the two good decks that resulted in net gain over time. Risk avoidance was defined as number of

**Table 1**
Substance dependence diagnoses in SDI ($n = 37$).

| Individual substance | Number with diagnosis | Percent with diagnosis |
|---|---|---|
| Stimulants Total | 37 | 100 |
| Stimulants (Cocaine) | 21 | 57 |
| Stimulants (Amphetamines) | 31 | 84 |
| Alcohol | 27 | 73 |
| Tobacco | 26 | 70 |
| Cannabis | 15 | 41 |
| Opioids | 10 | 27 |
| **Combination of dependence diagnoses** | | |
| Stimulants only | 2 | 5 |
| Stimulants plus alcohol and/or tobacco | 32 | 86 |
| Stimulants plus cannabis | 15 | 41 |
| Stimulants plus opioids | 10 | 27 |