

ARTICLE



Reward-related predictors of symptom change in behavioral activation therapy for anhedonic adolescents: a multimodal approach

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Anhedonia is a cardinal characteristic of depression which predicts worse treatment outcome and is among the most common residual symptoms following treatment. Behavioral Activation (BA) has been shown to be an effective treatment for depressed adults, and more recently, depressed adolescents. Given its emphasis on systematically and gradually increasing exposure to and engagement with rewarding activities and experiences, BA may be a particularly effective intervention for adolescents experiencing anhedonia and associated reward system dysfunction. In the present study, anhedonic adolescents (AA; $n = 39$) received 12 weekly sessions of BA and completed a multimodal (i.e., neural, behavioral, and self-report [ecological momentary assessment]) assessment of reward function at pre-treatment and post-treatment (as well as weekly self-report assessments of anhedonia). Typically developing adolescents (TDA; $n = 41$) completed the same measures at corresponding timepoints. Multilevel models tested pre-treatment reward-related predictors of anhedonia improvement, as well as change in reward measures over the course of BA. Analyses revealed significant reductions in anhedonia following BA treatment. Enhanced pre-treatment neural (striatal) reward responsiveness predicted greater anhedonia improvement. In contrast, baseline self-report and behavioral reward measures did not predict treatment outcome. A group \times time interaction revealed greater increases in both reward- and loss-related neural responsiveness among AA relative to TDA adolescents. Consistent with a capitalization (rather than compensatory) model, pre-treatment neural – but not self-report or behavioral – measures of relatively *enhanced* reward responsiveness predicted better BA outcome. In addition to alleviating anhedonia, successful BA may also increase neural sensitivity to affectively salient (e.g., reward- and loss-related) stimuli among anhedonic youth.

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INTRODUCTION

Depression rates surge during the adolescent years, and by age 18, approximately 15% of youth will have developed major depressive disorder (MDD) [1]. A range of empirically supported interventions are available for depressed adolescents, including psychotherapeutic (e.g., Cognitive Behavioral Therapy; CBT) and pharmacological (e.g., Selective Serotonin Reuptake Inhibitors; SSRIs) treatment options. However, rates of non-response remain high, with approximately 40–50% of depressed adolescents failing to respond to these interventions [2–4]. Anhedonia (i.e., loss of interest or pleasure) is a core characteristic of depression experienced by at least 50% of depressed adolescents [5, 6], which predicts both worse treatment outcome [7, 8] and elevated risk of suicide attempt [9], and is among the most common residual symptoms following pharmacotherapy or psychotherapy [10–12]. Common antidepressants not only have modest effects on anhedonia but may even worsen positive affect and reward responsiveness in some individuals [13–15]. Of relevance, a recent re-analysis of two randomized clinical trials revealed that for depressed individuals treated with CBT or an SSRI, post-treatment deficits in positive emotions were substantially more common

than residual negative affect [11]. Paralleling these findings, a recent neuroimaging study in depressed adolescents found that a course of CBT reduced neural hypersensitivity to negative stimuli but did not improve neural response to rewards [16]. In summary, our first-line treatments for depressed youth (e.g., CBT and SSRIs) fail to adequately target and alleviate anhedonia and underlying reward circuitry deficits, which may help account for their high treatment non-response rates.

Behavioral Activation (BA) is a brief behavioral intervention with accumulating evidence indicating that it significantly reduces depressive symptoms in adults [17–19] and adolescents [20–22]. BA focuses on gradually and systematically increasing exposure to and engagement with rewarding activities and experiences [23, 24]. In contrast to CBT, which focuses on identifying and changing negative patterns of thinking *and* behaviors that contribute to depression, BA is a relatively simpler approach which focuses specifically on modifying behaviors that contribute to the maintenance of depressive symptoms (e.g., social withdrawal, reduced engagement with activities that provide pleasure and/or a sense of accomplishment). The BA therapist works collaboratively with the client to help them counteract maladaptive avoidance patterns and

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to gradually re-engage with intrinsically rewarding and positively reinforcing activities. Given this emphasis, BA may be particularly effective at improving anhedonia and associated reward system dysfunction [18]. It is important to note that BA is a foundational component of CBT, and may, on average, play a greater role in contributing to depressive symptom change in adolescents relative to cognitive strategies [25].

Self-report anhedonia measures (e.g., the commonly used Snaith Hamilton Pleasure Scale; SHAPS) [26, 27] can assess the extent to which a given intervention successfully reduces anhedonia in adolescents. Beyond self-reported symptom change, BA may also help normalize neural and behavioral reward-related deficits which underlie anhedonia. More specifically, adolescents with elevated depression and anhedonia have been shown to have blunted response to rewards in the brain's core reward circuitry, in particular the ventral (i.e., nucleus accumbens [NAcc]) and dorsal striatum (i.e., caudate, putamen) [28–33]. Moreover, a pattern of medial prefrontal cortex (mPFC) hyperreactivity during reward processing has also been observed among depressed relative to non-depressed adolescents [34]. In addition to concurrent associations, blunted striatal and heightened mPFC activation have been shown to prospectively predict future depressive symptoms in adolescents [35–37].

In addition to neural (i.e., striatal and mPFC) reward-related abnormalities, depression and, especially, anhedonia have also been linked to aberrant behavioral responses to reward. In particular, blunted *reward learning* (i.e., the ability to modify behavior based on past rewards) has been observed in both depressed and anhedonic participants relative to healthy controls [38–40], as well as never-depressed adolescents who are at elevated risk of developing depression (by virtue of a parental history of the disorder) [41]. A very commonly used task to assess reward learning is the Probabilistic Reward Task (PRT), which is designed to provide an objective measure of anhedonic behavior [28, 38, 42]. In adult samples, performance on the PRT has been found to: (1) correlate with current and predict future anhedonic symptoms [38–40], (2) correlate with mPFC and striatal activation to rewards as well as extrastriatal dopamine release [43, 44]; and (3) predict treatment outcome [40]. Importantly, the PRT has also been validated in youth as a measure of responsiveness to rewards [41, 45–47]. The extent to which a depressed or anhedonic adolescent is sensitive to rewards (as indexed by the PRT) may improve over the course of BA, given that this treatment specifically focuses on increasing exposure to and engagement with rewarding activities and experiences.

The present study

The present study recruited a sample of adolescents known to be at elevated risk of poor treatment outcome (i.e., with high levels of anhedonia) who were then enrolled in a 12-week BA trial with a multimodal (i.e., self-report, neural and behavioral) assessment of changes in anhedonia and reward system function. The overarching goal of this study was to address two related questions. First, do individuals with relatively high levels of anhedonia and associated reward system dysfunction derive greater benefit from BA than those with more intact reward function? According to a *compensatory* model, BA may be better suited to anhedonic individuals given that it may specifically target and improve deficits in reward function [18]. Framed from the perspective of the National Institute of Mental Health's (NIMH) emphasis on experimental therapeutics [48], BA may directly engage and modify the "target" (i.e., underlying mechanism) of blunted reward system function (e.g., reduced striatal response to rewards) and thus may be particularly well-suited for individuals who enter treatment with greater deficits in this domain. Conversely, a *capitalization* model argues the opposite: Individuals with relatively intact reward system function may best be able to take advantage of an intervention that capitalizes on their existing strengths. For example, adolescents

with elevated depressive or anhedonic symptoms but relatively intact positive affect (assessed via self-report) or greater sensitivity to rewards (assessed via a neural [e.g., striatal response to reward-related stimuli] or behavioral [e.g., PRT] task) may be better able to successfully engage with and take advantage of the reward-focused activities of BA

