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Authors

Kryza-Lacombe, Maria
Pearson, Nana
Lyubomirsky, Sonja
[et al.](#)

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Changes in neural reward processing following Amplification of Positivity treatment for depression and anxiety: Preliminary findings from a randomized waitlist controlled trial

Maria Kryza-Lacombe^a, Nana Pearson^b, Sonja Lyubomirsky^c, Murray B. Stein^{a,b},
Jillian Lee Wiggins^{a,d}, Charles T. Taylor^{a,b,*}

^a San Diego State University, University of California, San Diego Joint Doctoral Program in Clinical Psychology, United States

^b Department of Psychiatry, University of California, San Diego, United States

^c Department of Psychology, University of California, Riverside, United States

^d Department of Psychology, San Diego State University, United States

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ABSTRACT

Positive valence system (PVS) deficits are increasingly recognized as important treatment targets for depression and anxiety. Emerging behavioral treatments designed to upregulate the PVS show initial promise; however, neural mechanisms underlying these approaches remain unknown. This study investigated neural reward-processing-related changes following Amplification of Positivity (AMP)—a treatment designed to enhance positive thinking, emotions and behaviors through positive activity interventions (Clinicaltrials.gov: NCT02330627).

Individuals with depression and/or anxiety ($N = 29$) were randomized to 10 sessions of AMP ($n = 16$) or waitlist (WL; $n = 13$). Participants completed a monetary incentive delay task during fMRI at baseline and post-assessment. Hypothesis-driven region of interest (ventral striatum, insula, anterior cingulate) and exploratory whole-brain activation and connectivity analyses evaluated pre-to-post changes for AMP vs. WL when anticipating potential monetary gain or loss.

No between-group brain activation changes emerged in regions of interest or whole-brain analyses. Increased neural connectivity from pre-to-post-treatment was observed in AMP vs. WL, including ventral striatum, anterior insula, and anterior cingulate connectivity with prefrontal, limbic, occipital and parietal regions—predominantly during loss anticipation.

This preliminary study is the first to examine neural mechanisms of positive activity interventions in depression and anxiety and suggests that AMP may strengthen brain connectivity in reward processing, attention, and emotion regulation networks.

1. Introduction

The positive valence system (PVS) and its role in depression and anxiety treatments is garnering increasing interest (Craske et al., 2016; Insel et al., 2010). The PVS is characterized by positive emotions (e.g., joy, awe) and cognitions (e.g., attentional deployment toward reward-relevant stimuli), and generates approach behaviors toward potentially rewarding stimuli (Fredrickson, 2013). Deficits in the PVS are common in depression and anxiety (Craske et al., 2016; Dillon et al., 2014), yet are not sufficiently addressed by current treatments (Dunn

et al., 2020). Emerging behavioral interventions targeting the PVS in samples of adults with depression and/or anxiety disorders have shown to be efficacious at increasing positive affect as well reducing negative affect and depression and anxiety symptoms (Craske et al., 2019; Dunn et al., 2019; Taylor et al., 2017). Theoretical models suggest that brain circuits related to reward processing may be targeted in these treatments (Craske et al., 2016; Layous et al., 2011), yet this hypothesis has not yet been empirically evaluated and the neural mechanisms of interventions that target the PVS remain poorly understood. Understanding such mechanisms is an important step toward refining interventions and

Abbreviations: AMP, Amplification of Positivity; PVS, Positive Valence System; WL, waitlist; MID, monetary incentive delay.

* Corresponding author. Department of Psychiatry, University of California, San Diego, La Jolla, CA, 92037, United States.

E-mail address: ctaylor@health.ucsd.edu (C.T. Taylor).

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creating more targeted treatments, and is a prominent direction in current mental health research efforts (Insel, 2014). To this end, we evaluated neural reward-processing-related changes following a randomized controlled trial (RCT) of Amplification of Positivity (AMP), a novel intervention that targets the PVS via engagement in positive activities, which demonstrated large and significant symptom improvements and increased positive affect among AMP, compared to WL (Cohen's d range = |0.94–1.57|; Taylor et al., 2017).

Reward processing mechanisms are thought to enable optimal PVS functioning by generating approach behaviors in the context of anticipating and receiving positive (rewarding) outcomes (Berridge et al., 2015) as well as motivation and sustained engagement with the environment. Brain regions involved in reward processing include limbic (e.g., striatum, amygdala) and prefrontal (e.g., anterior cingulate, insula, orbitofrontal cortex) structures (Berridge et al., 2015). These areas evince increased activation (Oldham et al., 2018) and connectivity (Cho et al., 2013; Gu et al., 2019) in the context of potential rewards as well as losses (i.e., removal of rewards; Camara et al., 2009; Cho et al., 2013).

Dysregulation of reward processing networks may be linked to clinical manifestations of PVS deficits. This includes losing the desire to engage in pleasurable activities and/or loss of enjoyment of such activities (i.e., anhedonia; Snaith, 1993), which correspond to the anticipation and consumption phases of reward processing, respectively, as well as expecting to experience less positive affect in anticipation of future positive events (Hoerger et al., 2012). Such deficits are prevalent in depression (Pelizza et al., 2009; Watson and Naragon-Gainey, 2010) with anhedonia specifically being a core diagnostic feature of depression. Anxiety disorders also often present with PVS deficits (Hopper et al., 2008; Kashdan et al., 2011; Prenoveau et al., 2010); most commonly in Generalized Anxiety Disorder and Social Anxiety Disorder, compared to Panic Disorder and Specific Phobias. Meta-analytic work has suggested that dysregulated corticostriatal connectivity may underlie reward processing deficits in MDD broadly (Ng et al., 2019), and some studies have linked PVS deficits to aberrant brain patterns such as reduced ventral striatum activation during reward anticipation specifically (Chung et al., 2015; Stoy et al., 2012; Ubl et al., 2015). Furthermore, anhedonia has also been related to neural hypoconnectivity of reward circuits during rest (Pornpattananangkul et al., 2019). Importantly, both anhedonia and anxious arousal have been shown to moderate prediction-error-related ventral striatum activation when a reward is expected (Greenberg et al., 2015), which highlights the need for transdiagnostic samples.

