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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 ($p = 0.001$) while right

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Contributors

Yamamoto and Tanabe contributed to design, analysis, data interpretation and manuscript preparation. Woo and Wager contributed to analysis, data interpretation and manuscript preparation. Regner contributed to data interpretation and manuscript preparation. All authors contributed to and have approved the final manuscript.

Conflict of Interest

The authors report no potential conflicts of interest.

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.

Keywords

Substance dependence; Mediation; Ventral striatum (VST); Dorsolateral prefrontal cortex (DLPFC); Decision-making; Impulsivity

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 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 (Figure 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.

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 (18M/19F) and 43 controls (23M/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 minutes loss of consciousness, or IQ < 80. All subjects provided written informed consent approved by the Colorado Multiple Institutional Review Board.

2.2 Behavioral measures

2.2.1. 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 2. 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).

2.2.2. 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 passes on bad decks. For each trial the card was presented for 2 seconds, during which time the subject responded. Outcomes were shown for 4 seconds. There were 50 trials of each deck, 200 trials total, plus 50 fixation crosses presented in pseudorandom order. Total task scan time was 26 minutes (2 13 minute runs).

2.3. MRI acquisition, pre-processing, and fMRI data analysis

Functional MR images were acquired on a 3T scanner with an 8-channel head coil using GRE-EPI sequence (TR 2s, TE 30 ms, matrix 64×64 , FOV 220 mm^2 , $3.4 \times 3.4 \text{ mm}^2$, slice thickness 3 mm, gap 1 mm). Data were analyzed with Statistical Parametric Mapping (SPM8). Pre-processing included motion correction, normalization to MNI space, and spatial smoothing with 6 mm FWHM Gaussian kernel. Motion exceeding 1-voxel was excluded from further analysis. First level analysis consisted of filtering low frequency noise, correcting for temporal autocorrelation, and convolving the stimulus function with a canonical hemodynamic response function. Nine conditions were modeled: decision and outcome for each of the four decks plus fixation. The contrast of interest was decision>fixation.

2.4. Region-of-interest (ROI) definition

VST was manually traced in MNI standard space using the anatomical landmarks from Mawlawi et al. (2001). The DLPFC ROI was based upon coordinates obtained from the metaanalysis framework Neurosynth (<http://neurosynth.org>; Yarkoni et al., 2011), which identifies neuroimaging studies reporting significant activity associated with a given feature, in this case, “decision-making”. Coordinates are given a z-score based on representation over multiple studies. Among 66 studies showing significant activity associated with “decision-making” (downloaded on 07-22-2014), the coordinate with the highest z-score (5.47) localized to the RDLPFC (MNI: 34, 32, 38). This coordinate was used to construct a 6 mm diameter sphere representing a decision-making node. Although evidence points preferentially to the RDLPFC as important for cognitive control of impulses in risky decision-making, the LDLPFC was also examined. LDLPFC was constructed to mirror the RDLPFC ROI (MNI: -34, 32, 38). Two ROIs were used as controls: primary sensory cortex (PSC; Brodmann area 1) because PSC is not known to be involved in risk avoidance; and dorsal striatum (DST) to assure that mediation results were not simply due to the group differences in VST and DST activity seen in our prior paper. DST was manually traced in MNI standard space according to anatomical landmarks from Mawlawi et al. (2001). For each ROI, fMRI signal during decision-making was extracted using the Marsbar toolbox.

2.5. Statistical analyses

2.5.1. Single level mediation—To test whether RDLPFC and VST activity mediated group differences in risk avoidance, analysis was performed using a mediation toolbox (<http://wagerlab.colorado.edu/tools>; Wager et al., 2008). A standard mediation model was used, with a bootstrap test (10,000 iterations) for statistical significance of the mediators (Efron and Tibshirani, 1994; Shrout and Bolger, 2002). Mediation quantifies the degree in which a relationship between two variables, X and Y, can be explained by another variable, M (Figure 1). We defined X as group (SDI or control), Y as risk avoidance and M as RDLPFC or VST activity during decision-making. When testing for two simultaneous mediators, the significance of each one is assessed while controlling for effects of the other. For example, the significance of paths a , b , and $a*b$ are assessed controlling for VST activity, and the significance of paths a_2 , b_2 , and a_2*b_2 are assessed controlling for RDLPFC activity (Figure 2). Paths a and a_2 measure the association between group (SDI vs.

control) and the mediator (RDLPFC or VST activity). Paths b and b_2 measure the association between mediator and risk avoidance while controlling for group. Controlling for group in paths b and b_2 tests whether RDLPFC or VST activity predict variations in risk avoidance conditionally independent of group. Path c measures the total relationship between group and risk avoidance including direct and indirect effects. Path c' measures the direct effect of relationship between group and risk avoidance, controlling for RDLPFC and VST activity. Finally, products $a*b$ and a_2*b_2 separately test the significance of the mediators (Wager et al., 2009, 2008).