The evidence supporting compensatory vs. capitalization models is mixed, and no study has been conducted with adolescents receiving BA. In support of a compensatory model, an initial small study [49] in adults with ($n = 12$) vs. without ($n = 15$) MDD reported pre- to post-treatment increases (i.e., in the direction of normalization) in neural response to rewards in reward-related regions (e.g., dorsal striatum) among MDD participants who received BA. Of relevance, two electroencephalogram (EEG) studies in adults with anxiety and/or depression reported that blunted pre-treatment neural response to rewarding outcomes (but not the anticipation of rewards [50]) predicted greater depressive symptom improvement to CBT [50] and SSRI [51]. In contrast, other CBT studies [16, 52, 53], a trial of CBT vs. supportive therapy [54], as well as one study of the transdiagnostic Unified Protocol [55] yielded findings consistent with a capitalization model, such that patients who received a treatment matched to their relative strengths had the best outcomes. Notably, of the abovementioned studies that tested pre-treatment neural predictors of treatment outcome, all found evidence of neural response to rewarding *outcomes* predicting symptom improvement [16, 50, 51, 54]. Informed by these prior findings, we tested whether baseline self-report (ecological momentary assessment; EMA), neural and behavioral reward measures predicted improvement in anhedonia among anhedonic adolescents receiving BA. Given the limited and mixed evidence across existing studies (none of which focused on BA for adolescents), and the fact that both the compensatory and capitalization models provide equally compelling and plausible perspectives, we did not have a hypothesis about the direction of these effects (i.e., whether relatively blunted or heightened reward responsiveness would predict better BA outcomes for anhedonic adolescents).

Finally, and relatedly, we also tested the extent to which a course of BA was associated with pre- to post-treatment changes in self-report, neural and behavioral measures of reward function in anhedonic adolescents. We hypothesized that a 12-week course of BA would be associated with significant changes in self-report (i.e., decreased anhedonia), neural (i.e., increased striatal and decreased mPFC response to rewards) and behavioral (i.e., increased reward learning on the PRT) measures of reward function.

METHODS AND MATERIALS

Participants

Adolescents ($n = 41$ typically developing [TDA]; $n = 39$ anhedonic adolescents [AA]) between the ages of 13–18 were recruited from the greater Boston area from January 2016 to November 2021 (see Table 1 for demographic and clinical characteristics). AA youth were required to have elevated anhedonia on both the SHAPS [27] (total score ≥ 3 based on original [binary] scoring) and on the anhedonia item from the depression module of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS [56]) (anhedonia item score > 1); whereas TDA youth reported no anhedonia on these measures. See Supplement for detailed inclusion and exclusion criteria. The clinical trial was pre-registered on clinicaltrials.gov (NCT02498925). The study was approved by the Mass General Brigham (MGB) IRB. Written informed consent was provided from participating parents and 18-year-old adolescents (those under 18 provided assent).

Procedure

During the initial session, participants were administered the K-SADS and completed self-report measures assessing anhedonia and depression symptoms. Participants also completed a brief "mock" MRI simulation session to familiarize themselves with the MRI procedure. For evidence of the benefits of mock scans in MRI studies with youth, see [e.g., ref. [57].

Table 1. Demographic and clinical characteristics of the sample.

Sample characteristics					
Anhedonic			Typically developing		
	N	%		N	%
Biological sex			Biological sex		
Female	26	66.7	Female	29	70.7
Male	13	33.3	Male	12	29.3
Race			Race		
American Indian or Alaska Native	0	0.0	American Indian or Alaska Native	0	0.0
Asian	3	7.7	Asian	3	7.3
Black or African American	1	2.6	Black or African American	6	14.6
Native Hawaiian or Other Pacific Islander	0	0.0	Native Hawaiian or Other Pacific Islander	1	2.4
White	32	82.1	White	29	70.7
Other	0	0.0	Other	0	0.0
More than one race	3	7.7	More than one race	2	4.9
Ethnicity			Ethnicity		
Hispanic or Latino	1	2.6	Hispanic or Latino	2	4.9
Not Hispanic or Latino	38	97.4	Not Hispanic or Latino	39	95.1
Current diagnoses (DSM-V)			Current diagnoses (DSM-V)		
Major depressive disorder	24	61.5	Major depressive disorder	0	0.0
Generalized anxiety disorder	9	23.1	Generalized anxiety disorder	0	0.0
Social anxiety disorder	5	12.8	Social anxiety disorder	0	0.0
Panic disorder	1	2.6	Panic disorder	0	0.0
Specific phobia	1	2.6	Specific phobia	0	0.0
Attention-deficit/hyperactivity disorder	3	7.7	Attention-deficit/hyperactivity disorder	0	0.0
Oppositional defiant disorder	2	5.1	Oppositional defiant disorder	0	0.0
Medication			Medication		
SSRI	7	18.0	SSRI	0	0.0
	M	SD		M	SD
Age (in years)	15.7	1.9	Age (in years)	16.2	1.7
Family income (dollars)	132,219	65,335	Family income (dollars)	151,794	90,157
SHAPS score	36.18	5.85	SHAPS score	17.85	3.91
CESD score	37.51	5.54	CESD score	5.05	4.36

Eligible participants returned to the lab for an fMRI scan session (average days between visits = 11.56; SD = 8.89), which included a monetary reward fMRI task [31, 58–60]. Participants also completed a behavioral probabilistic reward task (PRT) [41, 45–47] on a desktop computer outside of the scanner and self-report questionnaires. After the scanning session, both groups of participants completed 5 days of EMA via the MetricWire smartphone app. Participants received two to three surveys per day from Thursday through Monday to sample affect on weekdays and weekends. For similar EMA designs in adolescents, see [29, 60–62]. Following the MRI scan, AA participants were offered 12 sessions of BA (one 60-minute session per week) based on an established treatment manual [24]. Participants completed self-report assessments of anhedonia (SHAPS) immediately prior to each BA session. A second scanning session, with identical fMRI protocol was conducted post-treatment for AA youth and at a corresponding timepoint for TDA youth. Participants completed a remote follow-up assessment (including the SHAPS) 3-months after their second scan (see supplement for details).

Measures

Self-report questionnaires. Participants reported anhedonia symptoms on the SHAPS [27], a 14-item self-report measure, as well as reported depression

symptoms using the 20-item Center for Epidemiological Studies Depression (CES-D) measure [63]. The 9-item Behavioral Activation for Depression Scale – Short Form (BADSD - SF) [64] measures the putative target of activity engagement over the past week. See Supplement for details.

Ecological momentary assessment. At each EMA assessment, youth completed items (1–5 scale) probing their current affect, with three each assessing positive affect (PA)(e.g., “happy,” “interested,” and “excited”) and negative affect (NA)(e.g., “sad,” “nervous,” and “angry”) [65]. The ratings for the positive and negative affect words were averaged to create PA and NA variables, respectively (see Supplementary Information).

