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Behavioral approach and orbitofrontal cortical activity during decision-making in substance dependence

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Dorothy J. Yamamoto[a], Marie T. Banich[b,d], Michael F. Regner[a,c], Joseph T. Sakai[b], Jody Tanabe[a,b,*]

[a] Departments of Radiology, University of Colorado Anschutz Medical Campus, Aurora, CO, 80045, USA
[b] Department of Psychiatry, University of Colorado Anschutz Medical Campus, Aurora, CO, 80045, USA
[c] Department of Bioengineering, University of Colorado Anschutz Medical Campus, Aurora, CO, 80045, USA
[d] Institute of Cognitive Science, University of Colorado Boulder, Boulder, CO, 80309, USA

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ABSTRACT

Behavioral approach, defined as behavior directed toward a reward or novel stimulus, when elevated, may increase one's vulnerability to substance use disorder. Behavioral approach has been associated with relatively greater left compared to right frontal activity; behavioral inhibition may be associated with relatively greater right compared to left frontal brain activity. We hypothesized that substance dependent individuals (SDI) would have higher behavioral approach than controls and greater prefrontal cortical activity during decision-making involving reward. We hypothesized that behavioral approach would correlate with left frontal activity during decision-making and that the correlation would be stronger in SDI than controls. 31 SDI and 21 controls completed the Behavioral Inhibition System/Behavioral Approach System (BIS/BAS) scales and performed a decision-making task during fMRI. Orbitofrontal (OFC) and dorsolateral prefrontal activity were correlated with BIS and BAS scores. Compared to controls, SDI had higher BAS Fun Seeking scores (p < 0.001) and worse decision-making performance (p = 0.004). BAS Fun Seeking correlated with left OFC activity during decision-making across group (r = 0.444, p < 0.003). The correlation did not differ by group. There was no correlation between BIS and right frontal activity. Left OFC may play a role in reward-related decision-making in substance use disorder especially in individuals with high behavioral approach.

1. Introduction

Drug use is associated with novelty seeking and impulsivity, both of which play a role in Gray's Reinforcement Sensitivity Theory (Gray, 1970, 1981, 1987; McNaughton and Corr, 2004). Gray proposed systems controlling behavior and emotion: a behavioral activation (approach) system that directs behavior toward a reward and is associated with novelty seeking, impulsivity, and positive emotions and a behavioral inhibition system that analyzes risk, resolves conflicting goals, and is associated with negative affect. Behavioral approach has been linked to the dopaminergic system (Depue and Collins, 1999) and genetic polymorphisms associated with high dopamine activity (Reuter et al., 2006). Individuals with high behavioral approach sensitivity are more likely to abuse alcohol and drugs which have rewarding properties involving dopamine function (Franken et al., 2006). In contrast, a highly active behavioral inhibition system has been associated with anxiety and anxiety-related disorders (Johnson et al., 2003; Maack et al., 2012) that are often treated with drugs that modulate serotonin

(Ravindran and Stein, 2010).

To quantify individual differences in behavioral approach and inhibition, Carver and White developed the behavioral inhibition/behavioral approach (BIS/BAS) scale (Carver and White, 1994) which has shown validity in healthy and clinical populations (Jorm et al., 1998; Kasch et al., 2002; Leone et al., 2001). Alcohol, tobacco, and drug use are associated with high BAS scores (Balconi et al., 2014a; Franken et al., 2006; Johnson et al., 2003; Knyazev, 2004; Yen et al., 2009). The BAS Drive and Fun Seeking subscale scores, in particular, have been shown to be higher in heroin, cocaine, and amphetamine dependent subjects than controls (Franken et al., 2006; Perry et al., 2013). In contrast, high BIS scores have been weakly, if at all, associated with substance use (Franken and Muris, 2006; Knyazev, 2004).