2.5.2. Whole-brain mediation analyses—Mediation Effect Parametric Mapping (MEPM; Wager et al., 2008) is a form of structural equation modeling that makes it possible to map multiple brain mediators of group differences in behavior or of a brain/behavior relationship. MEPM was used to explore brain regions not hypothesized to be mediators *a priori*. Here, group was variable X, risk avoidance was variable Y, and voxels across the brain were serially tested as mediation variable M in order to form a brain map of mediation effects. To investigate mediators of the relationship between VST activity and risk avoidance across group, another MEPM test was conducted, in which VST was variable X, risk avoidance was variable Y, and voxels across the brain were tested as candidate mediators (M). Bootstrap tests (1,000 iterations) for statistical significance were performed for each voxel. For the exploratory whole-brain analyses, voxels were considered to be significant mediators if statistical significance reached $p < 0.005$, two-tailed, uncorrected, and at least five contiguous voxels in paths a , b , and $a*b$.

2.5.3. Impulsivity and risk avoidance—Impulsivity has been strongly correlated with addiction and poor decision-making, thus, impulsivity measured by BIS-11 was compared between SDI and controls using analysis of covariance (ANCOVA) controlling for education. Impulsivity was correlated with risk avoidance using Pearson's R in SPSS. To test if impulsivity mediated group difference in risk avoidance, single level mediation was performed: group was variable X, risk avoidance was variable Y, and impulsivity was variable M.

2.5.4. Drug symptom count and brain activity—SDI were recruited for stimulant-dependence, however most exhibited comorbid dependence with other drugs (Table 2). Drug use severity was measured by DSM-IV symptom counts (11 for each drug). Total symptoms were calculated for stimulants alone and all drugs combined, then correlated with activity within each ROI.

3. RESULTS

3.1. Demographics

SDI and controls were similar in age (34.4 ± 8.4 vs. 31.6 ± 9.3 years, $p = 0.17$) and gender (18M/19F vs. 23M/20F, $\chi^2 = 0.19$, $p = 0.67$). SDI had fewer years of education than controls (12.8 ± 1.4 vs. 14.7 ± 1.5 , $p < 0.001$).

3.2. Drug characteristics

Please see Table 2.

3.3. Single-level mediation

When RDLPFC and VST were entered simultaneously as candidate mediators, there were opposing, significant influences on the relationship between group (SDI vs. control) and risk avoidance (Figure 2). The total relationship between group and risk avoidance was highly significant, (path *c*, coefficient=-7.7, $z=-3.79$, $p<0.001$), indicating reduced risk avoidance in SDI. SDI showed greater RDLPFC activity (path *a*, coefficient=0.17, $z=1.66$, $p<0.05$). Greater RDLPFC activity predicted increased risk avoidance controlling for group and VST activity (path *b*, coefficient=6.25, $z=2.5$, $p<0.01$). The mediation effect was significant ($a*b$, coefficient=1.07, $z=1.77$, $p<0.05$). VST activity, by contrast, was associated with decreased risk avoidance. VST activity was higher in SDI (path a_2 , coefficient=0.42, $z=3.81$, $p<0.001$), predicted reduced risk avoidance (path b_2 , coefficient=-5.32, $z=-2.1$, $p<0.05$) and was a significant mediator (a_2*b_2 , coefficient=-2.26, $z=-2.09$, $p<0.05$). Thus, both RDLPFC and VST activity were higher in SDI, but whereas VST reduced risk-avoidant behavior, RDLPFC acted as a suppressor variable (MacKinnon et al., 2000) predicting enhanced risk-avoidance. There was no mediating effect of RDLPFC on group differences in risk avoidance. The control regions, PSC and DST, did not demonstrate any mediating effects separately or combined.