Probabilistic Reward Task (PRT). At both scanning sessions, adolescents completed the Probabilistic Reward Task [adapted from [38], which has been previously validated in adolescents [41, 45–47]. The task consists of two 100-trial blocks and is designed to assess reward learning (i.e., the ability to adapt behavior as a function of rewards received). See Supplement for a detailed description of the task.

fMRI reward task. The fMRI reward task is described in detail in Murray et al. [29] and in the Supplementary Information. Briefly, during the pre-

and post-treatment fMRI scan, youth completed an event-related card-guessing task designed to assess brain responses to the anticipation and receipt of monetary reward and loss. The task included four 6.5-min blocks in which youth guessed whether the value of a card was higher or lower than 5. Based on the trial type (win, loss, neutral), youth won or lost money (win trials +\$1.00, loss trials -\$0.50, total earnings \$16.00). Given the findings from relevant prior studies cited in the Introduction, we focused on neural response to win or loss (contrasted with neutral) outcomes. However, in the Supplement, we also report tests of neural responses to the anticipation of possible rewards vs. losses as predictors of anhedonia improvement and no significant findings emerged. See Supplement for additional details on the task and Supplementary Results.

MRI acquisition and processing

Twelve youth (TDA = 7; AA = 5; $X^2(1, N = 80) = 0.05, p = .827$) were scanned using a Siemens Tim Trio 3 Tesla MRI scanner equipped with a 32-channel coil, whereas the remaining youth were scanned using a Siemens Prisma 3 Tesla MRI scanner equipped with a 64-channel coil. Regardless of scanner, all functional images were acquired with the following parameters, TR = 720 ms, TE = 30 ms, FOV = 212 mm, multiband acceleration factor = 6, voxel size = $2.5 \times 2.5 \times 2.5$. Scanner type was included as a covariate in all analyses. Standard preprocessing steps were used (see Supplement for details). Individual contrast images were used to create second-level random effects models using one-sample *t*-tests for the win > neutral and loss > neutral contrasts. Mean beta weights for the medial PFC (mPFC) and striatal (NAcc, caudate, and putamen) regions of interest (ROIs) were extracted for each contrast (see Supplement).

Analytic approach

Given the multilevel, longitudinal data structure, we used multilevel models (MLMs; via lme4 [66] and lmerTest [67] packages in R [vers. 4.1.0]) to test whether baseline neural (i.e., striatal and mPFC response to rewards or losses), behavioral (PRT reward learning) and self-report (EMA of PA and NA) measures predict improvement in anhedonia over the course of BA. Separate MLMs were run for neural, behavioral, and self-report predictors of outcome. Specifically, for neural predictors, ROIs included the right and left striatum (i.e., caudate, putamen and NAcc) and mPFC. To test whether striatal or mPFC response to wins and/or losses predicted BA outcome, a MLM simultaneously including $Striatum_{Wins} \times Time$, $Striatum_{Losses} \times Time$, $mPFC_{Wins} \times Time$, and $mPFC_{Losses} \times Time$ interactions was modeled (*Time* centered to represent estimated post-treatment SHAPS scores, while adjusting for pre-treatment SHAPS and CES-D scores). To avoid multicollinearity due to the high correlation between right vs. left striatal response to wins ($r = 0.67$) and losses ($r = 0.85$), separate models were run for left and right striatal ROIs. Corresponding models were run for the behavioral (i.e., *Reward Learning* \times *Time*) and EMA measures (*PA* \times *Time* and *NA* \times *Time*, included in the same model). In each model, intercepts and slopes were treated as randomly varying across patients. All available data were used, including from dropouts ($n = 5$ AA participants), rendering these intent-to-treat analyses. The above analyses (neural, behavioral and EMA tests) were Bonferroni corrected for multiple comparisons ($p = 0.05/4 = 0.013$).

To examine pre-treatment to post-treatment changes in reward measures, and consistent with our pre-registered (clinicaltrials.gov; NCT02498925) outcome measures, we first tested a *Group (AA/TDA) \times Time (baseline and session-to-session SHAPS scores)* interaction via MLM to examine group differences in anhedonia change over time. Second, a *Group (AA/TDA) \times Time (Pre/Post) \times Condition (Wins/Losses)* interaction tested group differences in neural (striatal and mPFC) responses to wins vs. losses from the baseline to the post-treatment scan session. Finally, a *Group (AA/TDA) \times Time (Pre/Post)* interaction tested group differences in our behavioral (reward learning) measure of reward from the baseline to the post-treatment assessment session. Bonferroni corrections were applied for multiple comparisons ($p = 0.05/4 = 0.013$). All models controlled for age, sex, antidepressant medication (on SSRI [$n = 7$] vs not), and scanner type (the latter for imaging analyses). As noted above, five AA participants and six TDA participants dropped out of the study prior to the second (post-treatment) assessment and scan session, and thus were excluded from the latter analyses.

RESULTS

As expected, baseline anhedonia (SHAPS) scores were significantly higher in the AA group (mean = 36.18, SD = 5.85) relative to the TDA group (mean = 17.85, SD = 3.91), $t(65.86, Satterthwaite for$

unequal variances) = 16.39, $p < .001$; Hedges' $g = 3.67$. For comparison with clinically depressed samples, anhedonia severity for our AA adolescents was substantially higher relative to an MDD adolescent sample from a recent CBT trial [16] (SHAPS mean = 31.00; SD = 5.27; Hedges' $g = 0.90$) and a large meta-analysis [68] of SHAPS scores among individuals with MDD (mean = 33.1; SD = 2.7; Hedges' $g = 1.12$). The above values are based on continuous SHAPS total scores (i.e., range 14–56). In the original (binary) SHAPS scoring (i.e., range 0–14), a score of 3 or greater was used as a cutoff for anhedonia [27]. Our AA sample had a mean score over twice the cutoff (7.26; SD = 3.14). For comparison, the above two studies [16, 68] reported original (binary) SHAPS scores of 3.86 (SD = 3.26) and 5.8 (SD = 1.6), respectively.

BA outcomes

Intent-to-treat MLM analyses revealed a significant *Group \times Time* ($b = -0.63, t(82.77) = -5.46, p < 0.001$) interaction indicating, as expected, significantly greater reductions in anhedonia (SHAPS) among the AA group relative to the TDA group (see Fig. 1). When focusing specifically on the AA group, there was a significant effect of *Time* ($b = -0.54, t(37.3) = -5.54, p < 0.001$) indicating reductions in anhedonia over the course of BA treatment. Among AA treatment completers, pre-treatment (Mean = 36.21; SD = 6.27) to post-treatment (Mean = 29.15; SD = 7.75) reductions in anhedonia represented a large effect (Hedges' $g = 0.82$), which was maintained at a 3-month post-treatment follow-up (Mean = 27.21; SD = 6.78; Hedges' g for pre-treatment to follow-up comparison = 0.95). Mean number of BA sessions completed was 11.2 (SD = 2.3; range = 2–12). Number of sessions completed did not significantly moderate the extent of anhedonia improvement ($b = -0.09, p = 0.152$). If the BA intervention was delivered as intended, then we would expect significant increases in activation levels, which in turn would relate to anhedonia improvement. As expected, a significant *Group \times Time* interaction ($b = 1.10, p < 0.001$) emerged, driven by a significantly greater increase in BADS-SF activation subscale scores over time in the anhedonic group receiving BA relative to the control group. In addition, greater increases in BADS activation scores were associated with greater reductions in anhedonia in the anhedonic group ($r = -0.45, p = 0.004$). See Supplement for secondary trial outcomes, including significant reductions in total depressive symptoms.

