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Youth with Substance Abuse Histories Exhibit Dysfunctional Representation of Expected Value During a Passive Avoidance Task

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Abstract

Individuals with substance abuse (SA) histories show impairment in the computations necessary for decision-making, including expected value (EV) and prediction error (PE). Neuroimaging findings, however, have been inconsistent. Sixteen youth with (SA_{positive}) and 29 youth without (SA_{negative}) substance abuse histories completed a passive avoidance task while undergoing functional MRI. The groups did not significantly differ on age, gender composition or IQ. Behavioral results indicated that SA_{positive} youth showed significantly less learning than SA_{negative} youth over the task. SA_{positive} youth show problems representing EV information when attempting to avoid sub-optimal choices in bilateral inferior frontal gyrus and striatum. Furthermore, SA_{positive} youth showed a significantly increased differential response to reward versus punishment feedback modulated by PE in posterior cingulate cortex relative to SA_{negative} youth. Disrupted decision-making is likely to exacerbate SA as a failure to represent EV during the avoidance of sub-optimal choices is likely to increase the likelihood of SA. With respect to the representation of PE, future work will be needed to clarify the impact of different substances on the neural systems underpinning PE representation. Moreover, interaction of age/development and substance abuse on PE signaling will need to be explored.

Keywords

substance abuse; decision-making; expected value; prediction error

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1.0 Introduction

Substance abuse (SA) is a major societal problem with enormous economic and human costs (Patel et al., 2016). SA problems have consistently been associated with deficits in decision-making (Bechara et al., 2002; Bechara and Damasio, 2002; Mazas et al., 2000). Recently, these impairments have been related to specific neural systems (in particular, ventral striatum and ventromedial prefrontal cortex; Kalivas and Volkow, 2005). However, relatively little research has addressed the computational impairments underpinning decision-making in individuals with SA histories (Krmptich et al., 2015; Stout et al., 2005, 2004). Yet, determining the specific forms of impairment will provide treatment targets for novel interventions.

Successful decision-making involves the representation of at least two critical computations: (i) expected value (EV) and prediction error (PE; Rescorla, 2002; Rescorla and Wagner, 1972). EV is the subjective value associated with an action or stimulus, which an individual has learned over time through experience. When an individual first encounters a stimulus, its EV will be 0 (assuming the individual has no expectation that the stimulus is associated with either reward or punishment). However, if the individual responds to the stimulus and gains reward its EV will increase (the stimulus has gained a positive subjective value). Responding to a novel stimulus and gaining punishment will result in a reduction in EV (and the stimulus may gain a negative subjective value). PE is the difference between the EV of the stimulus and the value of the feedback received. PEs signal that learning should occur leading to a revision of EV and thus more appropriate choice behavior in the future (Rescorla and Wagner, 1972). A positive PE occurs when feedback is a greater reward or less severe punishment than expected. A negative PE occurs when feedback is a more severe punishment or a lesser reward than expected. Ventromedial prefrontal cortex (vmPFC), posterior cingulate cortex (PCC) and striatum have been implicated in EV and PE signaling (Clithero and Rangel, 2014; O'Doherty, 2011, 2004). In addition, inferior frontal gyrus/ anterior insula cortex (iFG/aIC), dorsal anterior cingulate cortex (dACC) and striatum have been implicated in the avoidance of sub-optimal choices (Budhani et al., 2007; Casey et al., 2001) as a function of EV (Kuhnen and Knutson, 2005; Liu et al., 2007). Failure to represent EV or PE have been associated with decision-making deficits in a number of disorders, including Parkinson's Disease (Averbeck et al., 2013), conduct disorder (White et al., 2014, 2013), depression (Kumar et al., 2008) and generalized anxiety disorder (White et al., in press).

Computational neuroimaging allows testing of hypotheses related to both *how* and *where* a particular computational process, such as EV or PE, is being conducted in the brain (O'Doherty et al., 2007). Very few studies have examined PE during decision-making in individuals with SA histories. Tanabe and colleagues (2013) examined a version of the Iowa Gambling Task in adults with SA histories involving stimulant abuse (e.g., methamphetamine). In addition to observing that substance abusing individuals showed hyposensitivity to loss and more inconsistent responding, Tanabe et al. (2013) reported that individuals with histories of stimulant abuse showed weaker representation of PE in regions including medial orbitofrontal cortex (OFC), ventral striatum and insula. In contrast, work in

alcohol dependent adults did not observe significant differences in PE signaling in striatum (Park et al., 2010).

