Journal of Psychotherapy Integration
2014, Vol. 24, No. 2, 109–121

1053-0479/14/$12.00 http://dx.doi.org/10.1037/a0036975

Co-Occurring Depressive and Substance Use Disorders in Adolescents: An Examination of Reward Responsiveness During Treatment

Kathryn D. Boger, Randy P. Auerbach, Pia Pechtel, Alisa B. Busch, Shelly F. Greenfield, and Diego A. Pizzagalli
Mclean Hospital, Harvard Medical School

The goals of the present study were to examine: (a) putative dysfunctions in reward responsiveness in a sample of adolescents ($n = 40$) with co-occurring depressive and substance use disorders; (b) possible links between reward responsiveness and symptoms of depression, anhedonia, anxiety, and motivation for change in relation to alcohol and drug use; and (c) potential gender differences in findings. Before and after a 2-week residential treatment, adolescents completed self-report assessments of depression, anhedonia, anxiety symptoms, and motivation for change in relation to substance use. In addition, participants completed a computer-based Probabilistic Reward Task (PRT) to examine reward responsiveness (i.e., participants' ability to modulate behavior as a function of reinforcement history). Results indicated that depression and anhedonia symptoms decreased, and motivation for change in relation to drug use increased. Improved reward responsiveness over the course of residential treatment emerged in female, but not male, participants.

Keywords: reward responsiveness, adolescent, substance abuse, depressive disorders

According to recent data from the National Survey on Drug Use and Health, approximately 7% of adolescents in the United States meet criteria for a substance use disorder (National Survey on Drug Use and Health, U.S. Department of Health & Human Services, 2009), signifying a serious and costly public health concern. Substance use problems in adolescents also tend to coexist with other psychiatric conditions, and approximately 75% of adolescents with current alcohol and/or drug use disorders also meet criteria for mood, anxiety, or conduct disorders (Kandel et al., 1999). Adolescence is a crucial period for social/emotional, cognitive, and neural development, and therefore, substance- and psychiatric-related problems may profoundly disrupt healthy development. In fact, the presence of co-occurring substance and other psychiatric diagnoses among adolescents is associated with poor outcomes in terms of psychosocial functioning, school difficulties, medical illness, legal problems, homelessness, and suicide (U.S. Department of Health & Human Services, 2002), and may persist into adulthood (Harrington, Fudge, Rutter, Pickles, & Hill, 1990; Leshner, 1999).

Anhedonia in Depression and Substance Use Disorders

Anhedonia is a feature of both depressive and substance use disorders. It is a core symptom and potential trait marker for major depressive disorder (American Psychiatric Association,

Kathryn D. Boger, Randy P. Auerbach, Pia Pechtel, Alisa B. Busch, Shelly F. Greenfield, and Diego A. Pizzagalli, Department of Psychiatry, Mclean Hospital, Harvard Medical School.

Dr. Pizzagalli has received consulting fees from ANT North America Inc. (Advanced Neuro Technology), AstraZeneca, Shire, Servier, and Ono Pharma U.S.A. for projects unrelated to the current research. No other authors reported conflicts of interest. Ariel Sternberg should be acknowledged for her role in the collection of these data. Kathryn Boger was supported by the Andrew P. Merrill Research Fellowship award through Mclean Hospital. Randy P. Auerbach was partially supported through a Kaplen Fellowship on Depression awarded through Harvard Medical School and NIMH K23MH097786. Diego Pizzagalli was partially supported by NIMH R01MH68376 and 1R01MH095809 during this project. Alisa B. Busch received funding through Mclean Hospital and Shelly F. Greenfield was partially supported by NIDA K24DA019855.

Correspondence concerning this article should be addressed to Kathryn D. Boger, Department of Psychiatry, Mclean Hospital, Harvard Medical School, 115 Mill Street, deMarneffe, Room 240, Belmont, MA 02478. E-mail: kboger@partners.org

2000; Loas, 1996). Among depressed adolescents, research indicates that anhedonia may be a poor prognostic indicator as it is associated with longer time to remission and fewer depression-free days (McMakin et al., 2012). Similarly, anhedonia plays a key role in the onset and development of substance use disorders (Bovasso, 2001; Gawin & Ellinwood, 1988; Heinz, Schmidt, & Reischies, 1994; Miller, Summers, & Gold, 1993). Research has shown robust associations between anhedonia and the intensity of withdrawal, cravings, and relapse in substance dependence (Hatzigiakoumis, Martinotti, Giannantonio, & Janiri, 2011). However, to date, research has not examined the relationship between hedonic functioning and clinical outcomes at discharge from residential substance use disorder treatment. Critically, depression treatment research suggests that targeting the mechanisms underpinning anhedonia may, ultimately, improve treatment prognosis (e.g., McMakin et al., 2012).

Treatment for Adolescents With Co-Occurring Substance Use and Other Psychiatric Disorders

Adolescents with co-occurring substance use and other psychiatric disorders present with complex treatment needs. They exhibit poor adherence and retention in outpatient treatment, and relapse after treatment more frequently and more quickly as compared with adolescents with only substance use disorders (Grella, Hser, Joshi, & Rounds-Bryant, 2001; Tomlinson, Brown, & Abrantes, 2004). Acute residential treatment programs are thus a valuable resource for adolescents who have struggled in outpatient treatment and require a higher level of care. Yet, there is currently a dearth of research examining outcomes at discharge from short-term residential treatment for adolescents with co-occurring substance use and other psychiatric disorders. Moreover, in line with the National Institute of Mental Health Strategic Mission (http://www.nimh.nih.gov/about/strategic-planning-reports/nimh-strategic-plan-2008.pdf), there is a pressing need to examine putative mechanisms underlying symptom change in the context of treatment. To address these critical research gaps, the current study examined outcomes at discharge from short-term residential treatment for dually diagnosed adolescents in terms of changes in depression, anhedonia, anxiety, motivation for change and underlying hedonic functioning.