EEG studies suggest that approach behaviors in controls are associated with greater left relative to right hemisphere activity (Coan and Allen, 2003; Harmon-Jones and Allen, 1998; Sutton and Davidson, 1997; Wacker et al., 2013), a finding supported by fMRI studies (Beaver et al., 2006; Krmpotich et al., 2013). Beaver et al. (2006) found an

association between BAS scores and left orbitofrontal cortex (OFC) activity in response to rewarding food cues in controls. Krmpotich et al. (2013) reported a correlation between BAS scores and resting state left dorsolateral prefrontal cortex (DLPFC) activity in controls and stimulant dependent individuals. However, these prior fMRI studies did not investigate decision-making. Filling this gap in the literature is important because reward related decision-making is an important feature of substance use disorder (SUD) and may elucidate mechanisms by which behavioral approach increases the risk for substance use.

Dorsolateral prefrontal and orbitofrontal cortex have been implicated in impaired decision-making in SUD (Li et al., 2010; Olsen et al., 2015). The OFC is important for salience attribution of a stimulus, and may be overly active in drug users especially in response to drug cues (Chase et al., 2011; Schoenbaum and Shaham, 2008). The DLPFC is important for cognitive control and response inhibition. Ersche et al. (2005) found that during risky decision-making right DLPFC activity was higher in healthy controls while left OFC activity was increased in drug users, possibly reflecting lowered cognitive control (associated with DLPFC) and increased salience attribution (associated with OFC) of reward in drug users. The relationship between these nodes of the decision-making network and behavioral approach has not been well studied in SUD.

Given the evidence that behavioral approach is associated with substance use and greater left relative to right hemisphere activity, the present study sought to investigate relationships between BIS/BAS and right and left prefrontal brain activity during risky decision-making in substance dependent individuals (SDI). We hypothesized that i.) compared to controls, SDI would have higher behavioral approach, ii.) SDI would have greater OFC activity during risky decision-making, iii.) left OFC and DLPFC activity during decision-making would correlate with BAS scores, and iv.) right OFC and DLPFC activity would correlate with BIS scores. Finally, we hypothesized that the association between left frontal activity and BAS would be stronger in SDI than in healthy controls.

2. Materials and methods

2.1. Subjects

Fifty-two subjects were recruited: 31 substance dependent individuals (SDI) and 21 controls. This sample has not been previously reported. All 52 subjects underwent diagnostic and drug dependence interviews and provided behavioral measures consisting of BIS/BAS and decision-making. One control did not have BIS/BAS data due to technical reasons; remaining subjects completed the entire BIS/BAS questionnaire. Seven subjects were excluded for excessive head motion (6 SDI) or claustrophobia (1 control). Hence, imaging data are reported on 45 subjects: 25 SDI (14M/11F) and 20 controls (11M/9F). Inclusion criteria: SDI met DSM-IV criteria for stimulant dependence. SDI were recruited from a residential treatment program at the University of Colorado Denver Addiction Research and Treatment Service (ARTS).

Average abstinence from drugs and alcohol was 13 months (range = 2–31, standard deviation = 7.9). Abstinence from drugs, nicotine, and alcohol was monitored by direct supervision and random drug screening at ARTS. Controls were recruited from the community and excluded if they met DSM-IV criteria for lifetime abuse or dependence on drugs or alcohol. Exclusion criteria for all subjects: neurological illness, schizophrenia, bipolar disorder, major depression within the last 2 months, head trauma with loss of consciousness > 15 min, HIV, or IQ ≤ 80. All subjects provided written informed consent approved by the Colorado Multiple Institutional Review Board. All subjects but two were confirmed right-handed: One subject was left-handed and for one subject handedness data was not obtained.

2.2. Screening and drug dependence assessments

All subjects received structured interviews administered by trained personnel. Lifetime drug dependence was assessed for stimulants, nicotine, alcohol, cannabis, opioids, club drugs, sedatives, and hallucinogens using the computerized Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM) (Cottler et al., 1989). The Computerized Diagnostic Interview Schedule–Version IV (C-DIS-IV) was administered to exclude subjects with schizophrenia, bipolar disorder, and current major depression. Subjects were not excluded for antisocial personality disorder (ASPD) as comorbidity of ASPD with stimulant use is common in the U.S. (Compton et al., 2005) particularly in residential treatment programs. Thirty of 31 SDI and 5 of 21 controls met DSM-IV criteria for ASPD. IQ was estimated with matrix and verbal reasoning Wechsler Abbreviated Scale of Intelligence subtests (Psychological Corporation, 1999).