There are several limitations to the extant computational neuroimaging work, however. First, previous work has considered only PE and has not examined whether representation of EV in individuals with SA histories is intact. Second, and relatedly, the tasks used in previous research do not allow for the examination of the computational processes underpinning choice (EV) or to separate blood-oxygen-level-dependent (BOLD) signal generated during choice from BOLD signal generated during feedback. The inclusion of a jittered interval between the choice-and decision-phases is necessary to appropriately avoid contamination of the decision-phase BOLD response with BOLD response from the choice-phase (Amaro and Barker, 2006). Third, the extant computational work, both behavioral (Krmopotich et al., 2015; Stout et al., 2005, 2004) and neuroimaging (Park et al., 2010; Tanabe et al., 2013), has been conducted in adults. As such, it may not be directly translatable to understanding the difficulties faced by substance abusing adolescents. Notably, healthy adolescents show, increased correlation between activity within striatum and EV (Barkley-Levenson et al., 2013; Barkley-Levenson and Galván, 2014) and activity within striatum and ventrolateral frontal cortex and PE (Cohen et al., 2010) relative to adults. This perturbation in the neural signals critical for decision-making in adolescents may interact differentially with respect to risk factors/consequences of substance abuse. Yet, understanding the neural deficits underpinning SA in adolescence is critical. Nearly two-thirds of adolescents relapse within six months of treatment completion (Garner et al., 2007) and relapse rates are substantially higher for individuals who began abusing substances in adolescence (Chung and Maisto, 2006).

The current study utilized a simple passive avoidance task in youth with SA histories (SA_{positive}) and youth without SA histories (SA_{negative}). Subjects chose to respond or not respond to objects. When participants chose to respond to an object, probabilistic feedback followed. When participants chose not to respond to an object, no feedback followed. Critically, this version of passive avoidance allowed for the examination of (a) the computational processes related to choice and feedback separately and (b) the computational processes underpinning both approach and avoidance. Given that SA_{positive} youth show impairment in reinforcement-based decision-making (Bechara et al., 2002; Bechara and Damasio, 2002; Mazas et al., 2000), we made the following four hypotheses: As EV representation in vmPFC, ventral striatum and PCC is critical for successful reinforcement-based decision-making (Clithero and Rangel, 2014; Rangel and Clithero, 2012), we hypothesized that SA_{positive} youth, relative to SA_{negative} youth, would (i) show reduced EV representation in these regions when responding to objects. As EV representation in iFG/aIC and caudate is critical in avoiding sub-optimal responses (Blair and Cipolotti, 2000; Casey et al., 2001; Kuhn and Knutson, 2005; Liu et al., 2007), we hypothesized that SA_{positive} youth, relative to SA_{negative} youth, would show (ii) reduced EV representation in these regions when not responding to (i.e., avoiding) objects. Finally, as representation of PE in vmPFC, ventral striatum and PCC is critical for successful reinforcement-based decision-making and given previous reports of disrupted PE representation in SA_{positive} adults, we hypothesized that during feedback, SA_{positive} youth, relative to SA_{negative} youth, would show

(iii) reduced positive PE representation when receiving positive feedback; and (iv) reduced negative PE representation when receiving negative feedback in these regions.