3.4. Whole brain mediation effect parametric mapping (MEPM)

Whole brain MEPM found no regions mediating between-group differences in risk avoidance. Across group, MEPM revealed positive mediation in RDLPFC and left temporoparietal junction and negative mediation in the right thalamus and left middle frontal gyrus (Figure 3, table 1) of the VST-risk avoidance relationship.

3.5. Impulsivity and risk avoidance: Group effects and mediation

Impulsivity was greater in SDI than controls (71.05 ± 12.0 vs. 56.49 ± 7.58 ; $F[1,78]=18.92$, $p<0.001$; figure 4a). Across group, impulsivity negatively correlated with risk avoidance ($r=-0.435$, $p<0.001$; figure 4b). Impulsivity mediated group differences in risk avoidance (figure 4c). The total relationship between group and risk avoidance was highly significant (path *c*, coefficient=-7.67, $z=-3.75$, $p<0.001$), indicating SDI displayed reduced risk avoidance. Impulsivity was greater in SDI (path *a*, coefficient=7.30, $z=3.61$, $p<0.001$), predicted reduced risk avoidance (path *b*, coefficient=-0.51, $z=-3.19$, $p<0.005$) and was a significant mediator ($a*b$, coefficient=-3.79, $z=-3.21$, $p<0.005$). Impulsivity was a full mediator, meaning that group differences in risk avoidance were no longer significant after controlling for impulsivity (path c' , coefficient=-3.88, $z=-1.42$, $p=0.15$).

3.6 Drug symptom count and brain activity

Neither stimulant symptom count nor total symptom count correlated with regional brain activity.

4. DISCUSSION

The current study sought to determine how frontal and striatal brain activity influences risk avoidance in long-term abstinent substance dependent individuals (SDI). Mediation analysis revealed opposing influences of right dorsolateral prefrontal cortex (RDLPFC) and ventral striatal (VST) activity on group differences in decision-making. RDLPFC acted as a positive mediator associated with improved risk avoidance while VST was a negative mediator associated with decreased risk avoidance. The findings are consistent with the proposed role of DLPFC in response inhibition (Blasi et al., 2006). A recent study on self-control showed that DLPFC was activated during successful response inhibition that involved foregoing an immediate smaller reward in favor of a delayed larger reward (Crockett et al., 2013). DLPFC is also involved in reward valuation and goal-directed decision-making, processes that play a role in mediating group differences in risk avoidance (Fecteau et al., 2007; Hare et al., 2009; Mohr et al., 2010). While RDLPFC appears to be involved in impulsive choice inhibition during decision-making (Ersche et al., 2005; Schonberg et al., 2012) the left DLPFC has been implicated in deliberative and inter-temporal cognitive processing (Hayashi et al., 2013; Pripfl et al., 2013). Our results are consistent with hemispheric specialization in that the decision-making task requires successful inhibition of a pre-potent response to 'Play' and win hypothetical money. Because the response must be made in less than 2 seconds, there is no time for deliberation. Our findings suggest that greater RDLPFC activity is associated with more successful inhibition of 'Play' responses on the risky decks.

Mediation analysis provides stronger tests than the component parts, as $a*b$ is not just the conjunction of path a and path b . It differs from simple correlation in that it brings in a third variable to explain the correlation (Baron and Kenny, 1986; MacKinnon et al., 2007; Preacher and Hayes, 2004). Mediation differs from another technique, psychophysiological interaction (PPI). PPI assesses the significance of differential connectivity between brain regions depending on task state (O'Reilly et al., 2012), but does not attempt to determine whether a connection is direct or mediated by another factor. Rather, PPI analysis is a special form of moderation, a test of whether connectivity differs based on the level of a 3rd variable (Friston et al., 1997). It is therefore suited for identifying conditional functional connectivity between two regions, but not functional pathways that involve more than two regions in 'series.' PPI analyses also do not allow multiple brain regions to simultaneously predict or explain a behavioral effect. Our goal was thus to use mediation to study how brain activity can explain the relationship between group and risk avoidance. Mediation can be used to build models in which multiple brain systems contribute to behavior (Lim et al., 2009; Wager et al., 2009, 2008). Those systems may have multiple separable effects, as seen here; the effects of RDLPFC and VST are opposing and separable.