2.3. Behavioral measures

2.3.1. Behavioral inhibition system/behavioral activation system (BIS/BAS)

Behavioral inhibition and approach were measured using the Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) scales (Carver and White, 1994). The BIS scale assesses the tendency to respond with negative affect and behaviors that respond to goal conflict and generate anxiety (e.g., "I worry about making mistakes."). The BAS scale assesses the tendency to respond with positive affect and behaviors that approach appetitive stimuli. BAS is divided into three subscales that focus on different aspects of approach behavior: (1) Drive, relating to persistent pursuit of desired goals (e.g., "I go out of my way to get things I want."); (2) Fun-Seeking, the tendency to seek out novel rewards and act impulsively (e.g., "I often act on the spur of the moment."), and (3) Reward Responsiveness, the tendency to experience a positive response to the occurrence or anticipation of reward (e.g., "It would excite me to win a contest."). These scales have shown validity in assessing differences among individuals on emotional response to aversive or appetitive stimuli (Carver and White, 1994; Leone et al., 2001). Each subscale measures a different aspect of approach and were analyzed separately (Carver and White, 1994).

2.3.2. Decision-making task

Subjects played a modified version of the Iowa Gambling Task during fMRI scanning, as described previously (Cauffman et al., 2010; Thompson et al., 2012). Briefly, subjects began with a hypothetical $2000, were presented four decks of cards, and instructed to earn as much money as possible. For each trial, the computer selected a deck and subject was asked to "Play" or "Pass" by pressing the appropriate button. "Play" resulted in a single positive or negative monetary value, along with the running total. "Pass" resulted in no change. Two decks resulted in a net gain (good) and two in a net loss (bad) when played over time. To perform well, subjects must learn to "Pass" on bad decks and "Play" on good decks. For each trial, the subject was given 2 s to make a decision followed immediately by feedback of 4 s duration. There were 50 trials of each deck (200 trials total). Decision-making trials were interspersed with 43 motor control trials and 59 fixation crosses in pseudorandom order to effectively jitter trial onsets. Motor control trials were identical to task trials except the subject was told which button to press. Task time was 26 min (two 13 min runs). The current task differed from prior studies (Yamamoto et al., 2014, 2015) in that we included an explicit control for motor activity. Decision-making variables of interest were the number of passes on bad decks, plays on good decks, and motor control (instructed presses).

2.4. MRI acquisition

Functional MR images were acquired on a 3T scanner with an 8-

channel head coil using a GRE-EPI sequence (TR 2s, TE 30 ms, matrix 64×64, FOV $220 \, mm^2$, $3.4 \times 3.4 \, mm^2$, slice thickness 3 mm, gap 1 mm, angled parallel to the AC-PC line).

2.5. Pre-processing and model specification

Data were pre-processed and analyzed with Statistical Parametric Mapping (SPM8) (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). The first three image volumes from each run were excluded for saturation effects. Functional data were realigned using rigid body transforms to the mean volume. Subjects were excluded for head motion > 3 mm. Realigned images were normalized to Montreal Neurological Institute (MNI) space. Data were smoothed with a 6-mm full-width-half-maximum Gaussian kernel. Final smoothness of the data after pre-processing was $8.2 \times 8.4 \times 7.9 \, mm^3$. Time series data were filtered using a high pass filter and corrected for temporal autocorrelation. The stimulus functions were convolved with a canonical hemodynamic response function.

Eleven conditions were modeled: decision and outcome for each of the four decks (i.e., 8) and the control condition (i.e., 2) plus fixation trials (i.e., 1). Session was modeled as a nuisance variable. Within-subject contrast maps of decision > motor control were calculated after adjusting for education and six motion parameters (three translation and three rotation parameters from the rigid-body realignment). These within-subject maps were brought to the second level for analysis.