2.0 Methods

2.1 Participants

Thirty-eight subjects participated: 22 SA_{negative} youth and 16 SA_{positive} youth (Table 1). Subjects were drawn from a residential treatment program. Youth were considered SA_{positive} if they endorsed using substances at intake (illegal substances and alcohol, but not tobacco) or if the participant's parent endorsed the youth using substances on the Child Behavior Checklist (CBCL; Achenbach, 2009). Youth endorsed abusing alcohol (N=3), marijuana (N=11) or both (N=2). It should be noted that use (as opposed to abuse) of other substances by youth in the sample is likely, but unknown. IQ was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI; two-subtest form; Wechsler, 1999). Exclusion criteria were pervasive developmental disorder, Tourette's syndrome, lifetime history of psychosis, neurological disorder, history of head trauma, on-going, non-psychiatric medical illness requiring medication that may have psychotropic effects (e.g. beta blockers or steroids) and IQ<80. All subjects had been enrolled in a treatment program and substance abstinent for at least 2 weeks at the time of scanning. The groups did not significantly differ on gender [$\chi^2=1.12$, $p=0.29$], race [$\chi^2=1.90$, $p=0.17$], age [$t(36)=0.96$, $p=0.34$] or IQ [$t(36)=0.65$, $p=0.52$]. Consistent with previous findings (Costello et al., 2003; Disney et al., 1999), SA_{positive} youth showed significantly higher levels of conduct problems as measured by the CD subscale of the CBCL [SA_{negative}=56.28, SA_{positive}=75.50; $t(36)=6.10$, $p<0.01$]. Informed consent and assent was obtained from parents/guardians and participating youth respectively. The Boys Town National Research Hospital Institutional Review Board approved all study procedures.

2.2 Passive Avoidance task

Participants completed a passive avoidance task presented in an event-related design where four images were presented (Figure 1). Images were basic shapes all of a single color (e.g. green square, blue cross). Trials began with a 1500ms image presentation, where participants either responded to the object (via button press) or chose not to respond. The image presentation was followed by a randomly jittered fixation (0–4000ms) and by a 1500ms feedback presentation. Choosing not to respond resulted in no feedback being presented (blank screen). Upon responding to an object, participants received one of four outcomes: win \$5, win \$1, lose \$1 or lose \$5. Each object could engender each of these outcomes. However, the feedback was probabilistic such that one object should result in a gain of \$18.57 over 10 trials, one a gain of \$7.14, one a loss of \$18.57 and one a loss of \$7.14. Failures to respond to either of the two objects that, over 10 trials, gained money were considered omission errors. Responding to either of the two objects that, over 10 trials, lost money were considered commission errors. Feedback was followed by another randomly jittered fixation (0–4000ms). Participants completed 108 trials (36 trials/object) over 3 runs.

EV and PE were modeled using computations developed by Averbeck and colleagues (Averbeck et al., 2013; Costa et al., 2014). A learning curve, based on participants'

behavioral data, was modeled establishing EVs and PEs for each object. EV for the first trial of each object was 0. PE was then calculated based on the feedback (F), which was coded 5 (\$5 win), 1 (\$1 win), -1 (\$1 loss) or -5 (\$5 loss) with the formula:

$$PE_{(t)} = F_{(t)} - EV_{(t)}$$

where the PE for the current trial_(t) equaled the feedback value for the current trial minus the EV for the current trial. EV was updated via the following formula:

$$EV_{(t)} = EV_{(t-1)} + (\alpha * PE_{(t-1)})$$

where the EV of the current trial_(t) equals the EV of the previous trial_(t-1) plus the PE of the previous trial multiplied by the learning rate (α). The learning rate is a data-derived estimate of the impact that new information has in updating EV for the next trial (Costa et al., 2014; O'Doherty et al., 2003; see Supplemental Materials). The learning rate of $\alpha=0.228$ was established on the basis of a population of youth ($N=77$), including the current participants, who performed the task used here.

2.3 MRI parameters

Participants were scanned using a 1.5-T Toshiba Vantage Titan scanner. A total of 93 functional images per run were taken with a gradient echo planar imaging (EPI) sequence (repetition time=3000 milliseconds; echo time=45 milliseconds; 64×64 matrix; 83° flip angle; 25cm field of view). Whole-brain coverage was obtained with 32 axial slices (thickness, 3mm; 1mm spacing; in-plane resolution, 3.91×3.91mm). A high-resolution anatomical scan (3-dimensional spoiled gradient recalled acquisition in a steady state; repetition time=12 milliseconds; echo time=5 milliseconds; 256mm field of view; 20° flip angle; 78 axial slices; thickness, 2mm; 256×256 matrix) in register with the EPI data set was obtained covering the whole brain.