Deconstructing Anhedonia: An Examination of Reward Responsiveness

Mounting evidence highlights reward responsiveness as a key feature of hedonic functioning (Henriques, Glowacki, & Davidson, 1994; Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008; Pizzagalli et al., 2005). Reward responsiveness refers to the ability to modulate behavior as a function of previous reinforcement history. Past research utilizing a laboratory-based objective measure of hedonic functioning found that, compared with healthy individuals, depressed participants exhibit blunted reward responsiveness, which emerged as reduced response bias toward more frequently rewarded cues (Pizzagalli et al., 2008; Pizzagalli, Jahn, & O'Shea, 2005; Vrieze et al., 2012). This impairment correlated with self-reported anhedonic symptoms and predicted self-reported anhedonia one month after the initial assessment (Pizzagalli et al., 2008, 2005). In an adult inpatient sample, blunted reward responsiveness at study entry predicted the persistence of a major depressive disorder diagnosis after eight weeks of treatment (Vrieze et al., 2012).

There are a few studies on reward responsiveness in adolescents; however, preliminary results suggest that depressed youth exhibit patterns of reward deficits similar to those of adults. In a preadolescent sample of boys, depressed individuals did not attend to large versus small rewards in high probability conditions as frequently as did healthy boys (Forbes, Shaw, & Dahl, 2007). Such reward dysfunction was predictive of depressive symptoms and disorders 1 year later. Surprisingly, in spite of substantial gender differences in the prevalence of mood disorders (e.g., females $>$ males; Hankin Lakdawalla, Carter, Abela, & Adams, 2007) and substance use disorders (males $>$ females; Cohen et al., 1993), gender-specific differences in reward responsiveness have not been explored in individuals with co-occurring depressive and substance use disorders and there is no current information on whether adolescent reward responsiveness differs by gender.

Taken together, these findings suggest that blunted reward responsiveness may be an im-

portant predictor of depression outcome in adults and youth. Given that: (a) adolescence is a key developmental period for the onset of both substance use and depressive disorders (Kessler, Avenevoli, & Merikangas, 2001; Swendsen et al., 2012); (b) hedonic functioning plays a role in relation to both substance use disorders and depression; and (c) opposing gender differences exist in the prevalence of depressive and substance use disorders, further research is warranted to examine reward responsiveness in adolescents with comorbid depressive and substance use disorders and whether this differs by gender. Understanding the role of anhedonia in the treatment of these disorders may elucidate a key mechanism underlying therapeutic change in adolescents with co-occurring depressive and substance use disorders.

Goals of the Current Study

The current study examines depression, anhedonia, anxiety symptoms, motivation for change in relation to substance use, and reward learning in adolescents with co-occurring depressive and substance use disorders. To this end, adolescents in an acute residential treatment program for substance abuse and other psychiatric disorders completed self-report measures of clinical symptoms and motivation for change in relation to substance use as well as a computer-based probabilistic reward task to measure reward responsiveness upon admission and at discharge. We hypothesized that over the course of residential treatment, patients would: (a) exhibit improvement in depressive, anhedonic, and anxious symptoms and enhanced motivation for change in relation to substance use; (b) show increased reward responsiveness from admission to discharge; and (c) show gender-specific differences in improvement in hedonic functioning as measured through self-report and objective behavioral assessment.

Method

Participants

Participants included adolescents ($n = 40$, 16 females and 24 males) between the ages of 15 and 19 ($M = 17.07$, $SD = .98$) in a partially locked residential treatment program in the greater Boston area. In order to be admitted to the unit, adolescents must present with a substance use disorder and at least one co-occurring psychiatric disorder. Participants in the current sample were those presenting with a substance use and a depressive disorder (e.g., 22.5% *MDD*, 67.5% mood disorder not otherwise specified (NOS), 7.5% depressive disorder NOS, and 2.5% dysthymic disorder). Twenty-five percent of these patients also carried a diagnosis of anxiety disorder NOS and 5.0% had generalized anxiety disorder. At discharge, 50.0% of the participants (six females and 14 males) were being administered a selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI). Eighty percent of the participants who were on an SSRI or SNRI (five females and 11 males) were also on at least one additional psychotropic medication (e.g., mood stabilizers, benzodiazepines, etc.). Participants endorsed utilizing a variety of drugs, and they identified the following substances as causing the most difficulty prior to admission: 28.2% alcohol, 25.6% marijuana, 10.3% sedatives or sleeping pills, 10.3% prescription opiods, 5.1% prescribed amphetamine-based stimulants, 2.6% cocaine, 2.6% hallucinogens, and 2.6% nonprescription cough medicine (12.8% endorsed no recent difficulty with substances, despite the fact that they had been hospitalized for a substance use problem). Sixty-five percent of the adolescents lived with parents who were either married or in a marital-like relationship and 35.0% had parents who were divorced, separated, or widowed. Regarding socioeconomic status, 17.5% of the adolescents were enrolled in a free or reduced lunch program at school and 5.0% of families received food stamps. The sample was largely Caucasian (97.5%) with one patient self-identifying as "Other."

Residential Treatment Program

All participants were admitted to a residential program that provided short-term treatment ($M = 15.43$ days, $SD = 4.66$) comprised of motivational interviewing (MI), 12-step facilitation, cognitive–behavioral (CBT), and dialectical behavioral (DBT) therapies. Treatment was provided in the form of assessment, group counseling, individual therapy, family meetings, psychopharmalogic management for patients, as well as psychoeducation groups for

parents. A multidisciplinary staff worked collaboratively with families, community-based clinicians, schools, and social service agencies to establish treatment goals and discharge plans.

Procedure

Mclean Hospital Internal Review Board provided approval for the study. Upon admission, adolescents and their parents were informed of the project aims, and then, adolescent assent and parent consent were obtained. Participants' diagnostic information was determined based on *DSMIV-TR* criteria by staff psychiatrists in consultation with the accompanying treatment teams (i.e., social worker and/or clinical psychologist), and participants identified their primary substance of abuse. Within 24 hr of admission, adolescents completed an assessment battery of self-report measures including the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977), the Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995), the Multidimensional Anxiety Scale for Children (MASC; March, Sullivan, & Parker, 1999), the Stages of Change Readiness and Treatment Eagerness Personal Drug Use and Drinking Questionnaires (SOCRATES; Miller & Tonigan, 1996) as well as a computerized probabilistic reward task. The same assessment battery was completed at discharge.