2.6. Region-of-interest (ROI) definitions

Two bilateral ROIs were created based on *a priori* predictions of their relevance in risky decision-making: OFC and DLPFC. OFC ROIs were based on the meta-analytic framework of Neurosynth (http://neurosynth.org) which identifies neuroimaging studies reporting significant BOLD activity associated with a given construct (Yarkoni et al., 2011). Among 336 studies showing significant activity associated with "decision-making" (queried 04/10/2015), a coordinate localized to the LOFC (MNI: $-22, 34, -16$; z-score 5.82) was used to construct a 6-mm diameter sphere. The ROFC mirrored the LOFC (MNI: $22, 34, -16$). Bilateral DLPFC ROIs consisted of 6 mm diameter spheres centered at MNI coordinates $\pm 34, 32, 38$ taken from a previous decision-making study using a similar task but on a completely independent group of subjects (Yamamoto et al., 2015). The DLPFC coordinates from the 2015 study were also obtained from Neurosynth (http://neurosynth.org). Beta estimates were extracted for each ROI for each subject from the first-level contrast maps using the Marsbar (Brett et al., 2002) toolbox in SPM8.

2.7. Statistical analyses

Whole brain analyses were conducted in SPM8. Whole brain cluster correction was determined using Monte Carlo simulation in AFNI (http://afni.nimh.nih.gov/afni/). All other analyses were carried out in SPSS (SPSS, 2016).

2.7.1. Demographic and behavioral data

Normally distributed continuous variables were analyzed with 2-tailed *t*-tests or analysis of covariance (ANCOVA) with group as between-subjects factor after adjusting for education. Categorical variables were analyzed with chi-squared tests. Significance was set at $p < 0.05$.

2.7.2. Group differences in brain activity

2.7.2.1. ROI. Beta estimates in each ROI were analyzed using ANCOVA with group as a between-subjects factor after adjusting for education. Significance was set at $p < 0.05$ using Bonferroni correction for 4 comparisons (i.e., $p \leq 0.0125$).

2.7.2.2. Whole brain. Whole brain group analysis was conducted in SPM8 using ANCOVA after adjusting for education. Multiple testing corrections were applied with family-wise error correction using AlphaSim Monte-Carlo simulations and a voxel-level threshold of $p < 0.001$, resulting in required cluster-level threshold of 117 contiguous voxels to achieve a whole-brain significance of $p < 0.05$.

2.8. Correlations between BIS/BAS and brain activity

Across group, BIS and BAS subscales were correlated with brain activity from each ROI using Pearson's *r*. Bonferroni correction for multiple comparisons was used. We used methods of Preacher to test whether the correlation coefficients differed between groups (Preacher, 2002).

3. Results

3.1. Demographics

SDI and controls were similar in age (35.2 ± 6.9 vs. 33.2 ± 8.6 years, $p = 0.37$) and sex (14 M/17F vs. 12 M/9F, $p = 0.397$). SDI had fewer years of education (12.6 ± 1.9 vs. 15.0 ± 1.4, $p < 0.001$) and lower IQ (102.5 ± 10.5 vs. 114.4 ± 11.2, $p < 0.001$) than controls (Table 1). Because education and IQ were highly correlated ($r = 0.707$, $p < 0.001$), only education was used as a covariate in subsequent analyses.

3.2. Drug characteristics

SDI were recruited for stimulant-dependence; however, most SDI exhibited dependence on other drugs. The number of SDI with specific drug dependence diagnoses were: stimulants, 31 (100%); nicotine, 22 (71%); alcohol, 18 (58%); cannabis, 13 (42%); opioids, 8 (26%); club drugs, 4 (13%); sedatives, 3 (10%); and hallucinogens, 1 (3%). Three (14%) of the 21 controls met criteria for nicotine dependence.

3.3. BIS/BAS

SDI scored higher than controls on BIS (21.3 ± 3.1 vs. 18.9 ± 3.9; $F = 6.9$, $p = 0.011$), BAS Drive (12.7 ± 2.3 vs. 9.8 ± 1.2; $F = 22.7$, $p < 0.001$), and BAS Fun Seeking (13.3 ± 1.6 vs 11.1 ± 1.8; $F = 16.0$, $p < 0.001$), with a trend for higher scores on BAS Reward Responsiveness (17.4 ± 2.1 vs. 15.9 ± 2.5; $F = 3.7$, $p = 0.059$) (Table 1).

Table 1
Demographics and behavior.