AMP (Taylor et al., 2017) leverages positive activity interventions (Layous et al., 2014) to address PVS deficits by increasing exposure and reactivity to pleasurable, engaging and meaningful events, including amplifying positive experiences in-the-moment (e.g., savoring) or memories thereof (e.g., reminiscing; sharing positive events with others). AMP also includes activities to increase awareness of positive outcomes (e.g., gratitude, strengths) and approach motivation (e.g., acts of kindness, make someone else happier). Together, these activities are intended to increase the salience of future opportunities for reward (i.e., positive emotions) and desire for such rewards, thereby targeting reward anticipation processes. Because patients with depression or anxiety tend to focus on negative outcomes (e.g., rumination, worry), AMP strategies also focus on attending to and capitalizing on positive outcomes which necessitates attention redirection in the context of anticipating or experiencing negative outcomes (e.g., loss or punishment). Successful implementation of AMP components in an individual's daily life and experiencing associated symptom improvement is presumably mediated by changes in reward-processing-related brain networks. In support of that proposition, several studies documented that non-clinical samples demonstrate increased activation in neural reward circuitry while engaging in specific positive activities such as recalling positive autobiographical memories (Speer et al., 2014), social sharing of emotions (Wagner et al., 2015), and engaging in altruistic actions (Moll et al., 2006). To our knowledge the neural mechanisms of

positive activity interventions have not been examined in clinical samples of individuals with depression or anxiety.

In the present study we aimed to examine neural changes (activation and connectivity) following AMP in a transdiagnostic sample of patients seeking treatment for depression and/or anxiety (Taylor et al., 2017). As AMP specifically targets the PVS, a monetary incentive delay task shown to reliably probe reward processing circuits (Oldham et al., 2018) was used during fMRI acquisition to examine treatment-related changes. We focused on reward anticipation in the present study because the monetary incentive delay task is well established as probing anticipatory reward processing (Knutson & Greer, 2008) and because neural dysfunction during anticipation of rewards has been linked to PVS dysfunction (Stoy et al., 2012; Ubl et al., 2015).

Positive affect has been shown to be positively related to ventral striatum activation (Wu et al., 2014) and anhedonia has been linked to attenuated striatal activation during reward anticipation (Stoy et al., 2012; Ubl et al., 2015). We therefore hypothesized increased activation in the ventral striatum among individuals who completed AMP relative to waitlist controls during anticipation of potential monetary gains (i.e., rewards). We also examined whether AMP effects generalized to parallel measures of the negative valence system (i.e., neural reactivity to aversive outcomes). Based on evidence that negative affect is related to anterior insula activation during anticipation of losses (Wu et al., 2014), we hypothesized decreased activation in this region post-AMP. We also planned to examine activation in medial prefrontal cortex regions as these have also been implicated in reward processing (Oldman et al., 2018). To complement these region of interest (ROI) analyses, we performed additional exploratory whole-brain analyses evaluating treatment-related neural activation changes among patients who underwent AMP vs. waitlist. Finally, given research suggesting diminished functional connectivity among reward processing regions in depression and anxiety (Jung et al., 2013; Rupprechter et al., 2020), we also explored whether AMP altered brain connectivity.

2. Methods and materials

2.1. Participants

Participants were treatment seeking adults (age 18–55) with clinically impairing depression and/or anxiety who participated in a randomized controlled trial (NCT02330627) evaluating Amplification of Positivity (AMP; Taylor et al., 2017). Recruitment procedures and sample characteristics were previously described in the outcomes report of this trial. To summarize, 29 participants were randomly allocated to a 10-session AMP group ($n = 16$) or a waitlist (WL) condition ($n = 13$); one participant in the AMP group discontinued treatment after session 7 due to changes in work commitment and therefore did not have a post-treatment MRI scan. One participant in the WL group was excluded from analyses due to having initiated treatment during the wait period. The present analyses therefore included 27 participants (AMP: $n = 15$; WL: $n = 12$). All participants had clinically elevated symptoms of depression (score ≥ 10 or higher on the Patient Health Questionnaire-9 [PHQ-9]) and/or anxiety (score ≥ 8 on the Overall Anxiety Severity and Impairment Scale [OASIS]), and 70% of the present sample had anhedonia levels that were more than one standard deviation above a community sample mean (measured via the Snaith Hamilton Pleasure Scale [SHAPS] (Franken et al., 2007)). Across participants, 35% were comorbid for depression and anxiety, 23% met criteria for major depression only, and 42% had an anxiety disorder without depression. Additional recruitment details (including CONSORT diagram, Fig. S1), and sample characteristics are described in the AMP outcomes report (Taylor et al., 2017) and have been summarized in the Supplemental Materials.

2.2. Amplification of Positivity intervention

Individuals in the AMP group underwent 10 1-h sessions of individual therapist-delivered treatment. Psychoeducation was provided in an introductory session on emotion science findings regarding the function of positive thoughts, emotions, and behaviors (Fredrickson, 1998, 2001, 2003, 2013; Garland et al., 2010). The core treatment exercises were designed to increase positive thinking, emotions, and/or behavior and were developed based on prior literature on positive affect interventions (Huffman et al., 2011, 2014; Layous et al., 2011, 2014; Lyubomirsky et al., 2013; Moskowitz et al., 2012). A summary of the treatment protocol is available in the Supplement (Table S2) and additional details are described in the outcomes report of this trial (Taylor et al., 2017). Waitlist participants completed the pre- and post-assessments at a 10-week interval and were offered AMP after the post-assessment.