2.4 Imaging data preprocessing

Imaging data were preprocessed and analyzed in AFNI (Cox, 1996). At the individual level, functional images from the first 5 repetitions, collected prior to equilibrium magnetization, were discarded. Functional images from the 3 time series were motion corrected and spatially smoothed with a 6-mm full-width half-maximum gaussian filter. The time series were normalized by dividing the signal intensity of a voxel at each point by the mean signal intensity of that voxel for each run and multiplying the result by 100. Resultant regression coefficients represented a percentage of signal change from the mean.

Following this, four parametrically modulated regressors were generated: objects chosen (modulated by EV), objects refused (modulated by EV), reward received (modulated by PE), punishment received (modulated by PE). All regressors were created by convolving the train of stimulus events with a gamma variate hemodynamic response function to account for the slow hemodynamic response. The participants' anatomical scans were then individually registered to the Talairach and Tournoux atlas (Talairach and Tournoux, 1988). The

individuals' functional EPI data were then registered to their Talairach anatomical scan. Linear regression modeling was performed using the 4 regressors described above entered both as un-modulated task regressors and parametrically modulated regressors plus regressors to model a first-order baseline drift function. This produced a modulated and un-modulated β coefficient and associated t statistic for each voxel and regressor. Effects of the modulated regressors can be interpreted as a measure of correlation between the parametric modulator and BOLD response in a region.

2.5 fMRI data analysis

The modulated coefficients from the individual subject analyses were entered into a 2 (group: SA_{negative}, SA_{positive}) by 2 (choice: approach, refuse) ANOVA in the choice-phase and a 2 (group: SA_{negative}, SA_{positive}) by 2 (feedback type: reward, punishment) ANOVA in the feedback-phase. The AFNI 3dClustSim program was used to establish a family-wise error corrected threshold (40 voxel clusters at $p=0.02$, corrected to $p=0.05$) for a whole-brain analysis. The results of the analysis using the un-modulated coefficients can be found in the Supplemental Results.

3.0 Results

3.1 Behavioral Results

A 2 (group: SA_{negative}, SA_{positive}) by 3 (run:1–3) by 2 (error type: commission errors, omission errors) repeated-measures ANOVA was conducted on the error data over the three runs of the task. A significant main effect of error type was observed [$F(1,43)=24.14$, $p<0.01$]. Participants made more commission errors than omission errors. A significant SA history-by-run interaction was observed [$F(2,42)=3.47$, $p=0.04$]. SA_{positive} and SA_{negative} youth did not differ in error rates during runs 1 and 2 [$t(43)=1.27$ & 0.81 , $p>0.21$]; however, SA_{positive} youth made significantly more errors than SA_{negative} youth in run 3 [$t(43)=2.58$, $p=0.01$]. A trend level effect of group was observed, where SA_{positive} youth showed more incorrect responses than SA_{negative} youth [$t(43)=3.26$, $p=0.08$]. No significant effects of run [$F(2,42)=1.88$, $p=0.17$], group-by-error type [$F(1,43)=1.17$, $p=0.29$], error-by-run [$F(2,42)=0.70$, $p=0.50$] or group-by-error-by-run were observed [$F(2,42)=.19$, $p=.83$].

3.2 fMRI Results

The goal of the current study was to examine the extent to which conduct problems levels were associated with aberrant correlation between BOLD signal and EV and/or PE. Group differences in the correlation between BOLD response and EV were tested using choice-phase data and a 2 (group: SA_{positive}, SA_{negative}) by 2 (choice: approach, refuse) ANOVA. Group differences in the correlation between BOLD response and PE were tested using feedback-phase data and a 2 (SA_{positive}, SA_{negative}) by 2 (feedback type: reward, punishment) ANOVA.

3.2.1 Choice-Phase Data Modulated by Expectancies of Reinforcement

3.2.2 Main Effect of Group—A significant main effect of group was observed in right middle frontal gyrus (Table 2). SA_{negative} youth showed a greater correlation between activity within this region and EV relative to SA_{positive} youth.

3.2.3 Main Effect of Choice—A significant main effect of choice was observed in regions including bilateral iFG/aIC and dmFC (Table 2). In all regions, a greater correlation between activity within this region and EV was observed when *not* choosing an object relative to choosing an object.