Demographics	Control (21)	SDI (31)	p-value
Sex [*]	12 M/9F	14 M/17F	0.397
Age (years)	33.2 ± 8.6	35.2 ± 6.9	0.371
Education (years)	15.0 ± 1.4	12.6 ± 1.9	< 0.001
IQ	114.4 ± 11.2	102.5 ± 10.5	< 0.001
Behavioral tests			
BIS	18.9 ± 3.9	21.3 ± 3.1	0.011
BAS			
Drive	9.8 ± 1.2	12.7 ± 2.3	< 0.001
Fun-Seeking	11.1 ± 1.8	13.3 ± 1.6	< 0.001
Reward Responsiveness	15.9 ± 2.5	17.4 ± 2.1	0.059
Performance			
Passbad	42.5 ± 19.9	25.5 ± 11.9	0.004
Playgood	73.6 ± 14.2	70.6 ± 11.1	0.810
Motor control (instructed presses)	39.7 ± 5.3	35.1 ± 9.9	0.372
Total money earned ($)	3634 ± 1682	2690 ± 785	0.102

[*] Chi-squared test for group and sex.

3.4. Decision-making

SDI passed on bad decks significantly fewer times than controls (SDI: 25.5 ± 11.9, controls: 42.5 ± 19.9; $F = 9.3$, $p = 0.004$), consistent with less risk avoidance or worse negative reinforcement learning. There were no group differences in playing on good decks (SDI: 70.6 ± 11.1, controls: 73.6 ± 14.2; $F = 0.058$, $p = 0.81$), suggesting that decision-making involving positive reinforcement learning did not differ across group. Motor control responses (computer instructed a press) did not differ between SDI and controls, indicating that general attention to the task and motor function was the same across group (SDI: 35.1 ± 9.9, controls: 39.7 ± 5.3; $F = 0.81$, $p = 0.372$). Total money earned was less in SDI vs controls, but not significantly (SDI: \$2690 ± \$785; controls: \$3634 ± \$1682; F = 2.77, p = 0.1) (Table 1).

3.5. Group differences in brain activity

3.5.1. ROI

SDI showed greater activity than controls in left OFC ($p < 0.003$) during decision-making. No other comparisons survived Bonferroni corrections (Fig. 1).

3.5.2. Whole brain

There were no significant clusters surviving a multiple comparisons correction for group differences of SDI > control or control > SDI

3.6. Correlations between BIS/BAS and brain activity

Left OFC activity correlated with BAS Fun Seeking across groups ($r = 0.444$, $p < 0.003$; Fig. 2 and Table 2). Correlation within groups (SDI: $r = 0.526$, $p = 0.007$; controls: $r = 0.056$, $p = 0.821$) did not survive multiple comparisons correction. Contrary to our hypothesis, there was no group difference in correlation coefficients between left OFC activity and BAS Fun Seeking ($z = 1.609$, $p = 0.11$). There were no correlations between BAS Drive or BAS Reward and brain activity or between BIS and right OFC or DLPFC activity.