Prediction of BA Outcomes

Greater pre-treatment right striatal response to wins ($b = -0.57, t(36.11) = -2.82, p = 0.008$) but not losses ($b = 0.14, t(35.55) = 0.92, p = 0.365$) predicted greater improvement in anhedonia (Fig. 2). See Supplement for sensitivity analyses removing covariates and adding the follow-up timepoint, which yielded the same pattern of findings. Left striatal ($ps > 0.07$) and mPFC ($ps > 0.50$) response to wins or losses did not significantly predict change in anhedonia. When rank ordering the correlations between (1) all striatal (NAcc, caudate and putamen) and mPFC ROIs (for Win vs. Neutral and Loss vs. Neutral contrasts separately) and (2) anhedonia improvement (MLM-derived slope), the top five predictors were all reward-related (i.e., Win vs. Neutral) contrasts (see Fig. 3). Pre-treatment right caudate ($r = 0.37, p = 0.026$) and right NAcc ($r = 0.29, p = 0.077$) response to wins had the numerically strongest correlations with improvement in anhedonia. Contrary to our hypotheses, neither behavioral (*Reward Learning* \times *Time*) nor EMA measures (*PA* \times *Time* and *NA* \times *Time*) predicted change in anhedonia (all $ps > 0.58$).

Changes in neural and behavioral response following BA

A *Group \times Time* interaction ($b = 0.74, t(61.00) = 2.19, p = 0.032$) revealed relatively greater pre- to post-treatment increases in right striatal response across condition (i.e., to both rewards and losses) among the AA group relative to the TDA group (see Fig. 4)

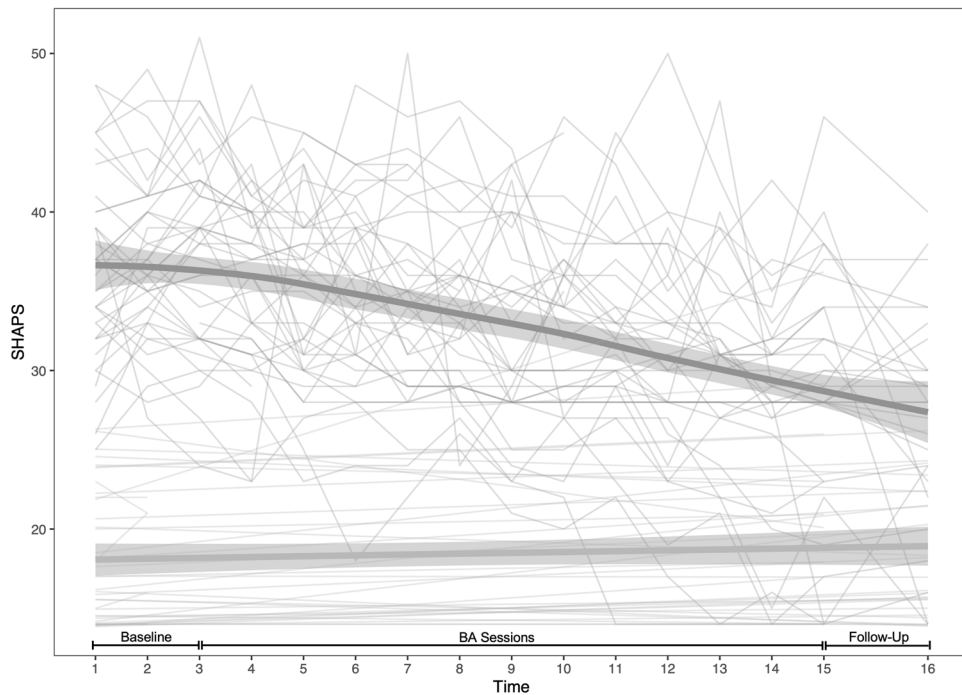


Fig. 1 Snaith Hamilton Pleasure Scale (SHAPS) scores over time for anhedonic participants (blue). Timepoints 1–2, 3–14, 15 and 16 represent the two baseline assessments, 12 BA sessions, the post-treatment assessment and the 3-month follow-up, respectively. Thicker blue line represents average change over time. Typically developing participants' SHAPS scores (gold) are also plotted for comparison.

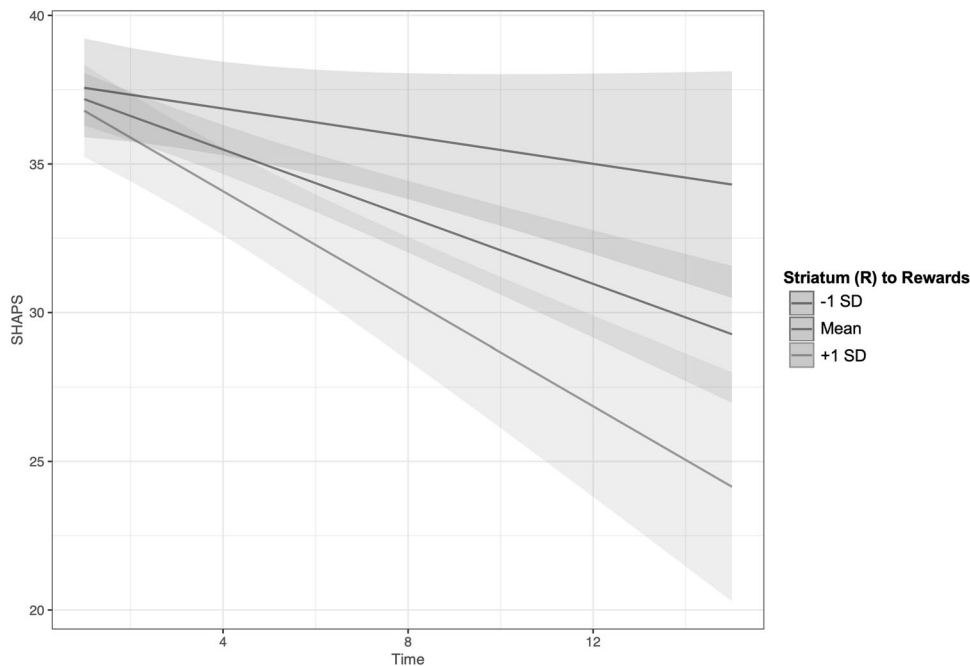


Fig. 2 Pre-treatment neural response to rewards and treatment outcome. Plot of pre-treatment right striatum (rewards > neutral) by time interaction from the model.

(within-group pre- to post-session scan Hedges' g for rewards: AA = 0.26 vs. TDA = -0.32 ; losses: AA = 0.42 vs. TDA = -0.02). However, the latter finding ($p = 0.032$) did not survive our pre-defined Bonferroni-corrected threshold. The percentage of participants who exhibited pre- to post-treatment increases in right striatal response to (1) rewards was 62.5% vs. 32.3% in the AA vs. the TDA group, respectively ($X^2(1, N = 63) = 4.62, p = 0.032$) and (2) losses was 62.5% vs. 48.4% in the AA vs. the TDA group,

respectively ($X^2(1, N = 63) = 0.76, p = 0.382$). The *Group \times Time* interaction for the other measures (neural and behavioral reward learning variables) were not significant ($ps > 0.15$).