3.2.4 Group-by-Choice Interaction—Significant group-by-choice interaction effects were observed in left iFG, right iFG/STG, caudate, PCC, left lateral frontal cortex, left inferior parietal and right temporal pole (Table 2). In all regions, SA_{negative} youth showed a greater correlation between EV and BOLD response relative to SA_{positive} youth when choosing not to approach an object versus choosing to approach an object [$t=3.54-4.96$, $p<0.001$] (Figure 2).

Feedback Data Modulated by PE

3.2.5 Main Effect of Group—No significant main effects of group were observed for the modulated feedback-phase data.

3.2.6 Main Effect of Feedback Type—A significant main effect of feedback type was observed in vmPFC, right iFG/aIC and rACC (Table 3). In all regions, the correlation between BOLD response and PE was greater for reward PEs than punishment PEs.

3.2.7 Group-by-Feedback Type Interaction—A significant group-by-feedback type interaction was observed in posterior cingulate cortex/precuneus/lingual gyrus and bilateral cuneus (Table 3). In all regions, SA_{positive} relative to SA_{negative} youth showed a significantly greater difference in the correlation between BOLD response and punishment PEs and the correlation between BOLD response and reward PEs [$t=3.64$ to 5.13 , $p=0.001$]. Specifically, SA_{positive} youth showed a greater positive correlation between BOLD response and reward PEs and a greater negative correlation between BOLD response and punishment PEs, relative to SA_{negative} youth (Figure 3). The same group-by-feedback type interaction was also observed in vmPFC, albeit at a size below the extant voxel threshold ($k=14$). Within this region also there was a significantly greater difference between the correlation of BOLD response and PE during punishment feedback relative to rewarding feedback in the SA_{positive} relative to SA_{negative} youth [$t=3.95$, $p=0.001$].

4.0 Discussion

The goal of this study was to investigate the neural representation of both EV and PE during decision-making in adolescence with SA histories. There were three main findings. First, SA_{positive} youth showed less learning over the course of the task than SA_{negative} youth. Second, SA_{positive} youth showed reduced representation of EV within iFG/aIC and striatum. Third, SA_{positive} youth showed significant differences in the differential correlation between BOLD response and reward PEs relative to punishment PE within PCC relative to SA_{negative} youth.

Consistent with both predictions, SA_{positive} youth showed impaired decision-making. Specifically, SA_{positive} youth showed less improvement in behavioral performance over time relative to SA_{negative} youth. This finding is consistent with previous observations of

substance abusers who show a failure to learn appropriately from environmental cues in laboratory tasks (Bechara et al., 2002; e.g. Bechara and Damasio, 2002; Mazas et al., 2000). Decision-making impairments likely put the individual at greater risk for beginning drug abuse given the negative consequences of its use (American Psychiatric Association, 2013). Failure to appropriately learn about the negative consequences of SA likely increases the probability of continuing substance abuse. Moreover, substance abuse itself appears to compromise the functioning of the neural systems involved in decision-making (Kalivas and Volkow, 2005).

Also consistent with predictions, SA_{positive} youth showed disruption of the neuro-computations underpinning decision-making. Specifically, SA_{positive} youth showed reduced correlation between BOLD response and EV within bilateral iFG and striatum during avoidance responses relative to SA_{negative} youth. EV representation in iFG/aIC is involved in response control and has been implicated in guiding individuals away from sub-optimal choices (Blair and Cipolotti, 2000; Kuhn and Knutson, 2005; Liu et al., 2007). Thus, failure to show EV representation in this area is indicative of impairment in response control as a function of EV and likely reduces the chance that sub-optimal choices will be avoided in the future. Previous work has suggested that the impaired decision-making shown by individuals with SA is associated with failure to appropriately incorporate loss information into decision-making (Knutson et al., 2015; Stout et al., 2005, 2004). The current data suggest that this might reflect a relative failure in the use of punishment information to organize avoidance responses. This form of impaired response control, due to inadequate representation of EV information, would be expected to increase the probability that the individual will try behaviors that likely have negative consequences such as substance abuse.