4. Discussion

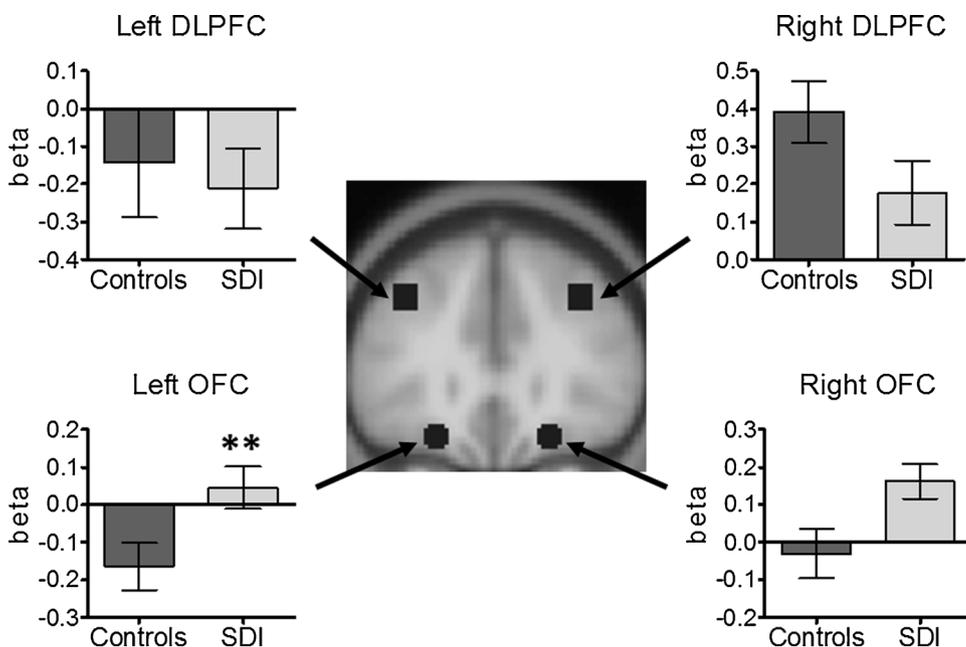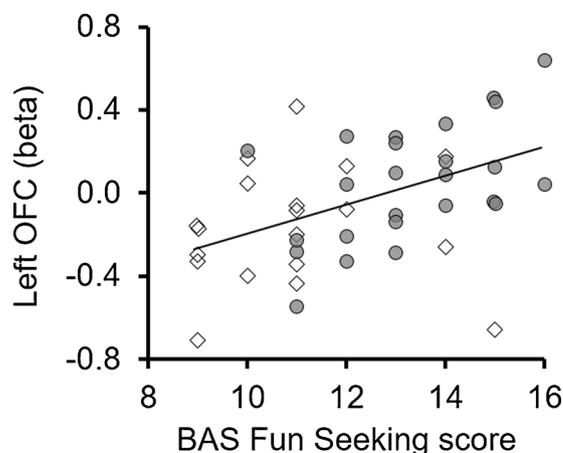The current study found that SDI have higher BAS and BIS scores

Fig. 2. Left OFC activity correlated positively with BAS Fun Seeking across groups (r = 0.444, p < 0.003), surviving Bonferroni correction for multiple comparisons. SDI (solid gray circles), controls (open diamonds).

Table 2
Region of Interest correlations with BIS/BAS.

All subjects	Left OFC	Right OFC	Left DLPFC	Right DLPFC
BIS	0.29	0.311	0.01	−0.084
BAS Drive	0.14	0.06	−0.17	−0.232
BAS Fun Seeking	0.444**	0.28	0.04	−0.050
BAS Reward Responsiveness	−0.04	0.18	0.08	−0.009

** p < 0.003, survives Bonferroni correction for multiple comparisons.

than controls and that left OFC activity during decision-making correlated with BAS Fun Seeking across group. Contrary to our hypotheses, we did not find that the association between left OFC activity and BAS was stronger in SDI than controls, nor did BIS correlate with right frontal activity during decision-making across or within group. Taken together, our findings suggest that left OFC is associated with behavioral characteristics that are relevant to substance use and could play a role in risky decision-making.

Higher BAS scores in SDI compared to controls is consistent with prior studies investigating personality predictors of drug and alcohol use (Franken and Muris, 2006; Knyazev, 2004). In a large sample of

Fig. 1. BOLD signal in SDI and controls during decision-making. SDI showed higher activity than controls in left OFC, **p < 0.003, surviving Bonferroni correction for multiple comparisons. Images are in neurological convention. Graphs mean ± SEM.

4501 Russian youths, Knyazev found that BAS was positively related to substance use and risky behavior. Franken and Muris reported that BAS correlated positively with drug and alcohol use in 276 non-clinical college students. Among the subscales, we found that BAS Fun Seeking and Drive were higher in SDI compared to controls, replicating the results of Perry et al. (2013) and supporting the hypothesis that greater behavioral approach may increase vulnerability to drug use disorders (Franken et al., 2006; Johnson et al., 2003). BAS Drive has been linked to cue-induced craving in alcoholics (Franken, 2002). Whether the relationship between the subscales and drug use differs by drug classes requires further study.