DISCUSSION

The present study tested whether pre-treatment measures of reward function predicted anhedonia improvement among

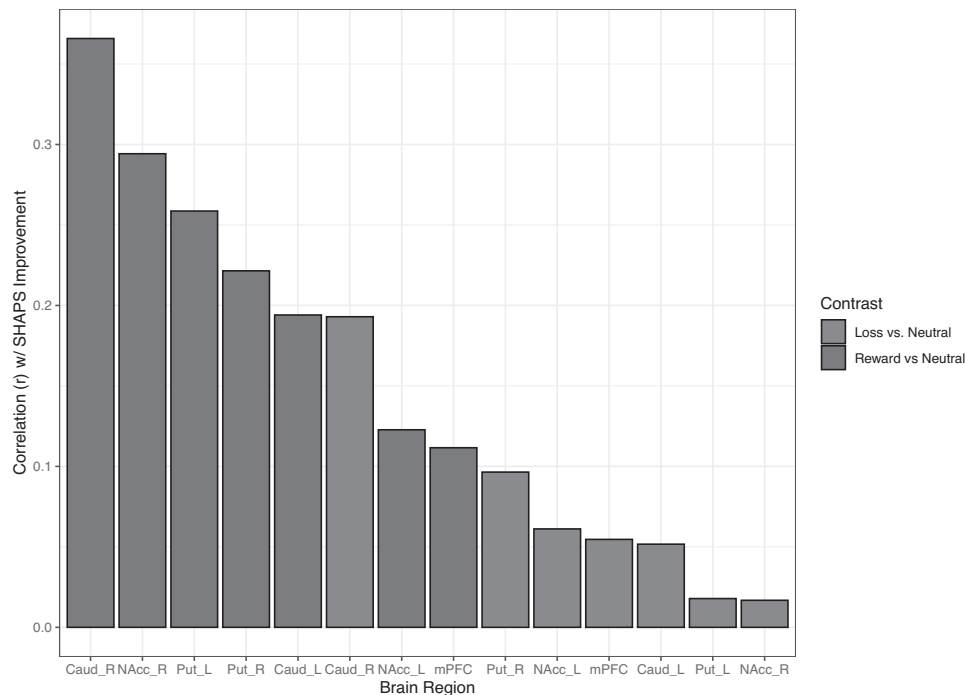


Fig. 3 Relation between anhedonia improvement and pre-treatment neural response to rewards vs. losses by brain region. Rank ordering of the correlations (r) between SHAPS improvement and each region of interest (ROI) and contrast (i.e., rewards > neutral [green] vs. loss > neutral [red]).

adolescents receiving an intervention putatively targeting reward system dysfunction (i.e., BA). In addition, we investigated the extent to which anhedonia and related reward dysfunction normalized over the course of BA. To our knowledge, this represents the first study of BA for anhedonic youth. Strengths of the study included (1) a multimodal assessment of reward system functioning, (2) well-validated neural [29, 31, 58–60] and behavioral [41, 45–47] measures of reward responsiveness in youth recommended by RDoC [69], (3) the use of smartphone-delivered EMA to acquire a more ecologically valid and real-world assessment of positive affective states in the daily lives of adolescents, (4) a follow-up assessment to examine the extent to which adolescents who received BA maintained their gains after completing treatment, and (5) recruitment of adolescents with a known risk factor of poor treatment outcome (i.e., high levels of anhedonia) [7, 8]. Highlighting the severity of anhedonia in our sample, and as described in more detail above, anhedonia scores for our AA adolescents were substantially higher relative to an adolescent MDD sample from a recent CBT trial [16] and a large meta-analysis [68] of anhedonia severity among individuals with MDD.

Multilevel modeling revealed that, among adolescents with high levels of anhedonia and depressive symptoms, pre-treatment neural – but not self-report or behavioral – measures of relatively enhanced reward responsiveness predicted greater improvement in anhedonia. It is important to highlight that our sample of teens were recruited for heightened anhedonia (and over 60% met criteria for MDD) and thus these findings indicate that individuals with relatively enhanced neural reward responsiveness experienced better BA outcome. This neural pattern of findings is consistent with a capitalization (rather than compensatory) model. Namely, those individuals with a more intact neural response to rewards (relative to the other anhedonic adolescents in the sample) experienced better BA outcomes. These findings are generally consistent with several prior studies supporting a capitalization model [16, 52–55], but not with other research supporting a compensatory model [49–51]. However, given the

substantial differences between the latter studies and the present study in sample (e.g., adults with depression or anxiety vs. anhedonic adolescents), imaging modality (e.g., EEG vs. fMRI), task (each used a different reward task) and intervention delivered (e.g., CBT, SSRI, or BA), it is very challenging to determine which study features contributed to the differences in findings.

It is also important to highlight that, similar to prior studies of pre-treatment neural predictors of response in depressed and/or anxiety disordered samples [16, 50, 51, 54], we tested the relation between *relative* striatal reward response (compared to the rest of the clinical sample) and treatment outcome. Conventionally, a “capitalization model” refers to an intervention interacting with or building on an individual’s existing strengths in a particular domain, which facilitates better treatment outcomes. Here, we did not assess “strengths” relative to the general population of adolescents. Instead, we recruited youth struggling with anhedonia (and associated reward system dysfunction) and found that those teens with *relatively* elevated striatal response to rewards had better outcomes.

Notably, when examining the pattern of findings across all the ROIs and contrasts, the reward-related striatal contrasts (i.e., neural response to rewards vs. neutral outcomes) exhibited the numerically strongest associations with improvement in anhedonia (see ordered rankings in Fig. 3). It may be that individuals with more responsive reward circuits are better able to actively engage in – and derive pleasure and positive reinforcement from – the reward-focused activities prescribed in BA (e.g., systematically increasing engagement in activities expected to stimulate pleasure and/or a sense of accomplishment). Alternatively, relatively heightened reward circuit sensitivity may be a general, intervention non-specific marker of one’s likelihood of experiencing improvement in anhedonia over time. In other words, it is unclear whether heightened striatal response to rewards represents a “prescriptive” (i.e., specific to BA or other similar reward-focused treatments) or general “prognostic” (i.e., intervention non-specific) predictor of anhedonia improvement. A future study with an active comparison condition (e.g., CBT or SSRI) is needed to test