In contrast to predictions, there were no group differences in the correlation between BOLD response and EV within vmPFC/striatum when *choosing* objects. Typically, healthy individuals demonstrate greater correlation between BOLD response and EV within vmPFC and striatum when choosing relative to not choosing an object (O'Doherty, 2011, e.g. 2004). We had predicted that SA_{positive} youth would show this to a lesser extent than SA_{negative} youth. However, neither of these regions showed a group-by-type interaction or a main effect of group. It should be noted, though, that these regions did not show significantly greater correlation between BOLD response and EV information for choose rather than avoid responses generally in the current study. While variants of the passive avoidance task have elicited EV representation in vmPFC and striatum previously (e.g. Finger et al., 2011; White et al., 2013), failure to generate EV signal in vmPFC and striatum has also been observed (e.g. White et al., 2014). It is possible that the passive avoidance task only reveals weak EV representation in vmPFC and striatum and that more consistent results would be observed in larger samples or a different paradigm (e.g., paradigms requiring participants to make explicit relative valuations of stimuli; c.f. Levy and Glimcher, 2011).

Also in contrast to predictions, SA_{positive} youth showed increased, rather than decreased differential correlation between BOLD response and PE within PCC/precuneus (and to a lesser extent vmPFC) to reward relative to punishment relative to SA_{negative} youth. The current findings stand in contrast to previous work suggesting that PE signaling in striatum is either reduced in SA_{positive} individuals (Tanabe et al., 2013) or intact in SA_{positive}

individuals (Park et al., 2010). The reason for the current inconsistency in findings is unclear. It may reflect age differences between the samples; the SA_{positive} participants in the current study were adolescents while those in Park and Tanabe were adults. Indeed, a meta-analysis examining BOLD response during reward anticipation and receipt found that adolescents show greater response to reward than adults (Silverman et al., 2015). Furthermore, Cohen and colleagues (2010) found that adolescents showed greater correlations between PE and activity within striatum relative to adults. It is possible that either risk factors for/ consequence of SA in *adolescents* exaggerate this increased PE signaling. Similarly, it is possible that the presumably shorter abuse histories of adolescents relative to adults might account for the differences observed in younger compared to older individuals. Alternatively, it may reflect differences in form of substance abuse history. The sample in the current study endorsed abusing marijuana and/or alcohol. Park and colleagues (2010) examined individuals with alcohol abuse histories while participants in the Tanabe et al (2013) study all abused stimulants (cocaine and methamphetamine). Future computational neuroimaging work will be necessary to distinguish between these possibilities.

It is also worth noting that differences BOLD response correlated with PE signaling were observed between SA_{positive} and SA_{negative} youth in a region encompassing PCC and precuneus (as well as lingual gyrus). It has been argued that exteroception, or neural representation of external/environmental stimuli, plays a key role in SA and that posterior midline structures, including PCC and precuneus, are dysfunctional during exteroception in SA_{positive} individuals (see DeWitt et al., 2015). Specifically, DeWitt and colleagues (2015) argue that “heightened exteroceptive processes” confer risk for and/or are a result of SA. For example, for an individual with SA problems, a cue associated with drugs (e.g. a syringe) might have increased salience and a stronger neural representation relative to an individual with no history of SA. It is possible that the increased differential correlation between BOLD response and PE observed in the current study may represent heightened exteroceptive processing. However, the current study was not designed examine exteroception specifically and the link between the current findings and the relationship between PE signaling and difficulties in exteroception experienced by SA_{positive} individuals will need to be explored.

The current data need to be interpreted in light of five caveats. First, the SA_{positive} youth had significantly higher levels of antisocial behavior relative to the SA_{negative} youth. It is possible that the dysfunction revealed in the current study relates to increased antisocial behavior rather than SA. It will be important to continue this work with antisocial behavior and SA only participant groups. Given the association between substance abuse and general antisocial behavior found here, it would not be statistically appropriate to covary out antisocial behavior in the current analysis (c.f. Miller and Chapman, 2001). Indeed, we hypothesize that the dysfunction revealed here may even *mediate* the relationship between SA and antisocial behavior. Second, callous-unemotional (CU) traits have been theorized to be implicated in decision-making deficits, particularly within antisocial youth (e.g. Blair, 2007). Notably, however, recent empirical work has found no relationship between CU traits and decision-making deficits (White et al., 2014, 2013). Similarly, no significant correlations between modulated BOLD response and CU traits were observed [$r = -0.06$ to 0.27 , $p > 0.31$], though this may reflect the small sample. Unfortunately, given the association between CU