2.3. Monetary incentive delay task

All participants completed a monetary incentive delay (MID) task while undergoing fMRI acquisition at baseline and post-treatment (or after a 10-week wait period). This task probes neural responses to the anticipation and receipt of reward and loss outcomes and reliably activates a well-delineated neurocircuitry implicated in reward (e.g., ventral striatum) and loss processing (e.g., anterior insula) (Knutson & Greer, 2008; Oldham et al., 2018; Wu et al., 2014). On each trial, participants were presented with a cue indicating potential gains or losses and could either gain or avoid losing money by pressing a button with their index finger when a target was presented. Participants were not excluded based on handedness. Cues signaled the possibility of winning or losing \$0.00, \$1.00, or \$5.00 resulting in six task conditions comprised of 15 trials each, totaling 90 trials. Each trial consisted of an anticipation phase, target presentation, and outcome presentation. The anticipation phase (4000 ms) began with the presentation of one of six cue shapes (2000 ms) and was followed by a crosshair (2000 ms). Then, a white target was briefly presented to which participants were required to quickly respond via button press. Target duration was variable and set to 250 ms at the beginning of the task, and then titrated such that participants succeeded on approximately 66% of their target responses. A delay followed (2000 ms - duration of target presentation for any given trial). Finally, the outcome was presented (2000 ms) notifying participants how much money they had gained or lost for that trial. Trials were separated by a variable inter-trial interval of 2000, 4000, or 6000 ms. Prior to entering the scanner, participants were trained and tested for explicit cue comprehension, and shown the cash they could win during the task. All participants had a hit rate of at least 30%, indicating task adherence.

2.4. Neuroimaging acquisition

Anatomical and functional brain images were acquired using a General Electric 3T MR750 Discovery MRI scanner and 8-channel head coil. Participants viewed task stimuli, which were projected onto a screen at the foot of the fMRI bed, via a mirror attached to the head coil. Participants used one button on a response box to respond to the target using their right hand. A 2D EPI pulse sequence acquired T2* blood oxygen level dependent (BOLD) images across 2 runs as 30 axial slices approximately parallel to the AC-PC line, with whole-brain coverage (voxel size = 3.5 × 3.5 × 3.5 mm, 275 image volumes per run, matrix size = 64 × 64, TR = 2s, TE = 32 ms, flip angle = 70°, FOV = 24 mm). A spoiled gradient recalled (SPGR) sequence was used for acquiring anatomical T1-weighted images (172 slices; thickness = 1 mm; TI = 450 ms, TR = 8 ms, TE = 3 ms; matrix size = 192 × 256; FOV = 256 cm; flip angle = 12°; sagittal plane).

2.5. fMRI data preprocessing

Analysis of Functional NeuroImages (AFNI; <https://afni.nimh.nih.gov/afni/>) preprocessing protocols were implemented and included slice-time correction, functional image realignment, EPI/anatomical registration, and non-linear registration to the Talairach template, followed by 6 mm spatial smoothing and voxelwise scaling into units of percent signal change. Image volume pairs with frame-wise displacement >.3 mm were censored from individual level analyses. Mean frame-wise displacement (head motion) was <0.08 mm across all participants.

2.6. fMRI data analysis

Broadly, our analyses evaluated whether neural changes (pre-to post-treatment) differed for AMP vs. WL in the context of anticipating potential monetary gain or loss. Neural responses to outcome presentation were modeled at the individual level to account for distinct psychological events. At the group level, only anticipation trials were evaluated because the MID task paradigm used in the presented study had a fixed interval (i.e., no jitter) between anticipation and outcome which precluded meaningful separation of BOLD signal in response to anticipation and outcome.

First-level models. Individual-level general linear models were created to estimate brain activation and connectivity during anticipation, target presentation, and outcome periods. The regressor of interest during the anticipation period (i.e., Reward Condition: low gain, high gain, no gain, low loss, high loss, no loss) was convolved with AFNI's 'BLOCK' function over 4000 ms duration. Target and outcome presentation were also modeled by convolving their regressors with AFNI's 'BLOCK' function over 2000 ms each. Regressors for target presentation (i.e., Reward Condition) included the same conditions as for the anticipation period and regressors for outcome presentation included Performance (hit, miss) in addition to Reward Condition. Nuisance regressors were added across all individual-level models to account for head motion in the x, y, z, roll, pitch, yaw directions and fourth-degree polynomials to model low-frequency drift. The activation analysis output consisted of beta coefficients at each voxel for each condition during each task period (anticipation, target presentation, outcome presentation). Functional connectivity during the anticipation period was calculated via generalized psychophysiological interaction (gPPI) analysis (McLaren et al., 2012) at the individual-level. Reward processing related ROIs (see second-level analyses below) were used as connectivity seeds. These analyses produced voxel-wise images representing connectivity between the seed region and the rest of the brain for each anticipation condition.

Second-level models. We used a two-pronged approach to address our study aims: 1) hypothesis-driven analyses evaluated neural activation in reward-processing-related regions of interest (ROIs), and 2) data-driven exploratory analyses evaluated whole-brain activation and connectivity.

ROI analyses. ROIs were functionally defined based on regions that emerged as important in the context of the PVS and reward processing in prior work (Knutson, Bhanji, et al., 2008; Stoy et al., 2012; Ubl et al., 2015; Wu et al., 2014). Due to the unique composition of the present sample (transdiagnostic depression/anxiety), we generated ROI coordinates via peak activations representing the main effect of Reward Condition during reward anticipation across all participants at baseline (Nikolova et al., 2012), rather than relying on past large-scale studies evaluating neural activation during the MID task in non-patient samples (Oldham et al., 2018) or samples composed of patients with major depressive disorder only (Zhang et al., 2013).

As expected, activation peaks were identified in the left (-9,6,7) and right (12,6,3) ventral striatum and in the left (-30,20,10) and right (33,20,-1) anterior insula. Consistent with medial prefrontal regions shown to be involved in reward anticipation (Oldham et al., 2018;

Vassena et al., 2014) an activation peak also emerged in the anterior cingulate cortex (5,31,31; peak was on the right but the cluster and sphere extended bilaterally). Seeds were created by drawing 8 mm spheres around peak activation coordinates (Talairach space), and voxel activation values in each seed were averaged for each individual and then extracted for analysis in SPSS v. 26 (IBM; Armonk, NY). Conditions were collapsed to reduce the number of comparisons, resulting in three conditions (i.e., Gain [high/low average], Loss [high/low average, No Incentive [no gain/loss]). We created three condition contrasts (Gain vs. No Incentive, Loss vs. No Incentive, Gain vs. Loss) to directly compare task conditions in the MID task as has been done in prior studies (Oldham et al., 2018), including the work our hypotheses are based on (Wu et al., 2014). Repeated measures general linear models were used to evaluate the following interactions: Group x Time x (Gain vs. No Incentive), Group x Time x (Loss vs. No Incentive), Group x Time x (Gain vs. Loss). Exploratory analyses of the Group x Time and Group x Time x Condition interaction effects were also completed.