In addition to predicting substance use, BAS Fun Seeking correlates with worse decision-making in healthy controls (Suhr and Tsanadis, 2007). Suhr and Tsanadis found a significant relationship of high BAS Fun Seeking and worse decision-making on the Iowa Gambling Task (IGT) in controls. BAS does not assess decision-making per se, but rather sensitivity toward reward, novelty and risk taking. Our interpretation is that differences in sensitivity to these factors influence decision-making behavior involving novelty or reward. BAS Fun Seeking scores combined with poor decision-making performance provide evidence that SDI may be more impulsive and less risk avoidant than controls. Decision-making is a highly complex process involving sensitivity to positive feedback, negative feedback, expectation, and, according to the somatic theory of the IGT, affect (Bechara and Damasio, 2002). We did not model these factors separately, but instead focused on risky decision-making in general.

Increased behavioral approach was associated with greater left OFC activity during decision-making. This is consistent with an fMRI study by Barros-Loscertales that found behavioral approach in healthy controls correlated with left prefrontal activity while subjects viewed erotic pictures (Barrós-Loscertales et al., 2010). An EEG study by Balconi et al. observed higher BAS Reward Responsiveness and BAS Drive in cocaine users compared to controls. In addition, there was relatively increased left compared to right alpha power when participants made disadvantageous decisions on the IGT (Balconi et al., 2014b), suggesting that behavioral approach was associated with left relative to right hemisphere activity. However, this study did not correlate EEG with behavioral approach. Our study extends that of Balconi et al. in that we correlated behavioral approach and brain activity and found that left OFC activity correlated with BAS Fun Seeking. Both BAS Fun Seeking and Reward subscales measure willingness to approach a reward; however, the Fun Seeking subscale incorporates impulsivity, a trait associated with the OFC (Berlin et al., 2004; Winstanley et al., 2004) and addiction (Moeller et al., 2002; Perry et al., 2013). Further, the BAS Fun Seeking component of willingness to approach a rewarding event or monetary incentive fits well with the purported role of the OFC in associating a stimulus and reward, in tracking the value of a predicted reward, and in behavioral reinforcement, all of which can be affected in substance use disorder (Schoenbaum and Shaham, 2008).

A large body of evidence indicates that drugs of abuse, especially stimulants, alter OFC signals and OFC-dependent behaviors (Schoenbaum et al., 2006). Specifically, the OFC is thought to play a role in signaling outcome expectancies. Our findings of increased OFC activity during decision-making in SDI compared to controls is consistent with previous imaging studies in abstinent stimulant-dependent individuals (Bolla et al., 2003; Ersche et al., 2005; Yamamoto et al., 2014). Greater OFC activity in SDI may reflect greater salience of possible reward cues during decision-making. Animal studies support the idea that the OFC measures incentive value of prior outcomes and uses this information to update decisions during a task (Schoenbaum et al., 2006). Another possible explanation for increased OFC activity in SDI is that it may reflect an inability to devalue a stimulus that no longer predicts reward. For example, in a Pavlovian devaluation experiment, rats exposed to cocaine were unable to appropriately devalue a conditioned reinforcer, mimicking the behavior of rats who have received OFC lesions (Schoenbaum et al., 2004). Thus, the OFC appears to

be critical for signaling outcome expectancies and may be disrupted by drug exposure. Taken together, we hypothesize that there are alterations in OFC signaling during decision-making in SDI and that trait behavioral approach might be a related factor.

It should be noted that while BAS Fun Seeking correlated with left OFC activity during decision-making across our entire sample, correlations did not survive multiple comparisons correction in either group when analyzed separately. The lack of within-group correlation was somewhat unexpected and most likely due to low power. In SDI, the correlation was strongly positive (r = 0.526), but did not survive multiple comparison correction. In controls, if we removed one outlier, the BAS correlation with left OFC became positive and stronger (r = 0.364), but not significant. Another explanation is that the association between approach behavior and left frontal activity may reflect a dimensional, rather than diagnostic, construct as proposed by the National Institute of Mental Health RDoC (http://www.nimh.nih.gov/research-priorities/rdoc) where behavioral constructs are measured on a continuum. Approach is modelled within the positive valence domain (Johnson et al., 2016). In this case SDI may lie more at the upper end of the behavioral approach spectrum. A third possible explanation, as proposed by (Spielberg et al., 2011), involves DLPFC modulation of OFC activity. DLPFC could provide attentional focus by inhibiting left OFC thus preventing interference from competing or distracting stimuli. In that study, controls showed a negative correlation between BAS score and left OFC activity during a Stroop interference task. Another group found that while controls showed a negative correlation of Stroop scores with OFC activity, drug users showed the opposite (Goldstein et al., 2001). Our results cannot be compared directly to these studies because of the different tasks used, nevertheless our results are consistent with an association between approach and left OFC, but one that may be influenced by top down cognitive control or modulation by DLPFC.