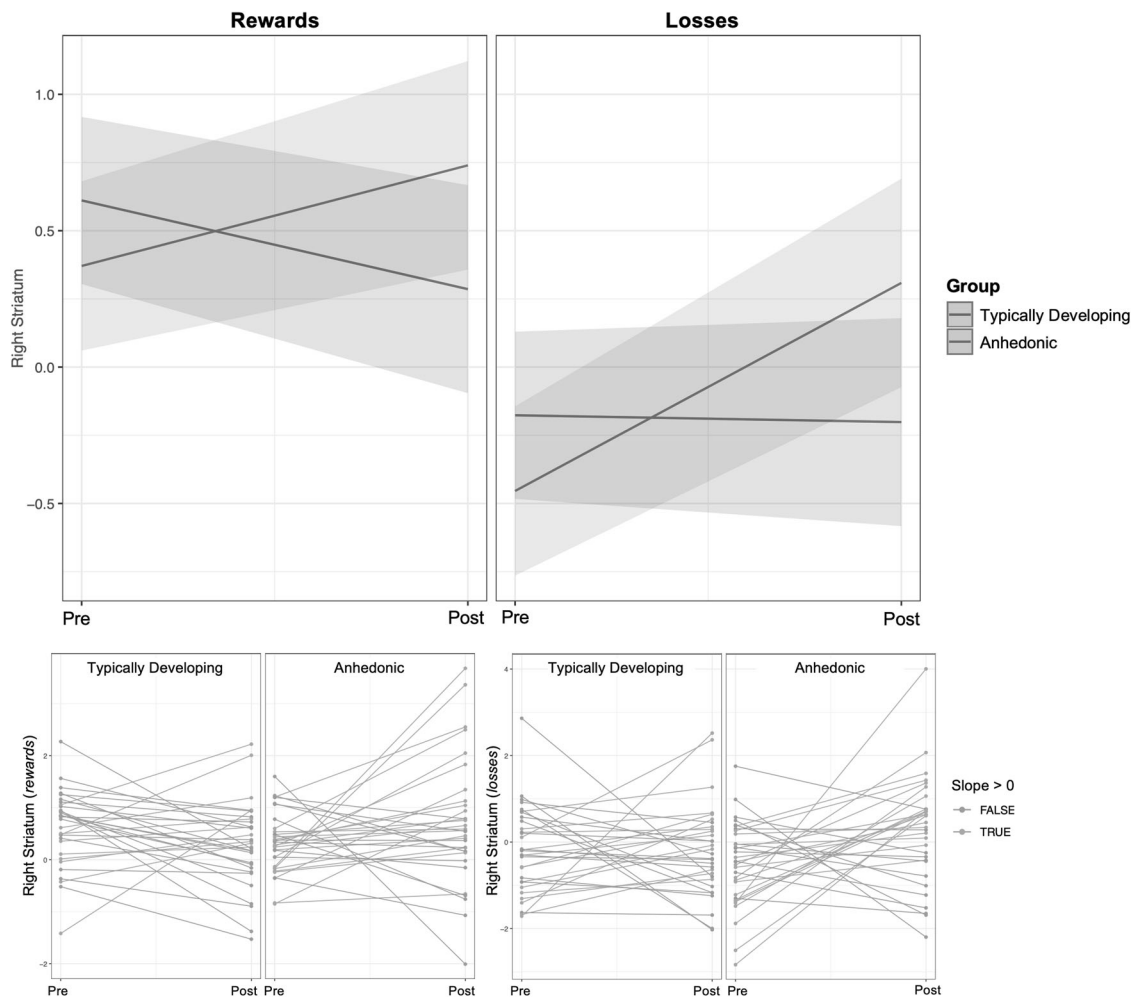


Fig. 4 Plot of group \times time interaction for right striatum response to rewards (top left panel) vs. losses (top right panel) from the model. The bottom panels display subject-specific changes in right striatum responses to rewards (bottom two left panels) and losses (bottom two right panels). Subjects with a positive sloping line (i.e., indicating increases in striatal response to rewards/losses over time) are shown in red, whereas negative sloping lines (or no change) are shown in black. Pre = pre-treatment MRI scan; Post = post-treatment (i.e., second) scan.

whether increased striatal reward response predicts better outcome to BA relative to these alternative interventions. It is also important to note that although heightened striatal response to rewards predicted anhedonic symptom change, it did not significantly predict overall depressive symptom change, highlighting some specificity (see Supplement).

It is worth emphasizing that the pattern of enhanced reward function predicting greater anhedonia improvement only emerged for our neural measure and was not observed for either self-report (EMA) or behavioral (PRT) reward measures. This pattern of findings will need to be replicated in a larger sample. Although speculative, it may be that our neural measure of reward-circuit (striatal) sensitivity – relative to a measure of self-reported momentary (EMA) PA or reward learning (PRT) – more directly probed a relevant dimension of reward functioning which signals one's likelihood of benefiting from a reward-focused intervention. Interpreted in the context of the RDoC framework, a neural measure of "initial response to rewards" may more directly signal the likelihood that an adolescent will engage with and benefit from a reward-focused treatment like BA, relative to a teen's tendency to adapt their behavior as a function of reward feedback (i.e., reward learning) or subjective experience of PA in day-to-day life. It is also worth noting that although neural response to rewarding outcomes predicted BA outcome, neural

response to the anticipation of rewards did not (see Supplement [also see [50, 54]. Future studies could test whether other relevant reward-related self-report (e.g., EMA measure of PA reactivity to naturally occurring rewards in daily life) and behavioral (e.g., willingness to expend effort for rewards [70]) measures do predict BA response in anhedonic adolescents.

Although there were significant reductions in self-reported anhedonia over the course of BA, we failed to find the expected pattern of improved reward response on our neural and behavioral measures. A significant effect (i.e., $p < 0.05$, but did not survive our Bonferroni-corrected threshold) did emerge for greater increases in striatal response to rewards and losses (small to moderate effect sizes) from the baseline to the final scan in the AA group relative to TDA adolescents. This effect was driven by increased pre- to post-treatment striatal response to rewards and losses in the AA group, as well as decreased striatal response to rewards (but not losses) for the TDA group (suggesting neural habituation to the monetary reward stimuli among controls). One interpretation of this finding is that BA does not specifically target reward responsiveness, but instead increases neural sensitivity to affectively salient (e.g., reward- or loss-related) stimuli in anhedonic individuals. The literature on anhedonia has traditionally emphasized blunted responses to rewarding stimuli and events. However, a growing body of research suggests that

anhedonia is related to decreased sensitivity to *both* rewarding and negative stimuli and events [45, 46, 71–73], consistent with an “emotional context insensitivity” hypothesis [also see, [74]. Considering these findings, anhedonic adolescents who successfully engage in the prescribed activities of BA may experience a broader re-sensitization to affectively salient stimuli.

This study had several limitations. First, sample size was relatively small, and thus replication in a larger sample is needed. Second, the inclusion of a group of non-anhedonic adolescents (TDA group) who completed neural and behavioral assessments at timepoints corresponding to the AA group controlled for the effect of repeated assessments and task practice effects. However, a future study with an active control condition is needed to test the specificity of findings to BA vs. relevant alternative interventions (e.g., CBT or SSRIs) for the treatment of anhedonia in adolescents. Third, our sample was largely White and non-Hispanic females, limiting the generalizability of our findings. These limitations notwithstanding, this study provides initial evidence for a capitalization (rather than compensatory) model such that BA may be more helpful for anhedonic youth with relatively greater reward circuitry response. Research is needed to identify the most therapeutically beneficial intervention for adolescents with the opposite reward-circuitry pattern (i.e., more blunted reward circuit sensitivity). In addition to alleviating anhedonia, a brief course of BA may also increase neural sensitivity to salient (i.e., both reward- and loss-related) stimuli among anhedonic youth, but this effect may be relatively modest.

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AUTHOR CONTRIBUTIONS

CW acquired funding for the project. CW, DP, and EF conceptualized the study. CW, AT, and LM acquired, processed, and analyzed the data. All authors contributed to interpretation of findings and drafting the manuscript. All authors approved the final version of the manuscript.

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COMPETING INTERESTS

Over the past 3 years, DAP has received consulting fees from Albright Stonebridge Group, Boehringer Ingelheim, Compass Pathways, Engrail Therapeutics, Neumora Therapeutics (formerly BlackThorn Therapeutics), Neurocrine Biosciences, Neuroscience Software, Otsuka, Sunovion, and Takeda; he has received honoraria from the Psychonomic Society and the American Psychological Association (both for editorial work) as well as Alkermes; he has received research funding from the Brain and Behavior Research Foundation, the Dana Foundation, Millennium Pharmaceuticals, and NIMH; he has received stock options from Compass Pathways, Engrail Therapeutics, Neumora Therapeutics, and Neuroscience Software; he has a financial interest in Neumora Therapeutics (formerly BlackThorn Therapeutics), which has licensed the copyright to the probabilistic reward task through Harvard University. DAP's interests were reviewed and are managed by McLean Hospital and Partners HealthCare in accordance with their conflict of interest policies. DAP is on the editorial board of Neuropsychopharmacology. In the past 3 years, EEF received an honorarium from Society for Psychological Science for editing. No funding from these

entities was used to support the current work, and all views expressed are solely those of the authors. The other authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41386-022-01481-4>.