Instruments

Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). The CES-D is a 20-item self-report measure examining the presence of depressive symptoms. Participants are instructed to rate, using a scale ranging from 0 (*rarely or none of the time*) to 3 (*most of the time*), how often they experienced particular feelings over the past week. Sample items include, "I felt depressed" and "I felt that everything I did was an effort." In the present study, the Cronbach's alpha ranged from .79 to .92 across administrations, indicating high internal consistency.

Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995). The SHAPS is a 14-item self-report inventory assessing hedonic capacity. Participants are asked to rate their ability to experience pleasure in the last few days and using a scale ranging from 0 (*strongly disagree*) to 3 (*strongly agree*). Examples of items are, "I would find pleasure in my hobbies and pastimes" and "I would enjoy seeing other people's smiling faces." In this study, the Cronbach's alpha ranged from .70 to .86 between administrations, indicating high internal consistency.

Multidimensional Anxiety Scale for Children (MASC; March et al., 1999). The MASC is a 39-item self-report inventory measuring the presence of anxious symptoms, including overall anxiety, physical symptoms, social anxiety, harm avoidance, and separation anxiety. Items are rated on a 4-point Likert scale, ranging from 0 (*never applies to me*) to 3 (*often applies to me*), and higher scores are indicative of greater anxiety. Examples of questions include, "I keep my eyes open for danger" and "I have trouble getting my breath." In this study, the Cronbach's alpha ranged from .89 to .94 across administrations, indicating high internal consistency.

The Stages of Change Readiness and Treatment Eagerness Personal Drug Use and Personal Drinking Questionnaires (SOCRATES 8d; Miller & Tonigan, 1996). The Socrates Personal Drug Use Questionnaire and the Socrates Personal Drinking Questionnaire are each 19-item self-report inventory measuring motivation for change in relation to drug and alcohol use, respectively. Items are rated on a 5-point Likert scale, ranging from 1 (*no, strongly disagree*) to 5 (*yes, strongly agree*), and higher scores are indicative of greater motivation for change in relation to drug and alcohol use. In this study, the Cronbach's alpha ranged from .89 to .95 (drug use) and .96 to .98 (drinking), respectively, across administrations, indicating high internal consistency.

Behavioral Task

Probabilistic Reward Task (PRT; Pizzagalli, Jahn, & O'Shea, 2005, modified after Tripp & Alsop, 1999). Participants completed a revised version of the PRT, which used an asymmetric reinforcement schedule of monetary feedback to examine reward responsiveness (i.e., ability to modulate behavior as a function of reward reinforcement history). The 15-min task was presented on a 17" laptop monitor using E-Prime software (Version 1.1.; Psychology Software Tools Inc., Pittsburgh, Pennsylvania). The task consists of 200 trials, divided into two blocks of 100 trials. Each trial

starts with a fixation cross (500 ms), followed by a mouthless cartoon face (500 ms) presented in the center of the screen. After a delay of 500 ms, either a short mouth (11.5 mm) or a long mouth (13 mm) is presented for 100 ms. Participants are instructed to press the respective keys ("c" or "m") on the keyboard to identify whether the mouth was short or long. The face without the mouth remains on the screen until a key response is made. Key responses were counterbalanced from pre- to posttreatment assessment in order to avoid practice effects. For each block, the long and short mouths are presented equally often in a pseudorandomized sequence. Critically, an asymmetrical reinforcer ratio is utilized in order to induce a response bias; specifically, correct identification for one stimulus (hereafter referred as the rich stimulus) is rewarded three times more frequently than correct identification of the other (lean) stimulus. Correct responses received points, and participants were instructed that the goal of the task was to earn a maximum number of points. Participants completed a short series of practice trials to ensure that they understood the instructions. In previous research, the PRT has demonstrated significant but moderate test–retest reliability (see Pizzagalli et al., 2005; Santesso et al., 2008).

Data Analytic Approach

Paired sample *t* tests were used to compare admission versus discharge symptom scores (depressive symptoms, anhedonia, and anxious symptoms). Bivariate correlations were utilized to examine baseline association among depressive symptoms, anhedonia, anxious symptoms, and motivation for change in relation to drug and alcohol use.

For the PRT, established criteria (e.g., Pizzagalli et al., 2005) were first used to identify and exclude outlier trials: (a) trials with RTs of $<$ 150 ms or $>$ 1,500 ms were removed and (b) RTs falling outside the mean $\pm$ 3 standard deviation of the remaining trials (after log transformation). Next, signal detection theory (Macmillian & Creelman, 2005) was used to compute response bias (i.e., the preference for the more frequently rewarded stimulus) and discriminability (i.e., the ability to distinguish between the stimuli types) following established procedures and formulas (see Pizzagalli et al., 2008; Pizzagalli et al., 2005). Accuracy (percent correct responses) and reaction time (RT) were used as secondary measures of overall task performance.

Response bias and *discriminability* were calculated as follow:

Response Bias:

$$Log\ b = \frac{1}{2}\log\frac{\text{RICH correct*LEANincorrect}}{\text{RICHincorrect*LEANcorrect}}$$

Discriminability:

$$Log\ d = \frac{1}{2}\log\frac{\text{RICH correct*LEANcorrect}}{\text{RICHincorrect*LEANincorrect}}$$

In line with prior recommendations (Hautus, 1995), 0.5 was added to every cell of the detection matrix to allow computations in cases with a zero in one cell of the formula. Response bias was the primary behavioral measure of interest reflecting the magnitude of participants' preference for the more frequently reinforced stimulus, which yields an objective measure of reward responsiveness. A high response bias emerges when participants correctly identify the rich and misclassify the lean stimulus as the rich stimulus.

To examine our hypotheses, a Treatment (pre, post) $\times$ Block (1, 2) $\times$ Gender (male, female) mixed ANOVA was run for response bias. An analogous (control) analysis was run on discriminability scores. For accuracy and RT values, separate Treatment (Pre, Post) $\times$ Block (1, 2) $\times$ Stimulus (rich, lean) $\times$ Gender (male, female) ANOVAs were performed. For all analyses, the Greenhouse-Geisser correction was used where applicable. Significant findings were followed-up with Bonferroni post hoc tests to provide a conservative test of all stated hypotheses. Finally, bivariate Pearson's correlations coefficient examined associations among response bias, depressive symptoms, anhedonia, anxious symptoms, and motivation for change in relation to drug and alcohol use at admission and discharge.