Whole-brain analyses. AFNI's 3dMVM program was used to build whole-brain ANOVA models and evaluate AMP vs. WL differences in pre to post neural activation and connectivity change for the same condition contrasts as in the ROI analyses. The interactions examined included Group x Time x (Gain vs. No Incentive), Group x Time x (Loss vs. No Incentive), Group x Time x (Gain vs. Loss). We completed additional exploratory analyses evaluating the full Group x Time x Condition model that yielded main effects and interactions between each of the factors. Separate models/analyses evaluated whole-brain activation and whole-brain connectivity for each of the five seeds. Each analysis was corrected for multiple comparisons on the whole-brain level, per the most recent recommendations on cluster correction (Cox, 2017). Cluster thresholds for each analysis were calculated via AFNI's 3dClustSim using the mixed-model spatial autocorrelation function (-acf) and the NN1 2-sided option and resulted in a cluster extent threshold of $k = 29$ at $p < .05$. We applied a conservative voxel-wise threshold of $p < 0.005$. Resulting clusters were visually inspected to identify their location in the brain and those that were fully situated in the white matter (see Table S3) were not further evaluated as they most likely represent noise. Effects of significant clusters situated in the gray matter were further examined by extracting each participant's cluster values for post-hoc analyses in SPSS. Two-sample t-tests evaluated group differences at each time point and paired sample t-tests examined change over time within each group; FDR-correction was employed to correct post-hoc analyses for multiple comparisons within each cluster.

3. Results

3.1. Activation

Analyses of functionally defined ROIs (ventral striatum, insula, anterior cingulate) showed robust task effects (i.e., main effect of Condition with greater activation during gain and loss trials compared to no incentive trials) but yielded no significant findings for any of the interactions examined. Whole-brain activation analyses also evinced robust task effects (see Fig. S2) but likewise no group differences over time for any contrast of interest.

3.2. Connectivity

Multiple connectivity clusters emerged for our contrasts of interest (i.e., Group x Time x [Gain vs. No Incentive], Group x Time x [Loss vs. No Incentive], Group x Time x [Gain vs. Loss]). These results are described below and listed in Table 1. Selected clusters are displayed in Figs. 1–3. Overall, AMP tended to demonstrate an increase in connectivity over time, whereas WL tended to show no change or a decrease in connectivity.

In the omnibus model (i.e., Group x Time x Condition), one cluster emerged for right ventral striatum connectivity with the right

Table 1

Significant clusters of interest resulting from whole brain analyses.

Left Ventral Striatum Connectivity							
Group x Time x Gain vs. Loss							
k	F _{1,26}	x	y	z	BA	Region	
42	34.6	30	-71	28	39, 19	Right Middle Occipital Gyrus	
Right Ventral Striatum Connectivity							
Group x Time x Loss vs. No Incentive							
k	F _{1,26}	x	y	z	BA	Region	
31	25.6	-19	-61	17	31	Left Cuneus	
Left Anterior Insula Connectivity							
Group x Time x Gain vs. No Incentive							
k	F _{1,26}	x	y	z	BA	Region	
32	20.5	26	-12	42	6	Right Middle Frontal Gyrus	
Group x Time x Loss vs. No Incentive							
k	F _{1,26}	x	y	z	BA	Region	
35	16.7	-16	20	3	-	Left Ventral Striatum	
Right Anterior Insula Connectivity							
Group x Time x Loss vs. No Incentive							
k	F _{1,26}	x	y	z	BA	Region	
52	21.5	-12	-96	3	18, 17	Left Lingual Gyrus	
33	25	-40	20	17	46	Left Middle Frontal Gyrus	
31	21.7	30	-75	28	31	Right Middle Occipital Gyrus	
Anterior Cingulate Cortex Connectivity							
Group x Time x Loss vs. No Incentive							
k	F _{1,26}	x	y	z	BA	Region	
109	32.5	-16	17	7	-	Left Ventral Striatum	
72	24.4	30	-75	21	19, 7, 39	Right Middle Occipital Gyrus	
54	24.8	5	-68	-1	18, 23	Bilateral Cuneus	
43	22.1	-16	-71	28	19, 7	Left Precuneus	
35	21.7	23	24	35	8	Right Middle Frontal Gyrus	
29	21.1	12	-57	59	7	Right Precuneus	

BA=Brodmann area; Clusters significant at whole-brain-corrected threshold of $p < 0.05$ (see Method for details on cluster threshold); extracted values for **bolded clusters** are presented in Figs. 1–3. A full list of clusters that emerged across all contrasts, including task effects, is available in the Supplement, Table S3.

precuneus/cuneus (see Table S3); however, post-hoc analyses revealed no significant effects and this cluster is therefore not further discussed. There were no significant connectivity findings for any seed for the Group x Time interaction.

Ventral striatum connectivity. Group x Time x Gain vs. Loss significantly predicted left ventral striatum connectivity with the right middle occipital gyrus ($k = 42$, $F_{1,26} = 34.6$, $xyz = 30, -71, 28$; Fig. 1A). Connectivity between these areas increased in the AMP group over time but did not change in WL; however, post hoc analyses were no longer significant after FDR correction for multiple comparisons. Furthermore, Group x Time x Loss vs. No Incentive significantly predicted right ventral striatum connectivity with the left cuneus ($k = 31$, $F_{1,26} = 25.6$, $xyz = -19, -61, 17$; Fig. 1B). FDR-corrected post-hoc analyses indicated that although there were no connectivity differences between AMP and WL at baseline, AMP had significantly higher connectivity at the post-intervention time point relative to WL ($p < 0.01$). Connectivity significantly increased in AMP ($p < 0.05$) and significantly decreased in WL ($p < 0.05$) over time.

