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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.

1. 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 (Krmpotich 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,

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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 (Krmpotich 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; Kuhnen 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. 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 [χ^2=1.12, p=0.29], race [χ^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 (Fig. 1). Images were basic shapes all of a single color (e.g. green square, blue cross). Trials began with a 1500 ms image presentation, where participants

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