Results

Descriptive Statistics

Bivariate correlations, means, standard deviations, and ranges of all admission measures are

presented in Table 1. Additionally, Table 2 provides descriptive data as a function of gender as well as bivariate correlations. Of note, there were no significant gender differences in depressive, anxious, or anhedonic symptoms upon admission.

Clinical Outcome Data

Over the course of acute residential treatment, adolescents exhibited significant reductions in depressive symptoms, $t(39) = 4.17$, $p < .001$, and anhedonic symptoms, $t(39) = 2.98$, $p = .005$, but not anxious symptoms, $t(39) = 1.76$, $p = .087$. Importantly, during the course of residential treatment, adolescents also demonstrated increased recognition of their drug problem, $t(39) = -3.15$, $p = .003$, as well as steps taken toward change in relation to drug use, $t(39) = -4.97$, $p < .001$. There were no significant differences in these outcomes between males and females. Of note, there were also no significant differences between males and females in the use of SSRI/SNRI medications ($\chi^2 = 1.67$, $p = .20$).

Response Bias

For response bias, a mixed ANOVA with Treatment (Pre, Post) × Block (1, 2), and Gender (male, female) revealed a main effect of Treatment, $F(1, 38) = 5.25$, $p = .028$. Post hoc tests confirmed that over the course of residential treatment, adolescents' reward responsiveness improved ($p = .028$; see Figure 1). Follow-up analysis (paired t tests) revealed that girls, $t(15) = -3.23$, $p = .006$, but not boys, $t(23) = -0.62$, $p = .542$, exhibited a significant increase in response bias from admission to discharge (see Figure 2), although the Treatment × Gender interaction did not reach significance, $F(1, 38) = 2.80$, $p = .10$. No other effects emerged (all ps > 0.14).

Discriminability

A mixed ANOVA with Treatment (Pre, Post) × Block (1, 2) × Gender (male, female) for discriminability revealed a significant Treatment × Block interaction, $F(1, 38) = 4.61$, $p = .038$. Paired t tests revealed a significant increase in discriminability between Blocks 1 and 2 at discharge, $t(39) = -2.22$, $p = .032$, but not admission, $t(39) = 0.74$, $p = .47$. No other main effects or interaction effects emerged (all ps $> .18$).

Reaction Time

A mixed ANOVA with Treatment (Pre, Post) × Block (1, 2) × Stimulus Type (rich, lean) × Gender (male, female) revealed a Main effect for Stimulus Type, $F(1, 38) = 14.68$, $p < .001$, which was qualified by a significant

Table 1
Pearson Correlations, Means, Standard Deviations, and Range for Baseline Instruments in the Total Sample (N = 40)

Variables	1	2	3	4	5	6	7	8	9
1. CESD	—								
2. SOCRATES–Drug recognition	.38*	—							
3. SOCRATES–Drug ambivalence	.49**	.69**	—						
4. SOCRATES–Drug taking steps	−.18	.25	.00	—					
5. SOCRATES–Drinking recognition	.21	.49**	.22	.05	—				
6. SOCRATES–Drinking ambivalence	.26	.29	.43**	−.14	.74**	—			
7. SOCRATES–Drinking taking steps	.01	.19	.10	.34*	.67**	.48**	—		
8. MASC	.51**	.22	.37*	.14	.07	.18	.04	—	
9. SHAPS	.28**	.01	.28	−.28	−.05	.16	−.07	.03	—
Mean	22.33	22.13	12.7	28.96	15.97	9.13	21.47	42.58	2.35
Standard deviation	12.89	7.20	3.76	5.90	8.21	4.55	9.73	16.10	2.99
Low score	3	7	4	10	7	4	8	13	0
High score	51	35	19	40	35	17	40	72	12

Note. CES-D = Center for Epidemiologic Studies Depression Scale; SOCRATES = The Stages of Change Readiness and Treatment Eagerness Scale; MASC = Multidimensional Anxiety Scale for Children; SHAPS = Snaith-Hamilton Pleasure Scale.
* $p < .05$. ** $p < .01$.

Table 2
Pearson Correlations, Means, Standard Deviations, and Range for Baseline Instruments in the Total Sample in Girls (n = 16) and Boys (n = 24)

Variables	1	2	3	4	5	6	7	8	9
1. CESD	—	.49	.65**	−.16	.26	.34	−.04	.52*	.49
2. SOCRATES–Drug recognition	.31	—	.70**	.32	.53*	.23	.29	.30	.11
3. SOCRATES–Drug ambivalence	.44*	.71**	—	.03	.32	.64**	.20	.52*	.37
4. SOCRATES–Drug taking steps	−.17	.17	−.09	—	.14	−.15	.30	.04	−.20
5. SOCRATES–Drinking recognition	.15	.48*	.18	−.02	—	.55*	.74**	.10	−.02
6. SOCRATES–Drinking ambivalence	.22	.36	.22	−.15	.88**	—	.41	.26	.32
7. SOCRATES–Drinking taking steps	−.00	.13	.06	.43*	.63**	.54**	—	.03	−.08
8. MASC	.55**	.13	.13	.26	.05	.12	.07	—	−.05
9. SHAPS	.47*	−.13	.21	−.41*	−.12	−.03	−.11	.20	—
Mean									
Boys	20.29	22.33	13.29	29.38	15.42	9.25	20.50	43.21	2.02
Girls	25.37	21.81	11.81	28.34	16.79	8.94	22.91	41.62	2.84
Standard deviation									
Boys	12.15	6.57	2.74	4.91	8.36	4.47	9.97	13.90	2.11
Girls	13.75	8.26	4.87	7.28	8.18	4.80	9.49	19.39	3.99
Low score									
Boys	3	7	7	18	7	4	8	13	0
Girls	3	7	4	10	7	4	8	17	0
High score									
Boys	41	33	18	39	34	17	40	67	8
Girls	51	35	19	40	35	17	37	72	12

Note. Pearson correlations for girls on the top portion of the diagonal and on the bottom portion of the matrix for boys. CES-D = Center for Epidemiologic Studies Depression Scale; SOCRATES = The Stages of Change Readiness and Treatment Eagerness Scale; MASC = Multidimensional Anxiety Scale for Children; SHAPS = Snaith-Hamilton Pleasure Scale.
* $p < .05$. ** $p < .01$.