traits and antisocial behavior (including SA), it is also not statistically appropriate to covary out CU traits in the current analysis (c.f. Miller and Chapman, 2001). Future work with larger participant samples will investigate these issues. Third, the current study uses a cross-sectional design. In the absence of longitudinal data is not possible to determine whether SA causes deficits in decision-making or if decision-making deficits increase risk for the development of SA. Longitudinal work tracking youth not yet using substances, but at high risk for doing so, will be needed to fully understand the development of SA problems. Fourth, the current paradigm cannot rule out the possibility that SA_{positive} youth were less motivated than SA_{negative} youth to complete the passive avoidance task (or were generally inattentive relative to the SA_{negative} youth). However, it is worth noting that a main effect of feedback type was observed in the modulated feedback data within rACC and right IFG/AIC. All participants showed greater positive correlations of activity within these regions with reward, relative to punishment, prediction errors. No group-by-feedback type interactions were present within these regions implicated in reinforcement-based decision-making. As such these data suggest that the SA_{positive} participants were, to some extent, motivated by the task since they showed typical levels of prediction error signaling in at least some core regions implicated in the response to reinforcement. Similarly, a main effect of choice was observed in the analysis on the unmodulated data (see supplemental materials). All participants showed greater responses when choosing an object relative to not choosing an object within inferior frontal and dorsolateral prefrontal cortex. Importantly, no group-by-choice interactions were observed in these regions implicated in attentional responding. These data suggest that the SA_{positive} participants showed the appropriate recruitment of attention-relevant regions when choosing relative to avoiding response options; i.e., they did not appear inattentive during choice. However, future work will need to disentangle the role of motivation relative to the role of EV in the decision-making deficits associated with SA. Fifth, while all SA_{positive} youth were enrolled in a treatment program at the time of scanning and should have been substance abstinent, subjects were not drug-tested before scanning. Thus, it is possible that some youth had used substances within 24 hours of scanning. However, the highly supervised, residential nature of the treatment program mitigates this possibility.

In summary, SA_{positive} youth show impaired decision-making and this impairment appears to be associated with problems representing EV information when attempting to avoid sub-optimal choices in bilateral iFG and striatum. In other words, SA_{positive} youth exhibit impairment in the neural representation of the computational components necessary for successful reinforcement-based decision-making. Disrupted decision-making is likely to exacerbate SA, as failures in response control are likely to increase the likelihood of making sub-optimal choices, including the decision to use substances. This may indicate that punishment-based SA intervention strategies will be less effective than reward-based strategies. Certainly, with respect to general antisocial behavior, there is evidence to suggest that punishing negative behaviors is less effective than rewarding positive replacement behaviors for some youth (Haas et al., 2011; Hawes and Dadds, 2005; Miller and Chapman, 2001). With respect to the representation of PE, future work will be needed to clarify the impact of different substances on the neural systems underpinning PE representation.

Moreover, interaction of age/development and substance abuse on PE signaling will need to be explored.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Youth with substance abuse histories demonstrated poorer learning in a passive avoidance task
- Youth with substance abuse histories showed dysfunction in representing expected value when avoiding sub-optimal choices
- Youth with substance abuse histories showed increased representation of prediction error in posterior cingulate cortex
- Failure to represent expected value during avoidance of sub-optimal choices may increase risk for substance abuse

Figure 1.

The Passive Avoidance Task. Participants were presented with four objects to which they chose to respond or not respond. Reinforcement was probabilistic. The selection of two of the objects would result in profit over the duration of the task; selection of the other two objects would result in loss. In column A, a participant chooses to respond and receives rewarding feedback. In column B, a participant chooses to respond and receives punishing feedback. In column C, a participant refuses to respond and receives no feedback. = participant chooses object

Figure 2.

Differential Correlations between BOLD response and Expected Value within the Inferior Frontal Gyrus During the Choice-Phase of a Passive Avoidance Task for 16 Youths with Substance Abuse Histories relative to 29 Youths without Substance Abuse Histories. Youth with substance abuse histories showed reduced representation of expected value in left inferior frontal gyrus relative to youth without substance abuse histories, suggesting disrupted representation of decision-making computations.