With regards to the BIS scale, which measures sensitivity to aversive stimuli or conflict, SDI scored higher than controls. High BIS scores have been related to anxiety and depression (Johnson et al., 2003; Maack et al., 2012), although a few studies reported a positive association of BIS scores with alcohol intake (Keough and O'Connor, 2014; Wardell et al., 2011; , 2013). In those studies, elevated drinking was associated with both high BIS and high BAS, suggesting that the two behavioral systems may influence alcohol consumption in an additive or synergistic manner. Accordingly, Wardell et al. (2011) found that high BIS predicted alcohol use only when BAS was high. A longitudinal study revealed that over time negative mood-related problems due to alcohol use were found only in subjects high on both BIS and BAS (Wardell et al., 2013). It was postulated that high BIS or negative mood combined with high BAS approach behavior may promote drinking to reduce bad feelings, suggesting that the combined effect of BIS and BAS is important for behavior. Approximately 60% of our SDI met criteria for alcohol dependence, another possible explanation for the observed high BIS.

We did not find a correlation between right OFC or DLPFC activity and BIS. The literature on an association of BIS with right hemisphere has been mixed. Our results are consistent with studies that did not find an association between BIS and relatively greater right compared to left hemisphere activity on EEG (Amodio et al., 2008; Coan and Allen, 2003; Hewig et al., 2006).

Strengths of this study include replication of prior results showing greater activation in the OFC using the modified gambling task in SDI compared to controls (Yamamoto et al., 2014) in an independent data set. We used a reproducible unbiased definition of ROIs derived from a large, publicly available dataset (https://neurosynth.org). Whereas a prior EEG study in cocaine users found higher BAS scores and, separately, relative left asymmetric activity during decision-making (Balconi et al., 2014b), we extend the literature in reporting for the first time in an fMRI study a direct correlation between BAS and left OFC activity across individuals.

4.1. Limitations

A limitation of this study is that although SDI were recruited for stimulant dependence, most were polysubstance users. Hence, our findings cannot be attributed to the action of a single drug class. Nonetheless, the study is relevant as polysubstance use is quite prevalent in the United States (Abuse, 2012; Barrett et al., 2006). Secondly, all but one SDI met DSM-IV criteria for ASPD. However, comorbidity of ASPD with stimulant use is common in the U.S. (Compton et al., 2005) and could even be considered as one facet of this complex disorder (Hicks et al., 2004). While decision-making deficits and approach behavior may be related to clinical symptoms of ASPD, they also may be part of the symptomatology of substance use disorders. We cannot definitively state whether our results relate specifically to substance dependence, ASPD or their interaction. Third, in addition to BIS and BAS, a third behavioral system, the fight-flight-freeze system (FFFS) (Pickering and Corr, 2008) is hypothesized to mediate reactions to aversive stimuli and involves fear and avoidance. FFFS could not be measured separately as the BIS scale contains some elements of both FFFS and BIS. Fourth, the sample size is small and may have reduced our power to detect group differences.

In conclusion, compared to controls, SDI had higher BAS and BIS scores and worse decision-making performance, consistent with the hypothesis that high behavioral approach may be a risk factor for substance use disorder. SDI exhibited significantly higher left OFC activity during decision-making compared to controls. Left OFC activity correlated with BAS Fun Seeking across groups. These results suggest that left OFC may play a role in poor decision-making in substance use especially in individuals with elevated approach behavior.

Author disclosures

Conflict of interest

The authors report no potential conflicts of interest.

Contributors

Yamamoto: design, analysis, data interpretation, manuscript; Banich: data interpretation, manuscript; Regner: data interpretation, manuscript; Sakai: data interpretation, manuscript; Tanabe: design, analysis, data interpretation, manuscript. All authors contributed to and have approved the final manuscript.

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