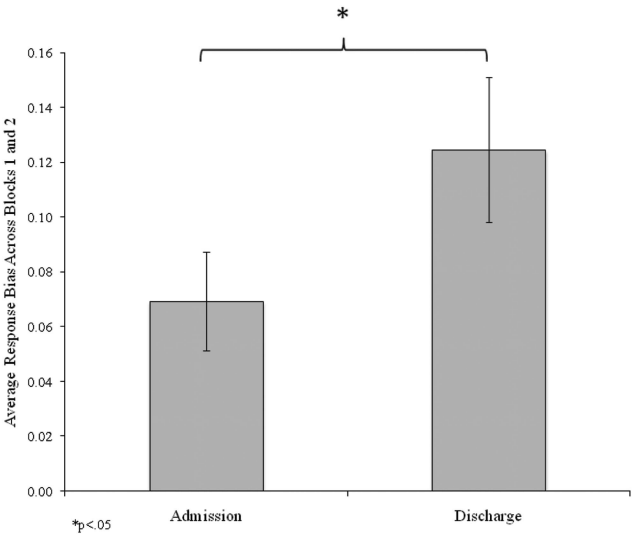

Figure 1. Overall task effect for response bias (averaged across blocks).

Block × Stimulus Type interaction, $F(1, 38) = 9.39$, $p = .004$. As expected in light of the asymmetrical reinforcement schedule, adolescents were faster in responding to the rich versus lean stimuli ($p < .001$); moreover, adolescents responded faster to the rich versus the lean stimulus in Block 2, $t(39) = -6.35$, $p < .001$, but not in Block 1, $t(39) = -1.27$, $p = .21$, indicating a successful reward manipulation. Critically, these effects were further qualified by a Treatment × Stimulus Type effect, $F(1, 38) = 9.63$, $p = .004$, which was due to the fact that adolescents were faster to respond to the rich versus lean stimuli at discharge, $t(39) = -5.22$, $p < .001$, but not admission, $t(39) = -1.34$, $p = .19$. Finally, there was a Block × Gender, $F(1, 38) = 7.87$, $p = .008$, effect, which indicated a trend for females to be faster

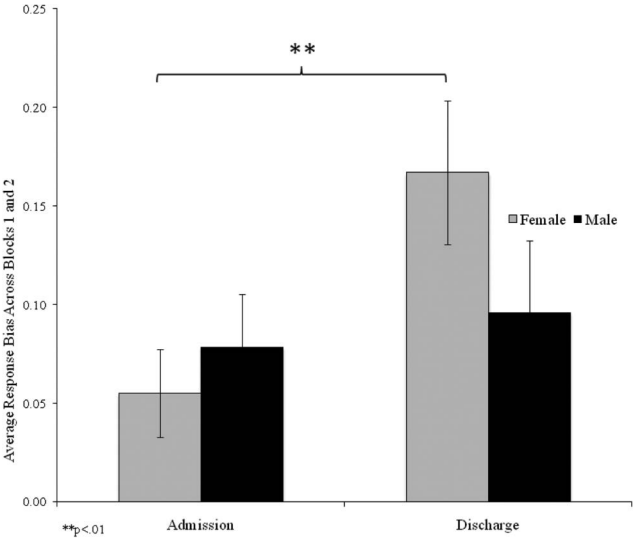

Figure 2. Overall task effect for response bias (averaged across blocks) by gender.

in Block 2 versus Block 1, $t(15) = -2.08$, $p = .055$, and a trend for males to be faster in Block 1 versus Block 2, $t(23) = 1.81$, $p = .08$. No other effects emerged (all $ps < .11$).

Accuracy

With regard to accuracy, a mixed ANOVA with Treatment (Pre, Post) × Block (1, 2) × Stimulus Type (rich, lean) × Gender (male, female) revealed a main effect for Stimulus Type, $F(1, 38) = 24.92$, $p < .001$, due to greater accuracy for the rich versus lean stimulus. There was also a Treatment × Block interaction, $F(1, 38) = 4.38$, $p = .043$. Paired t tests revealed a trend for improvement in accuracy between Blocks 1 and 2 at discharge, $t(39) = -1.97$, $p = .056$, but not admission, $t(39) = 0.99$, $p = .33$. No other effects emerged (all $ps > .11$).

Relationship Between Self-Report Data and Response Bias

Contrary to our hypotheses, there were no significant correlations between baseline or discharge response bias and depressive symptoms or anhedonic symptoms at these time points. There were also no significant correlations between change in response bias from admission to discharge and change in depressive symptoms or anhedonic symptoms over the course of treatment. However, change in response bias from admission to discharge was negatively correlated with change in anxiety from admission to discharge ($r = -.359$, $p = .023$). There were no significant differences between males ($r = -.384$, $p = .064$) and females ($r = -.325$, $p = .219$) in relation to this finding.

Discussion

In the current study, we investigated changes in symptoms and reward responsiveness in a sample of adolescents with co-occurring depressive and substance use disorders who completed acute residential treatment. To our knowledge, this is the first study to examine reward processing in relation to outcomes among adolescents with these co-occurring disorders. In line with our first hypothesis, adolescents demonstrated significant reductions in depressive and anhedonic symptoms and improved motivation for change in relation to drug use over the course of acute residential treatment. Consistent with our second hypothesis, the results showed improved reward responsiveness from admission to discharge. Partially confirming our third hypothesis, female, but not male, participants exhibited improvements in reward responsiveness during acute residential treatment. Taken together, these results suggest that, in the context of short-term, residential treatment (which included abstinence), adolescents experienced improvement in depressive symptoms as well as reward responsiveness, which is promising given the complexity of the presenting problems and potential chronicity of anhedonia. These findings also build upon the existing literature on reward deficits and adolescent depression by indicating that reward responsiveness may be a feature co-occurring depressive and substance use disorders that is responsive to treatment and/or abstinence. Several findings warrant additional attention.