The suppressive effect of RDLPFC activity on risky choices has potential implications for treatment. For example, using transcranial direct current stimulation, investigators demonstrated that increasing RDLPFC activity during decision-making decreased risky choices and increased error awareness (Fecteau et al., 2007; Harty et al., 2014) while disruption of RDLPFC by low-frequency repetitive transcranial magnetic stimulation (TMS) resulted in controls making riskier choices and showing worse performance (Knoch et al., 2006). Incorporating these neuromodulatory techniques in future work could bolster

causality claims, either by inducing a functional lesion with low frequency TMS or inducing functional augmentation with high frequency TMS.

VST activity was associated with decreased risk avoidance. Impulsive decisions have been associated with VST activity in healthy subjects (McClure et al., 2004; Plichta and Scheres, 2014). Thus, greater VST activity in abstinent SDI compared to controls may be associated with impulsive decision-making that is exacerbated if unopposed or weakly opposed by insufficient RDLPFC activity. Our results are consistent with reports of reductions in alcohol craving and improved abstinence in three patients treated with deep brain stimulation of the nucleus accumbens (Heinze et al., 2009; Müller et al., 2009) since DBS is thought to suppress neural activity. These promising studies underscore the need to understand more precisely the role of striatum in the neural circuitry of drug related behavior.

Few studies have examined brain activity during decision-making in long-term abstinent SDI (Ersche et al., 2005; Patel et al., 2013). Differences in brain activity between SDI and controls after prolonged abstinence suggests that the pattern we observed may be an endophenotype that predisposes one to drug use; or, alternatively, that neurocircuitry changes resulting from drug use are long-lasting. Longitudinal studies are needed to separate these possibilities. Regardless of the causal relationships, our findings suggest that brain activity differences appear to persist even with sustained, full remission.

Whole brain analysis found no mediation of group differences in risk avoidance. Perhaps with greater power (larger sample size) an effect would survive multiple comparisons. However, across-group analysis revealed that RDLPFC and an area of the left temporoparietal junction (TPJ) positively mediated the VST activity-risk avoidance relationship. The exact role of TPJ activity in the current study is unknown. There is evidence of a role for TPJ in social cognition, memory, and attention (Carter and Huettel, 2013) suggesting that TPJ may support cognitive processing that positively influences risk avoidance. Conversely, negative mediation of the relationship between VST activity and risk avoidance was found in the medial right thalamus. Thalamus and striatum influence each other through reciprocal circuitry (Haber and Knutson, 2010). Our findings are consistent with a prior study showing striatal-thalamic activity correlated with impulsivity during decision-making in cocaine users and healthy controls (Leland et al., 2006).

The fact that MEPM revealed RDLPFC as a positive mediator of VST activity and risk avoidance across group but not at the group level is consistent with classifying mental disorders based on dimensions of “observable behavior and neurobiological measures” (National Institute of Mental Health Research Domain Criteria (RDoC; <http://www.nimh.nih.gov/research-priorities/rdoc>). Addiction lies on one end of the behavioral spectrum of impulsivity, compulsivity, and sensation-seeking found in non-addicted individuals (Jentsch et al., 2014; Koob and Le Moal, 2008). Familial studies have shown that non-drug using family members of SDI exhibit behaviors intermediate between SDI and unrelated non-drug using healthy controls (Ersche et al., 2012) consistent with contributions from both genes and environment and supporting a role for analysis at the individual, in addition to group, level.

Impulsivity is a dimensional trait strongly associated with addiction and poor decision-making (Dolan et al., 2008; Hariri et al., 2006; Plichta and Scheres, 2014) and is both a risk factor for and a consequence of drug addiction (Feil et al., 2010; Jentsch and Taylor, 1999). VST reward sensitivity correlates strongly with impulsivity in healthy controls (Forbes et al., 2009) and striatal activity has been associated with impulsivity in alcoholics and cocaine users (Beck et al., 2009; Leland et al., 2006). The present study extends those results, demonstrating that impulsivity fully mediates group differences in risk avoidance: when impulsivity is removed as a factor, group differences in risk avoidance are no longer significant.

To our knowledge, this is the first study to investigate the influence of neuroanatomical regions on decision making in substance dependence using mediation analysis. It should be noted that this study was not designed to test causality, thus we can only state that the mediating regions influence the group-performance relationship. Neuromodulation with DBS or TMS is one way to directly manipulate striatum, DLPFC, or other regions to test for causal relationships for the mediators. The current task could be modified in future studies to address causality. Another limitation is that it is impossible to know if alterations in brain activity in SDI preceded or were a result of drug use.