Anterior insula connectivity. Left anterior insula connectivity analyses revealed two significant clusters across two contrasts. Group x Time x Gain vs. No Incentive significantly predicted left anterior insula connectivity with the right middle frontal gyrus ($k = 32$, $F_{1,26} = 20.5$, $xyz = 26, -12, 42$; Fig. 2A). Groups did not differ significantly at baseline but AMP demonstrated higher connectivity relative to WL at post-intervention ($p < 0.001$); connectivity significantly increased in AMP ($p < 0.05$) and significantly decreased in WL ($p < 0.001$). Additionally, Group x Time x Loss vs. No Incentive significantly predicted left anterior insula connectivity with the left ventral striatum ($k = 35$, $F_{1,26} = 16.7$, $xyz = -16, 20, 3$). Here, AMP vs. WL significantly differed at

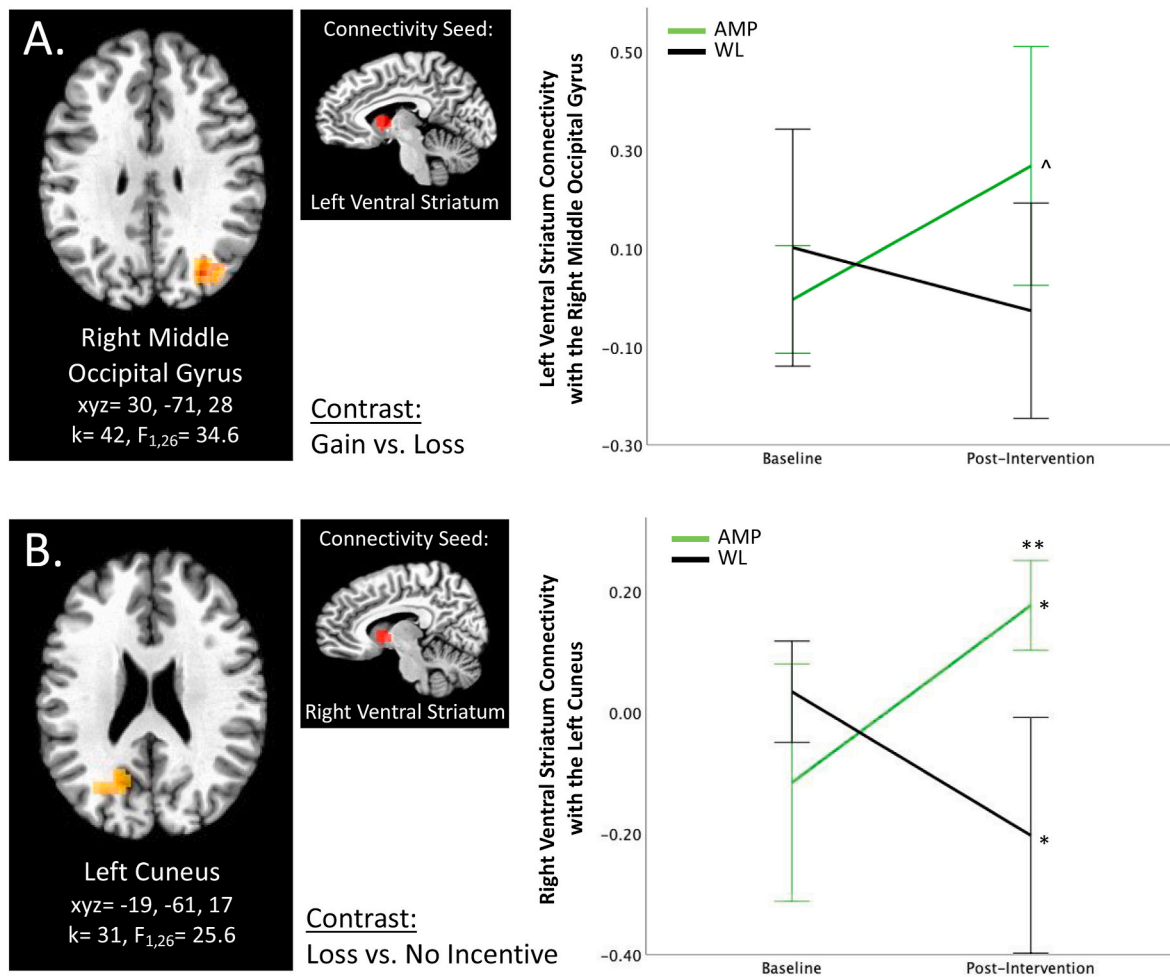


Fig. 1. Ventral Striatum Connectivity. A) Group x Time x Gain vs. Loss interaction predicts left ventral striatum connectivity with the right middle occipital gyrus. B) Group x Time x Loss vs. No Incentive interaction predicts right ventral striatum connectivity with the left cuneus. $^*p < 0.05$, $^{**}p < 0.01$, $^{\wedge}p < 0.1$, corrected. Error bars represent 95% confidence interval. AMP = treatment group that underwent Amplification of Positivity, WL = waitlist control group that did not undergo an intervention. For this and all figures, brain images represent axial sections (left = left) with threshold set at whole-brain-corrected $p < 0.05$.

both baseline ($p < 0.05$, AMP < WL) and post-intervention ($p < 0.05$, AMP > WL), however AMP demonstrated a significant increase in connectivity ($p < 0.05$) whereas WL showed a significant decrease ($p < 0.05$) over time.

Three clusters emerged for right anterior insula connectivity in the Group x Time x Loss vs. No Incentive contrast: the right middle occipital gyrus ($k = 31$, $F_{1,26} = 21.7$, $xyz = 30, -75, 28$; Fig. 2B), the left lingual gyrus ($k = 52$, $F_{1,26} = 21.5$, $xyz = -12, -96, 3$), and the left middle frontal gyrus ($k = 33$, $F_{1,26} = 25.0$, $xyz = -40, 20, 17$). For all three clusters, post-hoc analyses revealed that AMP vs. WL did not differ significantly at baseline. For the right middle occipital gyrus cluster, AMP but not WL, increased in connectivity from baseline to post-intervention ($p < 0.05$), and connectivity differed significantly between groups at post-intervention ($p < 0.05$, AMP > WL). Groups also differed significantly in connectivity with the left lingual gyrus at post-intervention ($p < 0.05$, AMP > WL), with AMP demonstrating no significant change in connectivity over time and WL a significant decrease in connectivity ($p < 0.05$). AMP showed an increase in right anterior insula connectivity with the left middle frontal gyrus over time but after correcting for multiple comparisons this was no longer significant.