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Supplementary Online Content

Reward-related predictors of symptom change in behavioral activation therapy for anhedonic adolescents: A multimodal approach

Supplemental Methods

Participants

Adolescents ($n = 41$ typically developing [TDA]; $n = 39$ anhedonic adolescents [AA]) between the ages of 13-18 were recruited from the greater Boston area (see **Table 1** for demographic and clinical characteristics). All participants were recruited to be English-speaking. AA youth were required to have elevated anhedonia on both SHAPS [1] (total score ≥ 3 based on original [binary] scoring) and on the anhedonia item from the depression module of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS [2]) (anhedonia item score > 1). AA youth were excluded if they endorsed a lifetime diagnosis of schizophrenia spectrum or other psychotic disorder, bipolar disorder, OCD, severe alcohol or substance use disorder, or past year alcohol or substance use disorder. AA youth were also excluded if they were currently receiving psychotherapy or psychotropic medication, with the exception of a stable dose of SSRIs ($n = 7$; medication status (on SSRI vs. not) was included as a covariate in all analyses). AA youth with chronic depression or current active suicidal ideation were excluded based on the brief, manualized BA protocol [3] that was not designed to target these concerns. AA youth with co-morbid anxiety or post-traumatic stress disorder were included (see current diagnoses in **Table 1**), provided these diagnoses were secondary to anhedonia.

Exclusion criteria for TDA youth included elevated anhedonia (i.e., required to have a SHAPS total score [original binary item scoring] = 0 and no anhedonia reported on the K-SADS depression module), lifetime DSM-5 psychiatric or substance use disorder, current use of any psychiatric medications, or any diagnoses of MDD, bipolar disorder, or psychotic disorder within a first degree relative. In addition, exclusion criteria for both groups included history of head trauma with loss of consciousness (>2 minutes), seizure disorder, serious or unstable medical or neurological illness, current use of dopaminergic drugs, hypothyroidism, color blindness, current anorexia nervosa or bulimia nervosa, pregnancy, and MRI contraindications.

Procedures

Five AA participants and six TDA participants dropped out of the study prior to the second (post-treatment) assessment and scan session, and thus retention rates were 87% (34/39) and 85% (35/41) for the AA and TDA group, respectively. There were no significant differences in the length of days between the first and second MRI session for the AA (mean [SD] = 111.8 [24.1]) vs. TDA (mean [SD] = 110.8 [25.5]) groups ($t(67.0) = -0.17, p = 0.87$). Participants completed a remote follow-up assessment (including the SHAPS) 3-months after their second scan. Among those who completed the post-treatment assessment, 85% (29/34) of AA participants and 74% (26/35) of the TDA group completed the 3-month follow-up.

Measures

Anhedonia

Participants reported anhedonia symptoms on the SHAPS [1], a 14-item self-report measure. The SHAPS includes items such as, “I would enjoy seeing people’s smiling faces,” and “I would get pleasure from helping others.” Items were assessed using a Likert scale, ranging from 1, “strongly disagree” to 4, “strongly agree.” Higher scores (total score range = 14-56)

indicated more severe anhedonia. Chronbach's alpha values at the baseline (0.96) and post-treatment assessment (0.92) were high.

Behavioral Activation

In response to an anonymous reviewer, we also conducted analyses with the BADS-SF measure (see main text). For these suggested analyses, we focused on the BADS Activation subscale (rather than the Avoidance subscale). This measure was assessed at baseline, immediately prior to every BA session and at the post-treatment assessment.

Depression Symptoms

Participants reported depression symptoms using the 20-item Center for Epidemiological Studies Depression (CES-D) self-report measure [4]. It includes items such as, "I felt I was just as good as other people," and "I felt hopeful about the future." Answers were measured on a Likert scale ranging from 1, "rarely or none of the time (less than 1 day)," to 4, "most or all of the time (5 - 7 days)." Higher scores indicated greater frequency of depressive symptoms. Chronbach's alpha values at the baseline (0.97) and post-treatment assessment (0.93) were high.

fMRI Reward Task

The slow event-related reward fMRI task has been used in previous studies [5–9] and consisted of four 6.5-min, 32-trial blocks. Youth were instructed to guess whether the value of a card would be higher or lower than 5. If they were correct, they would win a monetary reward (\$1.00), and if they were incorrect, they would lose money (\$0.50). Neutral trials would result in no change in earnings (\$0.00). On each trial, youth made a guess via button press (3000 ms) and then viewed a fixation cross (500-7000 ms). They then learned the trial type (i.e., possible win, possible loss, neutral, or mixed win/loss; 1000 ms), viewed a fixation cross (500-700ms), and received feedback on the outcome (i.e., win, loss, or no-change; 1000 ms), followed by a jittered

inter-trial fixation cross (500-7000 ms). Trials were presented in pseudorandom order with pre-determined outcomes. Each run included 8 win outcomes (4 from reward anticipation trials, 4 from mixed anticipation trials), 8 loss outcomes (4 from loss anticipation trials, 4 from mixed anticipation trials), 8 no change/neutral outcomes (from neutral anticipation trials). Eight additional no-change outcome trials (i.e., incorrect reward trial ‘no-win’; correct loss trial ‘avoid loss’) were not used in the current analysis. Total earnings across the four runs was \$16.00.

Probabilistic Reward Task (PRT)

Each trial began with a fixation cross (500 ms) followed by a cartoon face without either a mouth or a nose (counterbalanced across subjects and session). After a 500 ms delay, a short or long mouth/nose was presented (100 ms). Participants then indicated whether they saw a short or long mouth or nose. For each block, 40 trials with correct responses resulted in a monetary reward of \$0.20. In these cases, participants were presented with a screen that said “*Correct! You won 20 cents.*” While long and short mouths or noses were presented with equal frequency across the block, one length received a reward for correct identification three times more frequently (i.e., rich stimulus; n=30) than the other (i.e., lean stimulus; n=10). Response bias favoring the rich stimulus was calculated using the following formula:

$$\text{Response bias : } \log b = \frac{1}{2} \log \left(\frac{\text{rich}_{\text{correct}} * \text{lean}_{\text{incorrect}}}{\text{rich}_{\text{incorrect}} * \text{lean}_{\text{correct}}} \right)$$

Following established procedures, 0.5 was added to each cell of the formula to allow calculations in cases of no errors. Reward learning was calculated as the change in response bias from block 1 to block 2. Data were excluded based on published guidelines [10], which resulted in one subject being removed. In addition, due to the implementation of infection control procedures at the beginning of the COVID pandemic, PRT data (obtained from a computer in our lab) from nine additional subjects were not collected.

Ecological Momentary Assessment

EMA Items were selected from the Positive and Negative Affect Schedule for Children [11]. Participants reported to what extent they were currently feeling each of these emotions using a Likert scale ranging from 1, “very slightly or not at all,” to 5, “extremely.” The ratings for the positive and negative affect words were averaged to create PA and NA variables, respectively. Two AA subjects did not have access to a personal smartphone and thus did not contribute EMA data.