In summary, we report two separate, opposing pathways influencing group differences in risk avoidance during decision-making: a positive pathway through the RDLPFC that increased risk avoidance, and a negative pathway through the VST that decreased risk avoidance. Furthermore, impulsivity may play a role in the circuit-behavior relationships across individuals. Future studies aimed at confirming an imbalance in frontal-striatal influence on risk avoidance could lead to novel treatments in addiction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

Drug users display impaired risk avoidance compared to controls.

We use formal mediation analysis to investigate neural correlates of risk avoidance.

Prefrontal cortex positively and striatum negatively mediated risk avoidance.

Imbalanced fronto-striatal activity may predict risky decision-making in addiction.

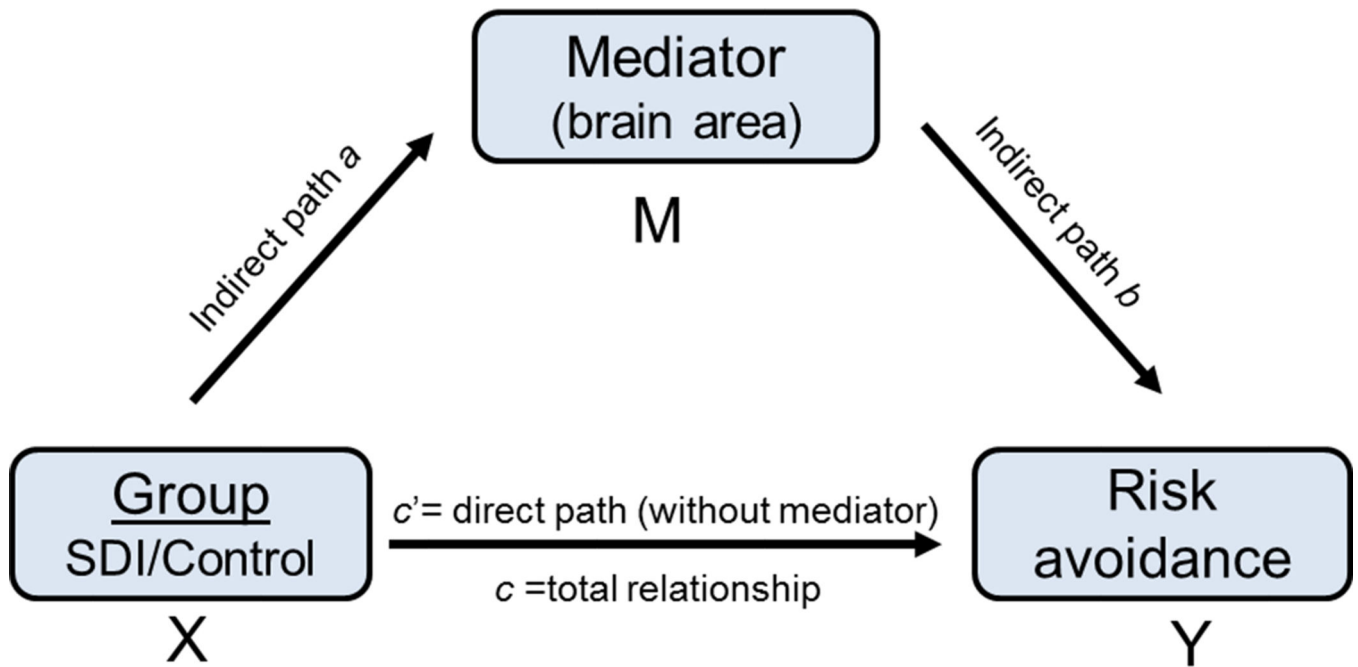


Figure 1. Single-level mediation model

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).