Presently, the effectiveness of short-term residential treatment for youth with co-occurring depressive and substance use disorders is not established. Importantly, results from the current study indicate that patients showed significant improvements in depressive symptoms, hedonic capacity, and motivation for change in relation to drug use over the course of acute residential treatment with a relatively brief length of stay ($M = 15$ days). Although adolescents improved significantly in terms of their depressive symptoms, their average depressive symptom score at discharge ($M = 15.93$) approached the clinical range. Previous research indicates that a higher level of depressive symptoms upon treatment discharge is associated with a greater likelihood of relapse to substance use (Dodge, Sindelar, & Sinha, 2005), and adolescents also exhibited greater recognition of their drug problem and increased motivation for change in relation to drug use upon discharge. Thus, these improvements in depressive and anhedonic symptoms could have implications for sustained sobriety, recovery, and outpatient functioning. Further posttreatment follow-up assessments would be necessary to examine the extent of these potential implications over time.

Treatment response has typically been assessed through symptom change over the course of treatment (Siegle, Carter, & Thase, 2006). Yet, the National Institute of Mental Health

(NIMH) mission underscores the critical need to investigate putative mechanisms that may underlie symptom change in treatment. This study is among the first to examine changes in anhedonia using an objective measurement. The results indicate that reward responsiveness improves during acute residential treatment. With regard to the specific indicators of task performance, adolescents became faster and more accurate in responding to the more frequently rewarded versus the less rewarded stimulus over time, lending support to the effectiveness of the task in establishing a preferential response to positive reinforcement. Additionally, adolescents did not exhibit difficulty in differentiating the rich and lean stimulus. These results are consistent with previous findings (e.g., Pizzagalli et al., 2008; Pizzagalli et al., 2005). As adolescents were faster in responding to the rich as opposed to the lean stimulus over time, it suggests that the probabilistic behavioral reinforcement schedule was effective in establishing a preference for the more frequently rewarded stimulus. These results bolster the response bias findings and provide preliminary support for the use of this current task with a dually diagnosed adolescent population.

Our findings are consistent with what we would expect to find in a depression-only sample (Vrieze et al., 2012), and they hold promising implications for adolescents with co-occurring depressive and substance use disorders as anhedonia is believed to be a poor prognostic indicator among patients with depression and substance use (Hatzigiakoumis, Martinotti, Giannantonio, & Janiri, 2011; McMakin et al., 2012). Therefore, improvements in reward responsiveness may suggest a reduced likelihood for depressive disorder recurrence *and* substance relapse. Specifically, at discharge, improved hedonic functioning may result in sustained engagement in goal-directed recovery behaviors, such as attending outpatient treatment, self-help groups, school, and extracurricular activities.

As a whole, these findings suggest that this clinical complex adolescent population experiences improvements in self-reported symptoms and reward processing during acute residential; however, it is not yet clear *how* these critical changes occur. Prior research indicates that response bias is associated with striatal (Santesso et al., 2008) and dopaminergic functioning (Vrieze et al., 2013), and unmedicated subjects with major depression show reduced striatal reactivity to rewards (Pizzagalli et al., 2009). Thus, the improved reward responsiveness exhibited in this study may reflect improvements in striatal functioning as a result of treatment. Although the current study was not designed to specifically address this issue, it highlights the importance of assessing core behavioral indicators that underlie depressive and substance use disorders. Future studies would benefit from examining symptom, behavioral, and neurobiological mechanisms in order to ascertain the direction of effects associated with treatment response, and in doing so, may better target key mechanisms implicated in the maintenance and recurrence of psychopathology.

This study also highlights gender differences as females, but not males, exhibited significantly improved reward responsiveness following acute residential treatment. Critically, there were no significant gender differences in depressive or anhedonic symptoms at baseline, nor were there significant differences in self-reported symptom change as a function of gender. It is interesting that subjective reports of symptom change were similar between the genders although the objective measurement of hedonic functioning (i.e., reward responsiveness) was not. These findings suggest that improvements in reward responsiveness could reflect clinical change that is less prone to the biases of self-report, which underscores the importance of assessing core behavioral markers that underlie depressive and substance use disorders. Furthermore, these data may provide information about who is likely to improve with acute residential treatment (and/or abstinence). It is possible that, owing gender differences in maturity and social development during adolescence (Silberman & Snarey, 1993), female participants are better able to engage and capitalize upon the treatment. However, given the preliminary nature of these findings and the small sample size, study replication is warranted to better understand these gender differences.

Another important component of these findings is that half of the participants in the study were taking medications targeting the serotonin or norepinephrine systems implicated in reward processing. SSRI's can reduce reward responsiveness, even over a short period of time (i.e., after only 7 days; McCabe, Mishor, Cowen, & Harmer, 2010). Yet, reward responsiveness *in-*

creased in this study, despite the number of adolescents on SSRI/SNRI medications. Furthermore, males and females did not differ significantly in their use of these medications, indicating that gender differences in response bias were not due to medication alone. Hence, the degree of improvement following treatment/abstinence in this investigation may represent a conservative estimate of the magnitude of improvement.

Several limitations should be noted. First, individuals in this study received a variety of interventions, including acute residential treatment (which entailed individual and group psychosocial interventions, family interventions, and psychopharmacologic treatment) and abstinence. Given this, it is difficult to determine the specific active ingredient(s) contributing to symptom attenuation. Ideally, one could determine the degree to which abstinence specifically contributed to these observed improvements; however, a relevant comparison group would be difficult to obtain in usual care acute residential treatment settings given that: (a) residential treatment programs are abstinence-based as the standard of care, and (b) adolescents who could remain abstinent during outpatient treatment would not meet admission criteria for acute residential level of care. Additionally, this usual care study sample included patients with multiple psychiatric diagnoses, representing different levels of symptomatology and readiness for change. However, this study sample and methodology is consistent with the aims of effectiveness research that underscores the importance of studying outcomes in usual care patient populations and settings (see Depp & Lebowitz, 2007; Weiss, Guidi, & Fava, 2009; Weisz, Donenberg, Han, & Weiss, 1995). Second, the sample was relatively small and largely Caucasian, and it is therefore unclear whether the findings would generalize to more diverse samples.