Anterior cingulate cortex connectivity. Group x Time x Loss vs. No Incentive significantly predicted anterior cingulate cortex connectivity with six clusters: the left ventral striatum ($k = 109$, $F_{1,26} = 32.5$, $xyz = -16, 17, 7$; Fig. 3A), the right middle occipital gyrus ($k = 72$, $F_{1,26} = 24.4$, $xyz = 30, -75, 21$), the bilateral cuneus ($k = 54$, $F_{1,26} = 24.8$, $xyz = 5, -68, -1$), the left precuneus ($k = 43$, $F_{1,26} = 22.1$, $xyz = -16, -71, 28$), the right middle frontal gyrus ($k = 35$, $F_{1,26} = 21.7$, $xyz = 23, 24, 35$; Fig. 3B), and the right precuneus ($k = 29$, $F_{1,26} = 21.1$, $xyz = 12, -57, 59$). Anterior cingulate cortex connectivity with the left ventral striatum was significantly lower in AMP vs. WL at baseline; however, there was a significant increase in connectivity over time in AMP ($p < 0.001$), but not in WL, such that AMP demonstrated significantly higher connectivity at post-intervention ($p < 0.05$). Across the other five anterior cingulate cortex connectivity clusters, post-hoc analyses revealed that AMP did not differ from WL at baseline, that there was no change over time in connectivity among WL, but at least a trend-level increase in connectivity over time among AMP, such that AMP showed higher connectivity compared to WL at post-intervention; after correcting for multiple comparisons, this difference at the post-intervention timepoint remained significant ($p < 0.05$) in the left precuneus, the right middle frontal gyrus, and the right precuneus gyrus.

5, -68, -1), the left precuneus ($k = 43$, $F_{1,26} = 22.1$, $xyz = -16, -71, 28$), the right middle frontal gyrus ($k = 35$, $F_{1,26} = 21.7$, $xyz = 23, 24, 35$; Fig. 3B), and the right precuneus ($k = 29$, $F_{1,26} = 21.1$, $xyz = 12, -57, 59$). Anterior cingulate cortex connectivity with the left ventral striatum was significantly lower in AMP vs. WL at baseline; however, there was a significant increase in connectivity over time in AMP ($p < 0.001$), but not in WL, such that AMP demonstrated significantly higher connectivity at post-intervention ($p < 0.05$). Across the other five anterior cingulate cortex connectivity clusters, post-hoc analyses revealed that AMP did not differ from WL at baseline, that there was no change over time in connectivity among WL, but at least a trend-level increase in connectivity over time among AMP, such that AMP showed higher connectivity compared to WL at post-intervention; after correcting for multiple comparisons, this difference at the post-intervention timepoint remained significant ($p < 0.05$) in the left precuneus, the right middle frontal gyrus, and the right precuneus gyrus.

4. Discussion

The present study examined potential treatment mechanisms of Amplification of Positivity (AMP), a novel intervention targeting the Positive Valence System (PVS) shown to increase positive affect and reduce symptoms in patients with depression and/or anxiety (Taylor et al., 2017). To this end, we examined neural pre-to post-treatment activation and connectivity changes in response to reward and loss