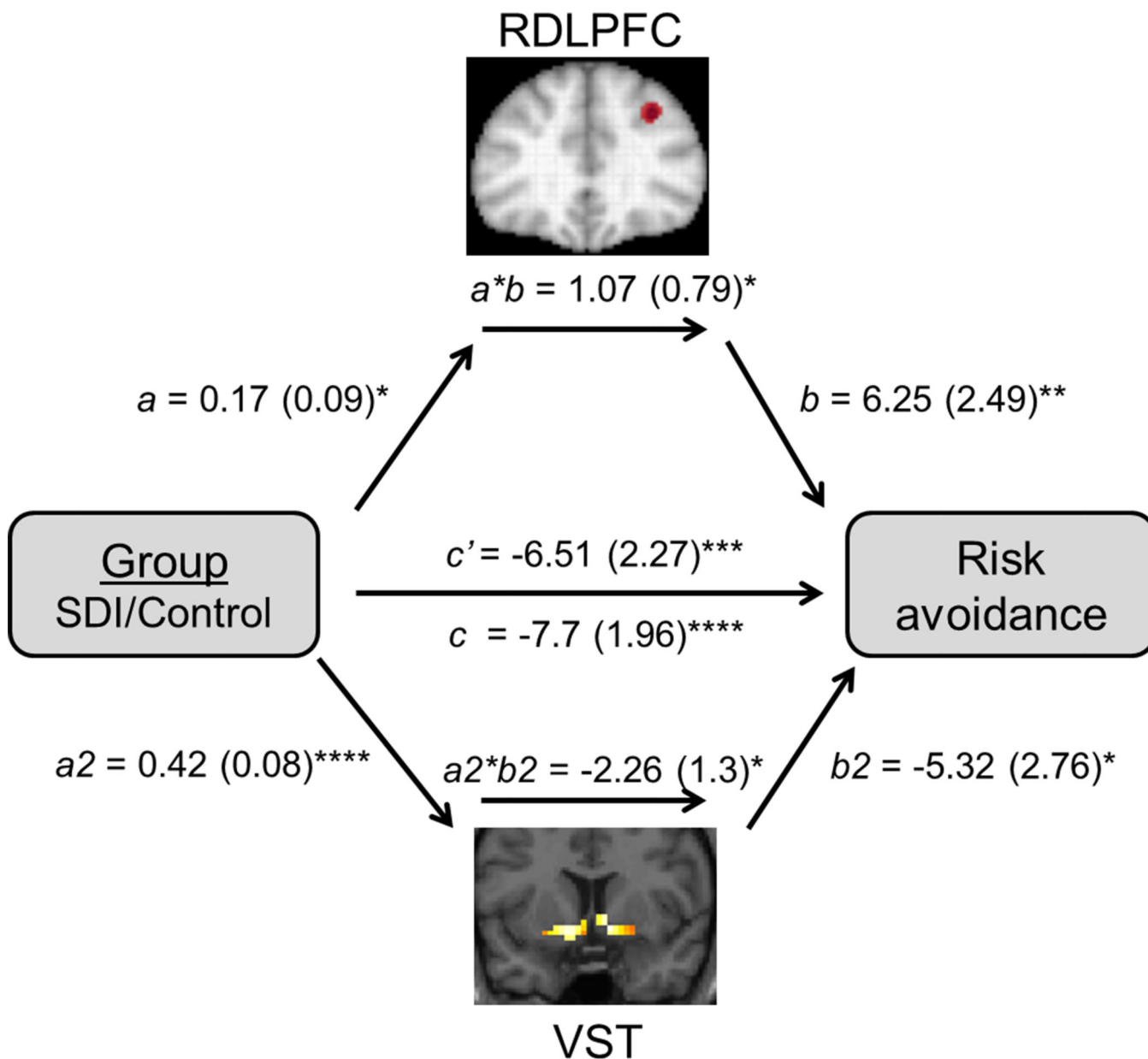


Figure 2. Single-level mediation analysis

RDLPFC and VST oppositely mediate group differences in risk avoidance. Path coefficients are shown next to arrows with standard errors in parentheses. Path a is from the group (X) to the RDLPFC (M1). Path b is from RDLPFC (M1) to risk avoidance (Y). Path a_2 is from the group (X) to the VST (M2). Path b_2 is from VST (M2) to risk avoidance (Y). Paths b and b_2 are calculated controlling for group (X). Paths a , b , and a^*b control for VST (M2), and Paths a_2 , b_2 , and a_2*b_2 control for RDLPFC (M1). The direct path c' is calculated controlling for both mediators. **** $p < 0.001$, *** $p < 0.005$, ** $p < 0.01$, * $p < 0.05$, one-tailed; right dorsolateral prefrontal cortex (RDLPFC), ventral striatum (VST), mediator (M1, M2)