Psychotherapy Integration

Comorbidity is the rule rather than the exception with approximately 79% of patients experiencing comorbidity (Kessler et al., 1994). Although randomized clinical trials (RCTs) are the gold standard to examine the efficacy of specific psychotherapeutic and pharmacologic approaches, there is a critical need to understand successful components that drive effectiveness-based treatment. The current study underscores the importance of targeting core phenotypes (i.e., anhedonia) that cut across disorders, in the context of a multimodal approach to treatment. On the one hand, it is unclear which component of treatment implementation (i.e., CBT, IPT, DBT, family therapy, medication) is leading to the most significant symptom reductions. At the same time, given the heterogeneity in terms of symptoms, severity, substance use, family environment, and motivation within treatment, an integrative approach provides an ideal opportunity to meet a patient (and family) at place of his or her own readiness. The truth of the matter is that different patients attach to different aspects of treatment—some of which are more easily measurable (i.e., skill acquisition) – some of which are more difficult to operationalize (i.e., milieu effect). Residential facilities, especially insurance-based programs, do not have the luxury of pruning their patient population to satisfy RCT-equivalent inclusion and exclusion criteria, and thus, utilizing an integrative approach to treatment addresses the profound diversity surrounding patient needs. Such an approach provides the most success as it allows different patients with an array of needs to find relevant and identifiable therapeutic anchors from which they can build toward recovery. Thus, although the therapeutic options within the treatment program follow the guidelines of empirically based treatments, it may in fact be the gestalt, or integration therein, which helps drive successful outcomes.

Implications and Future Directions

This study highlights reward processing as a potentially important mechanism underpinning anhedonia among adolescents in acute residential treatment for depressive and substance use disorders. Incorporating objective markers with self-reported symptom reduction may shed important light on “how” and “why” symptom functioning improves. Such work is critical for both the development and refinement of treatment programs and may, in time, lead to an improved understanding of the etiological mechanisms that underpin substance and related disorders, which would allow us to provide more efficient and effective interventions.

References

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: American Psychiatric Association

Bovasso, G. B. (2001). Cannabis abuse as a risk factor for depressive symptoms. *The American Journal of Psychiatry, 158,* 2033–2037. doi:10.1176/appi.ajp.158.12.2033

Cohen, P., Cohen, J., Kasen, S., Velez, C. N., Hartmark, C., Johnson, J., . . . Streuning, E. L. (1993). An epidemiological study of disorders in late childhood and adolescence—I. Age-and gender-specific prevalence. *Journal of Child Psychology and Psychiatry, 34,* 851–867. doi:10.1111/j.1469-7610.1993.tb01094.x

Depp, C., & Lebowitz, B. D. (2007). Clinical trials: Bridging the gap between efficacy and effectiveness. *International Review of Psychiatry, 19,* 531–539. doi:10.1080/09540260701563320

Dodge, R., Sindelar, J., & Sinha, R. (2005). The role of depression symptoms in predicting drug abstinence in outpatient substance abuse treatment. *Journal of Substance Abuse Treatment, 28,* 189–196. doi:10.1016/j.jsat.2004.12.005

Forbes, E. E., Shaw, D. S., & Dahl, R. E. (2007). Alterations in reward-related decision making in boys with recent and future depression. *Biological Psychiatry, 61,* 633–639. doi:10.1016/j.biopsych.2006.05.026

Gawin, F. H., & Ellinwood, E. H. (1988). Cocaine and other stimulants: Actions, abuse and treatment. *The New England Journal of Medicine, 318,* 1173–1182. doi:10.1056/NEJM198805053181806

Grella, C. E., Hser, Y., Joshi, V., & Rounds-Bryant, J. (2001). Drug treatment outcomes for adolescents with comorbid mental and substance use disorders. *Journal of Nervous and Mental Disease, 189,* 384–392. doi:10.1097/00005053-200106000-00006

Hankin, B. L., Lakdawalla, Z., Carter, I. L., Abela, J. R. Z., & Adams, P. (2007). Are neuroticism, cognitive vulnerabilities and self-esteem overlapping or distinct risks for depression? Evidence from exploratory and confirmatory factor analyses. *Journal of Social and Clinical Psychology, 26,* 29–63. doi:10.1521/jscp.2007.26.1.29

Harrington, R., Fudge, H., Rutter, M., Pickles, A., & Hill, J. (1990). Adult outcomes of child and adolescent depression. I. Psychiatric status. *Archives of General Psychiatry, 47,* 465–473. doi:10.1001/archpsyc.1990.01810170065010

Hatzigiakoumis, D. S., Martinotti, G., Giannantonio, M. D., & Janiri, L. (2011). Anhedonia and substance dependence: Clinical correlates and treatment options. *Frontiers in Psychiatry, 2,* 1–12.

Hautus, M. J. (1995). Corrections for extreme proportions and their biasing effects on estimated values of *d′*. *Behavior Research Methods, Instruments & Computers, 27,* 46–51. doi:10.3758/BF03203619

Heinz, A., Schmidt, L. G., & Reischies, F. M. (1994). Anhedonia in schizophrenic, depressed, or alcohol-dependent patients. *Pharmacopsychiatry, 27,* 7–10. doi:10.1055/s-2007-1014317

Henriques, J. B., Glowacki, J. M., & Davidson, R. J. (1994). Reward fails to alter response bias in depression. *Journal of Abnormal Psychology, 103,* 460–466. doi:10.1037/0021-843X.103.3.460

Kandel, D. B., Johnson, J. G., Bird, H. R., Weissman, M. M., Goodman, S. H., Lahey, B. B., . . . Schwab-Stone, M. E. (1999). Comorbidity among adolescents with substance use disorders: Findings from the MECA study. *Journal of the American Academy of Child and Adolescent Psychiatry, 38,* 693–699. doi:10.1097/00004583-199906000-00016

Kessler, R. C., Avenevoli, S., & Merikangas, K. R. (2001). Mood disorders in children and adolescents: An epidemiological perspective. *Biological Psychiatry, 49,* 1002–1014. doi:10.1016/S0006-3223(01)01129-5

Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., . . . Kendler, K. S. (1994). Lifetime and 12-month prevalence of *DSM–III–R* psychiatric disorders in the United States: Results from the national comorbidity survey. *Archives of General Psychiatry, 51,* 8–19. doi:10.1001/archpsyc.1994.03950010008002

Leshner, A. I. (1999). Science based views of drug addiction and its treatment. *The Journal of the American Medical Association, 282,* 1314–1316. doi:10.1001/jama.282.14.1314

Loas, G. (1996). Vulnerability to depression: A model centered on anhedonia. *Journal of Affective Disorders, 41,* 39–53. doi:10.1016/0165-0327(96)00065-1

Macmillian, N. A., & Creelman, C. D. (2005). *Detection theory: A user's guide, 2nd ed.* Mahwah, NJ: Erlbaum, Inc.