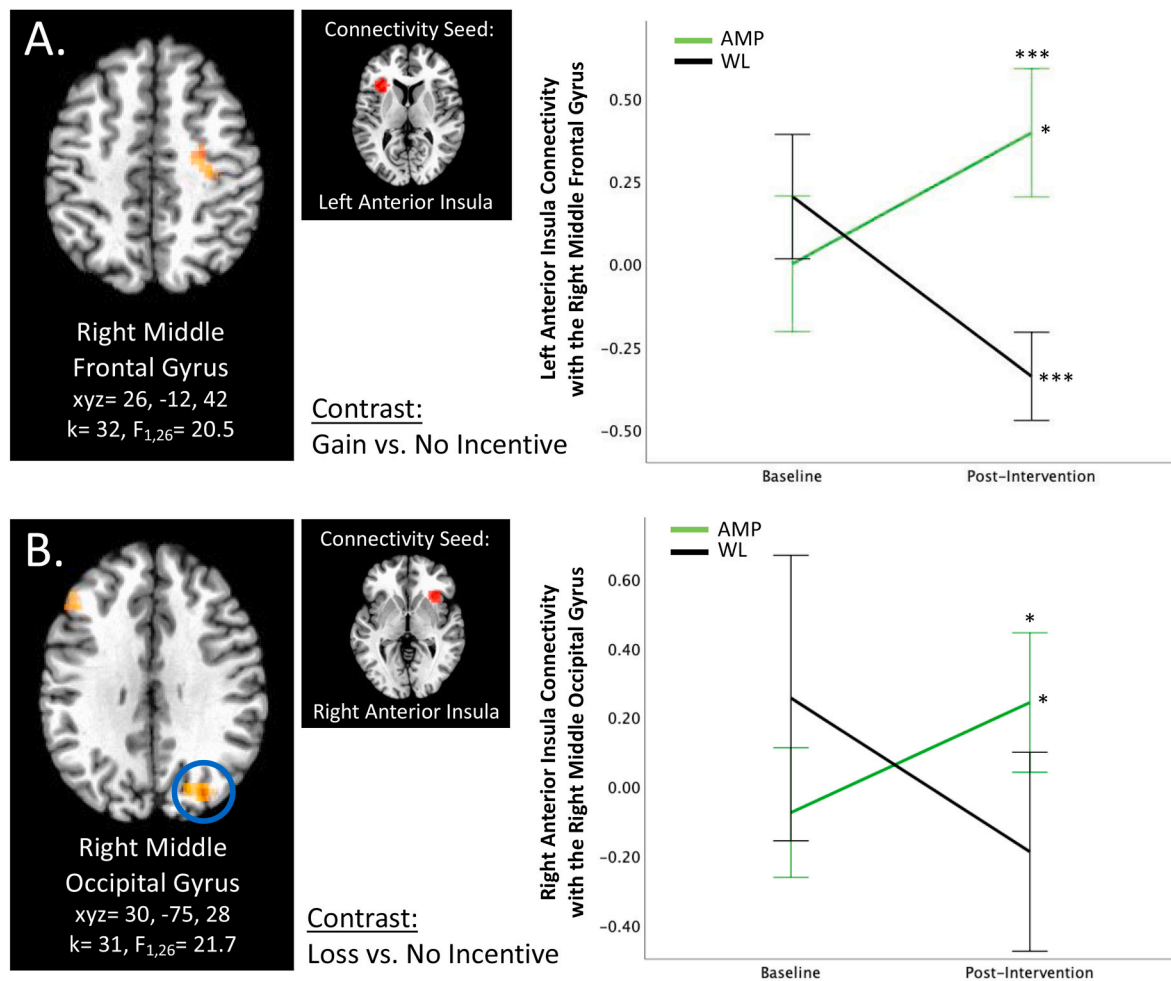


Fig. 2. Anterior Insula Connectivity. A) Group x Time x Gain vs. No Incentive interaction predicts left anterior insula connectivity with the right middle frontal gyrus. B) Group x Time x Loss vs. No Incentive interaction predicts right anterior insula connectivity with the right middle occipital gyrus. * $p < 0.05$, *** $p < 0.001$, corrected. Error bars represent 95% confidence interval. AMP = treatment group that underwent Amplification of Positivity, WL = waitlist control group that did not undergo an intervention.

anticipation in individuals who underwent AMP vs. a waitlist control group. Activation changes in reward-processing-related regions of interest did not emerge in our analyses, nor in our exploratory whole-brain activation analyses. However, our exploratory connectivity analyses revealed significant brain connectivity changes in reward processing and emotion regulation networks: connectivity increased among individuals who underwent AMP but not in waitlist controls. To our knowledge, this is the first study to examine neural treatment mechanisms of an integrated positive activity intervention protocol for depression and anxiety. Our findings suggest that improved functioning post-AMP may work through synchronization of reward-processing, attention, and emotion-regulation networks; formal mediation analyses in larger samples are needed to test this hypothesis.

4.1. Brain activation changes

Participants in our study displayed robust reward circuit activation at baseline. This finding suggests that the current sample may not be characterized by marked neural reward anticipation deficits, which may in part account for the lack of differential change in activation between treatment groups. Direct comparison to healthy controls would be necessary to establish this, however. Although some previous studies demonstrated reduced ventral striatum activation during reward anticipation in depression (e.g., [Ubl et al., 2015](#)), others have failed to identify robust evidence of reward anticipation related neural circuit

dysfunction in adult depression ([Keren et al., 2018](#); [Knutson, Bhanji, et al., 2008](#)). It is possible that neural dysfunction in transdiagnostic samples of depression and anxiety is more pronounced in other facets of reward processing (e.g., responsiveness; [Keren et al., 2018](#)), which may be more sensitive to the effects of positive activity interventions, or that only a subset of patients with depression or anxiety (e.g., those characterized by anhedonia) display reward processing deficits in the context of reward anticipation ([Reilly et al., 2020](#)). Although the majority of participants (70%) experienced levels of anhedonia that were one standard deviation or greater from community normative levels, it is possible that the transdiagnostic nature of our sample prevented us from identifying specific reward anticipation deficits. Small samples such as ours are prone to sampling bias and are not sufficiently powered to detect medium or smaller treatment effects. Future research in larger samples is needed to reconcile those possibilities.

4.2. Connectivity changes

Exploratory connectivity analyses revealed treatment-related connectivity changes among regions involved in reward processing ([Oldham et al., 2018](#)), including the ventral striatum, insula, anterior cingulate, and prefrontal cortex. Specifically, we observed increased reward-anticipation-related connectivity among individuals who underwent AMP vs. WL. Previous literature demonstrated reward-processing-related hypoconnectivity among patients with