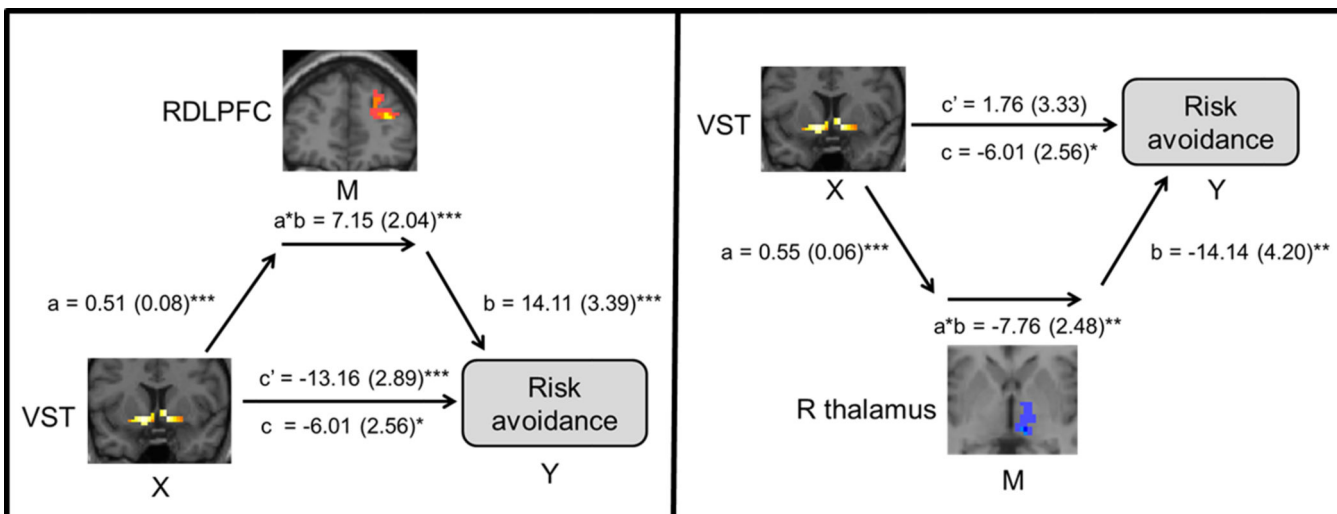


Figure 3. Mediation Effect Parametric Mapping (MEPM)

Across group, RDLPFC positively mediated and the right thalamus negatively mediated the VST-risk avoidance relationship. The *a* path is from the VST (X) to each mediating region. The *b* path is from the mediating region (M) to risk avoidance (Y). The *b* path is calculated controlling for VST (X) and for other mediators. Path coefficients are shown next to arrows with standard errors in parentheses. The direct path *c'* is calculated controlling for the mediator. Coefficients and p values were calculated using maxstat. ****p*<0.001, ***p*<0.005, two-tailed. Ventral striatum (VST), right dorsolateral prefrontal cortex (RDLPFC), right thalamus (R thalamus)