March, J. S., Sullivan, K., & Parker, J. (1999). Test-retest reliability of the Multidimensional Anxiety Scale for Children. *Journal of Anxiety Disorders, 13,* 349–358. doi:10.1016/S0887-6185(99)00009-2

McCabe, C., Mishor, Z., Cowen, P. J., & Harmer, C. J. (2010). Diminished neural processing of aversive and rewarding stimuli during selective serotonin reuptake inhibitor treatment. *Biological Psychiatry, 67,* 439–445. doi:10.1016/j.biopsych.2009.11.001

McMakin, D. L., Olin, T. M., Porta, G., Dietz, L. J., Emslie, G., Clarke, G., . . . Brent, D. A. (2012). Anhedonia predicts poorer recovery amount youth with selective serotonin reuptake inhibitor treat-

ment-resistant depression. *Journal of the American Academy of Child and Adolescent Psychiatry, 51,* 404–411. doi:10.1016/j.jaac.2012.01.011

Miller, N. S., Summers, G. L., & Gold, M. S. (1993). Cocaine dependence: Alcohol and other drug dependence and withdrawal characteristics. *Journal of Addictive Diseases, 12,* 25–35. doi:10.1300/J069v12n01_03

Miller, W. R., & Tonigan, J. S. (1996). Assessing drinkers' motivations for change: The Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES). *Journal of Psychology of Addictive Behaviors, 10,* 81–89. doi:10.1037/0893-164X.10.2.81

Pizzagalli, D. A., Holmes, A. J., Dillon, D. G., Goetz, E. L., Birk, J. L., Bogdan, R., . . . Fava, M. (2009). Reduced caudate and nucleus accumbens response to rewards in unmedicated subjects with Major Depressive Disorder. *The American Journal of Psychiatry, 166,* 702–710. doi:10.1176/appi.ajp.2008.08081201

Pizzagalli, D. A., Iosifescu, D., Hallett, L. A., Ratner, K. G., & Fava, M. (2008). Reduced hedonic capacity in major depressive disorder: Evidence from a probalistic reward task. *Journal of Psychiatric Research, 43,* 76–87. doi:10.1016/j.jpsychires.2008.03.001

Pizzagalli, D. A., Jahn, A. L., & O'Shea, J. P. (2005). Toward an objective characterization of an anhedonic phenotype: A signal-detection approach. *Biological Psychiatry, 57,* 319–327. doi:10.1016/j.biopsych.2004.11.026

Radloff, L. S. (1977). The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement, 1,* 385–401. doi:10.1177/014662167700100306

Santesso, D. L., Dillon, D. G., Birk, J. L., Holmes, A. J., Goetz, E., Bogdan, R., & Pizzagalli, D. A. (2008). Individual differences in reinforcement learning: Behavioral, electrophysiological, and neuroimaging correlates. *NeuroImage, 42,* 807–816. doi:10.1016/j.neuroimage.2008.05.032

Siegle, G., Carter, C., & Thase, M. (2006). Use of FMRI to predict recovery from unipolar depression with cognitive behavior therapy. *The American Journal of Psychiatry, 163,* 735–738. doi:10.1176/appi.ajp.163.4.735

Silberman, M. A., & Snarey, J. (1993). Gender differences in moral development during early adolescence: The contribution of sex-related variations in maturation. *Current Psychology, 12,* 163–171. doi:10.1007/BF02686821

Snaith, R. P., Hamilton, M., Morley, S., Humayan, A., Hargreaves, D., & Trigwell, P. (1995). A scale for the assessment of hedonic tone: The Snaith-Hamilton Pleasure Scale. *The British Journal of Psychiatry, 167,* 99–103. doi:10.1192/bjp.167.1.99

Swendsen, J., Burstein, M., Case, B., Conway, K. P., Dierker, L., He, J., & Merikangas, K. R. (2012). Use and abuse of alcohol and illicit drugs in US adolescents: Results of the National Comorbidity Survey-Adolescent Suppl. *Archives of General Psychiatry, 69,* 390–398. doi:10.1001/archgenpsychiatry.2011.1503

Tomlinson, K. L., Brown, S. A., & Abrantes, A. (2004). Psychiatric comorbidity and substance use treatment outcomes of adolescents. *Psychology of Addictive Behaviors, 18,* 160–169. doi:10.1037/0893-164X.18.2.160

Tripp, G., & Alsop, B. (1999). Sensitivity to reward frequency in boys with attention deficit hyperactivity disorder. *Journal of Clinical Child Psychology, 28,* 366–375. doi:10.1207/S15374424jccp280309

United States Department of Health and Human Services. (2002). *Report to Congress on the Prevention & Treatment of Co-occurring Substance Abuse and Mental Disorders*. Rockville, MD: Substance Abuse and Mental Health Services Administration.

United States Department of Health and Human Services. (2009). *National survey on drug use and health*. Rockville, MD: Substance Abuse and Mental Health Services Administration.

Vrieze, E., Ceccarini, J., Pizzagalli, D. A., Bormans, G., Vandenbulcke, M., Demyttenaere, K., . . . Claes, S. (2013). Measuring extrastriatal dopamine release during a reward learning task. *Human Brain Mapping, 34,* 575–586. doi:10.1002/hbm.21456

Vrieze, E., Pizzagalli, D. A., Demyttenaere, K., Hompes, T., Sienaert, P., de Boer, P., . . . Claes, S. (2012). Reduced reward learning predicts outcome in major depressive disorder. *Biological Psychiatry, 73,* 639–645.

Weiss, A. P., Guidi, J., & Fava, M. (2009). Closing the efficacy-effectiveness gap: Translating both the what and the how from randomized controlled trials to clinical practice. *Journal of Clinical Psychiatry, 70,* 446–449. doi:10.4088/JCP.08com04901

Weisz, J. R., Donenberg, G. R., Han, S. S., & Weiss, B. (1995). Bridging the gap between laboratory and clinic in child and adolescent psychotherapy. *Journal of Consulting and Clinical Psychology, 63,* 688–701. doi:10.1037/0022-006X.63.5.688

Received February 7, 2014
Revision received February 20, 2014
Accepted March 19, 2014 ■