MRI Acquisition and Processing

Twelve youth (TDA = 7; AA = 5; $X^2(1, N = 80) = 0.05, p = .827$) were scanned using a Siemens Tim Trio 3 Tesla MRI scanner equipped with a 32-channel coil, whereas the remaining youth were scanned using a Siemens Prisma 3 Tesla MRI scanner equipped with a 64-channel coil. Regardless of scanner, all functional images were acquired with the following parameters, TR=720 ms, TE=30 ms, FOV =212 mm, multiband acceleration factor = 6, voxel size = 2.5 x 2.5 x 2.5. Scanner type was included as a covariate in all analyses.

Preprocessing was conducted in SPM12 and included grey matter segmentation, realignment and unwarping with a field map, slice-timing correction, co-registration, normalization to MNI space, resampling to 2 x 2 x 2 mm voxels, and smoothing with a 4 mm FWHM gaussian filter. Movement artifacts were screened and censored from subject-specific first-level models using Artifact Detection Tool (>3 SD from mean intensity or >1 mm movement in any direction; http://www.nitrc.org/projects/artifact_detect/). Participants with >15% movement outliers were excluded (baseline scan exclusions: TDA = 1; AA = 2; post-treatment scan exclusions: TDA = 0; AA = 2).

Individual contrast images were used to create second-level random effects models using one-sample t-tests for the win > neutral and loss > neutral contrasts. Mean beta weights for the medial PFC (mPFC) and striatal (NAcc, caudate, and putamen) regions of interest (ROIs) were extracted for each contrast. The mPFC and striatal ROIs were selected based on the extensive literature demonstrating frontostriatal dysfunction in youth depression and anhedonia [6,12–18]. Consistent with prior work [19,20], striatal ROIs were created from the FSL Harvard-Oxford Subcortical Atlas using a 40% probability threshold. The mPFC ROI was identical to that used in Murray et al.[5] and has been linked to reward-related treatment response in depressed adolescents [7]. Participants with less than 90% coverage in any ROI were excluded (n = 2 TDA participants at the baseline scan). One additional TDA participant was excluded at baseline and another at the second scan due to a computer malfunction.

Power analyses and determination of sample size. Informed by our preliminary findings and relevant prior studies, we estimated the sample size required to test our hypotheses. The power analysis was conducted for a NIH K23 grant (power analyses completed February 2015), which supported this project. Behavioral data: Preliminary data (n = 48) on pre- to post-treatment improvement in reward learning (PRT) in mood-disordered adolescents receiving CBT is in the medium to large effect size range ($d = .74$). Neural data: Preliminary data indicated blunted neural response to rewards in MDD (n = 17) relative to HC (n = 16) teens ($d = .69$). In a previous small trial of BA for depressed adults [21], a significant *Group* (MDD [n=12], HC [n=15]) x *Time* (pre-treatment, post-treatment) interaction emerged in striatal (caudate) activation to rewards (Cohen's $d = .86$), reflecting greater normalization of caudate activation to monetary gains in the MDD group. Self-report data: Relative to behavioral and neural data, effect sizes of improvement in self-report measures of anhedonia are more modest (i.e., pre- to

post-treatment change in self-reported anhedonia in MDD group in latter study $d = 0.44$; and for preliminary data ($n = 48$) $d = 0.33$), yielding a mean $d = 0.39$. Although not a direct measure of anhedonia, a trial of BA for depressed adolescents [22] reported increased behavioral activation ($d = .43$) and reduced avoidance ($d = .95$) following BA treatment. Assuming 15% attrition/data loss (e.g., due to dropout, head movement in scanner), 35 HC and 35 AH participant will be recruited (increased if attrition is found to be higher) to achieve a final completer sample of 30 per group. This sample size will be associated with >0.87 power to detect pre-treatment group differences in neural data, as well as adequate power to detect pre- to post-treatment improvements in PRT (>0.96), fMRI (>0.98), and self-report (>0.80) data, respectively.

Supplemental Results

Secondary trial outcomes. Although the present study was focused on the treatment of anhedonia, it is important to highlight that there were also significant reductions in overall depressive (CES-D) symptoms from pre-treatment (Mean = 36.03; SD = 8.11) to post-treatment (Mean = 19.58; SD = 12.03; Hedges' $g = 1.31$) (effect of *Time*, $b = -1.20$, $t(37.5) = -8.01$, $p < .001$), which were maintained at the 3-month follow-up (Mean = 18.46; SD = 10.23; Hedges' g for pre-treatment to follow-up comparison = 1.59). In addition, therapist post-treatment reports of their client's global improvement (Clinical Global Impressions [CGI] scale) [23] significantly correlated with adolescent self-reported anhedonia (SHAPS; $r = 0.65$, $p < .001$) and depressive (CESD; $r = 0.77$, $p < .001$) symptom improvement.

Sensitivity analysis. The main text reports a significant pre-treatment right striatum response to wins x time interaction, which indicated that baseline right striatum response to rewards predicted improvement in anhedonia over time. This analysis was re-run including SHAPS scores from the 3-month follow-up timepoint which yielded the same significant

interaction ($b = -0.59$, $t(35.26) = -3.20$, $p = .003$). To test whether the inclusion of covariates in the pre-treatment right striatum x time interaction influenced findings, we re-ran the original model removing all covariates (apart from simultaneously including both the *StriatumWins* x *Time* and *StriatumLosses* x *Time* in the model). Again, the same pattern of finding emerged with a significant right striatum response to wins x time interaction ($b = -0.57$, $t(34.16) = -2.84$, $p = .007$; striatum to loss x time $p = 0.282$).

In response to an anonymous reviewer, we also re-ran the pre-treatment right striatum to wins x time interaction substituting overall depression (CES-D) symptoms for anhedonic (SHAPS) symptoms as the outcome measure. The correlation between symptom change on both measures was $r = 0.68$ ($p < .001$). The pre-treatment right striatum to wins x time interaction was not significant in predicting depressive symptom change ($b = -0.54$, $t(36.36) = -1.67$, $p = .104$; For left striatum to wins x time interaction, $p = .324$).

In the main text we focus on neural response to reward *outcome* as a predictor of treatment outcome (given the prior findings cited in the Introduction). As a supplemental analysis, and in response to an anonymous reviewer, we also tested neural (striatal and mPFC) response to the anticipation of possible rewards vs. losses (contrasted with anticipation of neutral outcomes) as predictors of anhedonia symptom change. No significant finding emerged (all $ps > .24$).

Relation between pre-to post-treatment changes in striatal reward response and outcome. In the main text, we report a significant effect (i.e., $p < .05$, but did not survive our Bonferroni-corrected threshold) of greater increases in right striatal response to rewards *and* losses (small to moderate effect sizes) from the baseline to the final scan in the AA group

relative to TDA adolescents. Pre- to post-treatment changes in neither right striatal response to wins nor losses were significantly related to anhedonia improvement in the AA teens ($ps > .61$).

Adverse Events During the Study Period

Two adverse events occurred which were deemed unrelated and unexpected after discussions with the study team and the IRB Chair at the Mass General Brigham IRB (both were formally reported to the IRB). One anhedonic teen in the treatment arm experienced a seizure at home, and another teen attempted suicide (first lifetime attempt) prior to receiving any BA sessions (and was referred to a higher level of psychiatric care after discussions with the study team and participating parents).

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Figure Captions

Figure 1. CONSORT flow diagram

CONSORT 2010 Flow Diagram