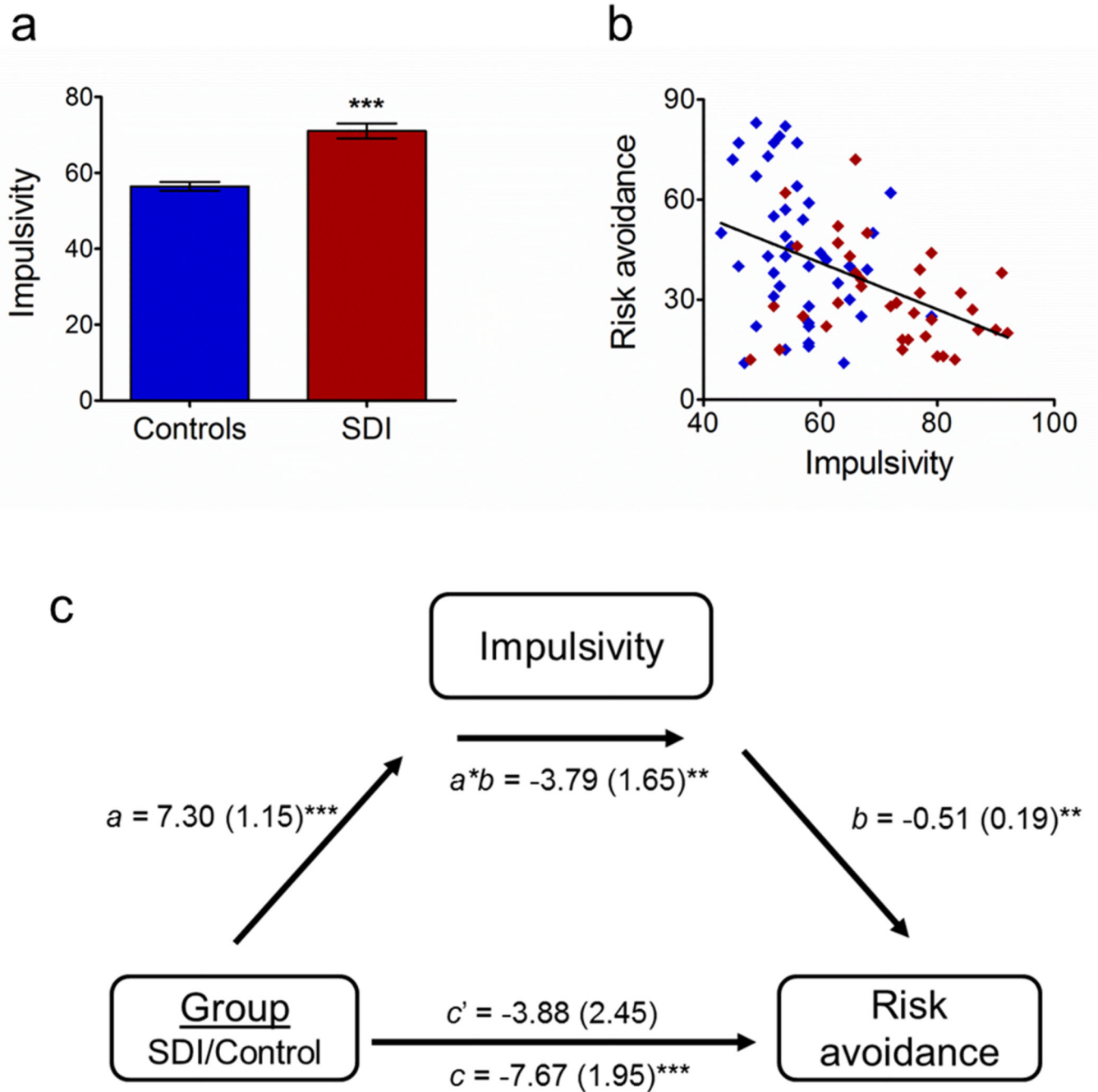


Figure 4. Impulsivity affects risk avoidance

a) Controls (blue) were less impulsive than SDI (red; $p < 0.001$). b) Risk avoidance and impulsivity were negatively correlated across groups ($r = -0.435$, $p < 0.001$). c) Mediation analysis results depicting the mediating effect of impulsivity on group differences in risk avoidance. After controlling for the mediating effect of impulsivity, the relationship between group and risk avoidance was no longer significant. $^{***}p < 0.001$, $^{**}p < 0.005$, two-tailed

Table 1

Mediators of the VST relationship with risk avoidance

Mediators	Name	Coordinates			a Path		b Path		ab Path		Conjunction (voxels)					
		x	y	z	Z	p	Z	p	Z	p	Z	p	p<0.05	p<0.01	p<0.005	
Positive	RDLPFC	30	38	34	5.81	<0.001	3.94	<0.001	3.37	<0.001	3.20	0.001	5	18	24	185
	LTPJ	-42	-22	37	5.69	<0.001	3.71	<0.001	3.20	0.001	3.20	0.001	11	24	288	
Negative	Rthal	9	-16	-2	7.12	<0.001	-3.24	0.001	-3.03	0.003	-3.03	0.003	6	12	108	
	LMFG	-27	2	55	5.70	<0.001	-3.10	0.002	-2.79	0.005	-2.79	0.005	14	22	48	

LTPJ, left temporoparietal junction; RDLPFC, right dorsolateral prefrontal cortex; Rthal, right thalamus; LMFG, left middle frontal gyrus; p values calculated using maxstat.

Table 2

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

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