Figure 3. Differential Correlations between BOLD response and Punishment Prediction Error and BOLD response and Reward Prediction Error within Posterior Cingulate Cortex for 16 Youths with Substance Abuse Histories relative to 29 Youths without Substance Abuse Histories. Youth with substance abuse histories, relative to youth without substance abuse histories, showed a significantly greater difference in the correlation between BOLD response and punishment PEs and the correlation between BOLD response and reward PEs within posterior cingulate cortex (PCC).

Table 1

Characteristics of Youth with Substance Abuse Histories and Youth without Substance Abuse Histories.

	Youth without Substance Abuse Histories (N=29)		Youth with Substance Abuse Histories (N=16)	
Female youth	27.3%		43.8%	
Minority youth	22.7%		56.3%	
Alcohol abuse	0%		33.3%	
Marijuana abuse	0%		83.3%	
	Mean	Standard Deviation	Mean	Standard Deviation
Age	14.88	1.25	15.58	1.55
IQ	102.14	11.92	102.56	10.66

Brain Regions Demonstrating Differential BOLD Response Modulated by Expected Value During the Choice-Phase of a Passive Avoidance Task in 16 Youths with Substance Abuse Histories and 29 Youths without Substance Abuse Histories.

Table 2

Region ^a	Coordinates of Peak Activation ^b						p	Voxels
	Left/Right	BA	x	y	z	F		
Group-by-Choice Interaction								
inferior frontal gyrus	Left	47	-37.5	19.5	-21.5	14.93	0.0004	45
inferior frontal gyrus/superior temporal gyrus	Right	38	34.5	16.5	-21.5	14.63	0.0004	65
caudate	Left		-1.5	16.5	8.5	11.82	0.0013	69
posterior cingulate cortex	Left	31	-13.5	-43.5	38.5	13.10	0.0008	62
lateral frontal cortex	Left	10	-31.5	43.5	14.5	15.82	0.0003	50
inferior parietal cortex	Left	40	-55.5	-34.5	35.5	11.82	0.0013	57
temporal pole	Right	36	31.5	-4.5	-30.5	20.68	0.0001	81
Main Effect of Group (SA _{negative} > SA _{positive})								
middle frontal gyrus	Left	6	22.5	7.5	62.5	12.58	0.0009	47
Main Effect of Choice (object not chosen > object chosen)								
inferior frontal gyrus/anterior insula cortex	Right	13	31.5	19.5	5.5	15.41	0.0003	47
inferior frontal gyrus/anterior insula cortex	Left	13	-31.5	16.5	11.5	18.10	0.0001	53
dorsomedial frontal cortex	Right	6	1.5	13.5	47.5	21.86	0.0001	55

^aAccording to the Talairach Daemon Atlas (<http://www.nitrc.org/projects/tal-daemon/>).

^bBased on the Tournoux & Talairach standard brain template, BA= Brodmann's Area

Table 3

Brain Regions Demonstrating Differential BOLD Response Modulated by Prediction Error During the Feedback-Phase of a Passive Avoidance Task in 16 Youths with Substance Abuse Histories and 29 Youths without Substance Abuse Histories.

Region ^a	Coordinates of Peak Activation ^b					
	Left/Right	BA	x	y	z	F p Voxels
Group-by-Choice Interaction						
posterior cingulate cortex/precuneus/lingual gyrus	Left	19	-16.5	-49.5	-0.5	22.87 <0.0001 493
cuneus	Left	29	-10.5	-46.5	20.5	14.04 0.0005 48
cuneus	Right	18	13.5	-52.5	2.5	12.25 0.0011 47
Main Effect of Feedback Type (reward > punishment)						
ventromedial prefrontal cortex	Left	10	-1.5	49.5	11.5	22.45 <0.0001 141
rostral anterior cingulate cortex	Right	32	10.5	34.5	14.5	13.39 0.0007 60
inferior frontal gyrus/anterior insula cortex	Right	13	37.5	16.5	2.5	10.94 0.0019 43

^a According to the Talairach Daemon Atlas (<http://www.nitrc.org/projects/tal-daemon/>).

^b Based on the Tournoux & Talairach standard brain template, BA= Brodmann's Area