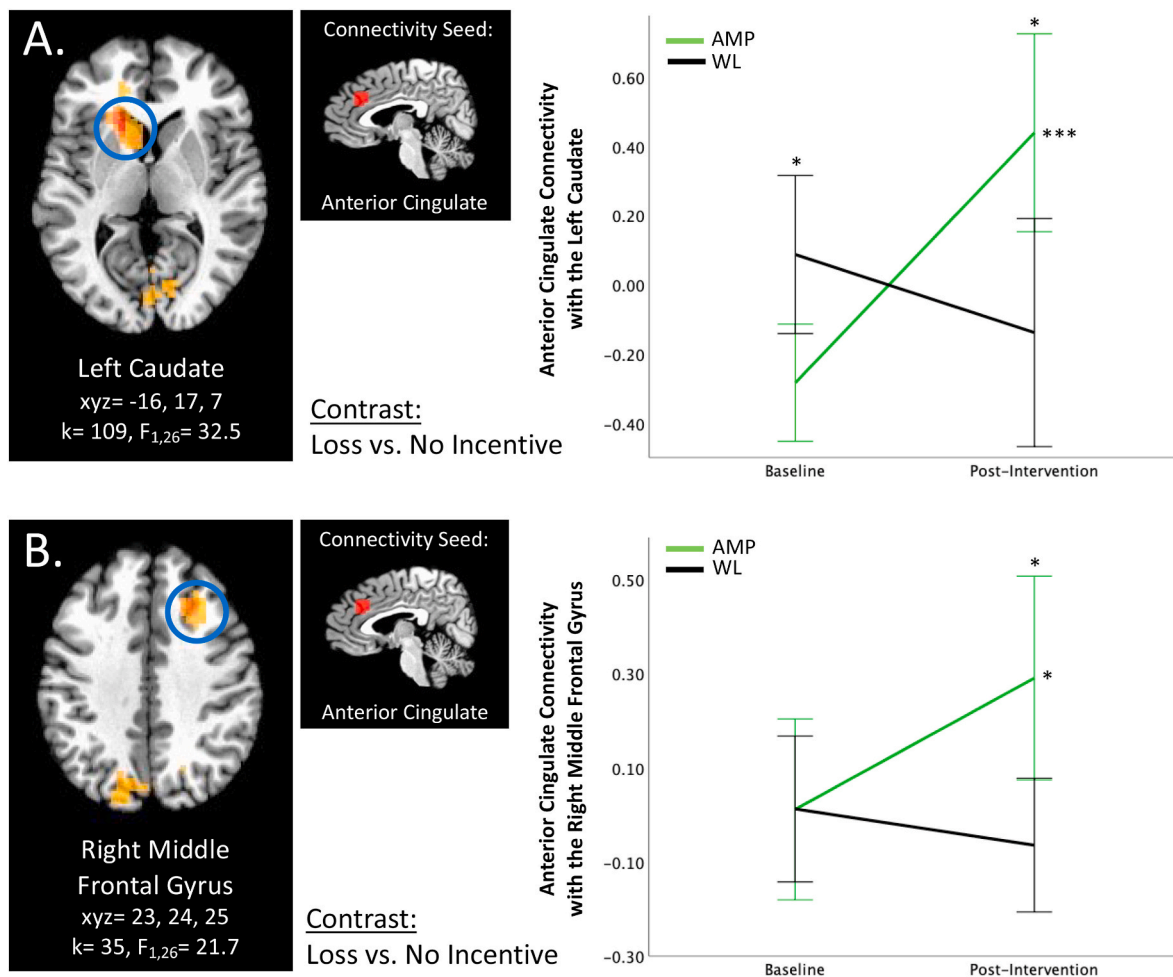


Fig. 3. Anterior Cingulate Cortex Connectivity. A) Group \times Time \times Loss vs. No Incentive interaction predicts left anterior cingulate connectivity with the left ventral striatum. B) Group \times Time \times Loss vs. No Incentive interaction predicts right anterior cingulate connectivity with the right middle frontal gyrus. $*p < 0.05$, $***p < 0.001$, corrected. Error bars represent 95% confidence interval. AMP= treatment group that underwent Amplification of Positivity, WL = waitlist control group that did not undergo an intervention.

depression (Admon et al., 2015; Rupprechter et al., 2020) and although no previous studies to our knowledge have investigated connectivity during reward processing in anxiety, hypoconnectivity of reward circuits during rest has been documented in patients with anxiety disorders (Jung et al., 2013). Resting state hypoconnectivity is also linked to anhedonia (Pornpattananangkul et al., 2019). Several studies documented treatment-related connectivity changes in reward networks. For example, cortico-striatal connectivity increased in the context of drug treatment for depression and was linked to improved functioning (Admon et al., 2017). Furthermore, several studies have demonstrated normalization of connectivity between limbic and prefrontal regions following Cognitive Behavioral Therapy (for a review, see Young et al., 2018) and changes in the reward networks are also thought to underlie treatment related changes following Behavioral Activation for depression (Nagy et al., 2020), but have yet to be established. Based on these previous studies, our findings suggest that AMP may strengthen connectivity deficits in reward processing circuits and that these changes may be related to improved clinical outcomes.

Connectivity findings primarily emerged in the Loss vs. No Incentive contrasts. Changes in reward processing networks in response to loss anticipation are consistent with the broader literature demonstrating engagement of reward processing networks in response to both gain and loss trials (Camara et al., 2009) and that reward network connectivity is predominantly seen during loss anticipation (Cho et al., 2013). How might AMP—a treatment targeted at upregulating positive affect and

reward sensitivity—influence neural processing of potential losses? One possibility is that in this transdiagnostic sample of depression and anxiety loss avoidance is perceived as more salient or rewarding relative to gain acquisition (Alden et al., 2004). It is also possible that the monetary incentive delay task was unable to capture the effect that AMP aims to increase positive emotions by leveraging autobiographical events that are meaningful to the individual—a process that may not generalize to monetary reward expectation. Previous work documented that the specific brain areas recruited for reward appraisal depend on the type of reward, such that the regions recruited in the context of secondary reinforcers including monetary rewards do not completely overlap with regions recruited in the context of primary reinforcers (Sescousse et al., 2013). Evaluating neural changes in responses to positive events that are meaningful to the individual is an important research direction and may shed light on how responsivity to positive events changes in individuals who undergo AMP.

Altogether, our findings provide preliminary evidence that AMP may work by strengthening reward processing networks. This may occur by directly ameliorating dysfunction in those networks or through compensatory processes in other systems that support reward processing. Beyond their involvement in known reward processing networks, the specific connectivity clusters that emerged in our analyses can be separated into three broad functional networks: 1) increased ventral striatum, anterior insula, and anterior cingulate connectivity with occipital and parietal areas may be linked to pre- to post-AMP changes in

stimulus driven attention and semantic representation; 2) increased anterior insula connectivity with the ventral striatum and lateral prefrontal cortex may be related to decreased loss aversion and increased readiness to engage with rewards; and 3) increased anterior cingulate connectivity with the ventral striatum and the lateral prefrontal cortex may be linked to improved automatic and voluntary emotion regulation. Each of these broad functional networks is discussed below.

4.3. Connectivity changes with occipital and parietal areas

We found that ventral striatum, anterior insula, and anterior cingulate connectivity with multiple occipital areas (e.g., middle occipital gyrus, cuneus, lingual gyrus) increased pre-to-post-treatment for AMP vs. WL. Aberrations in occipital areas have been documented in depression (Teng et al., 2018; Yue et al., 2013) and anxiety (Liao et al., 2010; Wang et al., 2018), and are predictive of symptom change post-treatment (Marwood et al., 2018). The occipital cortex is primarily implicated in visual processing but has also been shown to be involved in reward anticipation (Hangya et al., 2015; Shuler et al., 2006) and goal-directed and stimulus driven attention (Corbetta et al., 2002). A core component of AMP involves directing one's attention toward positive experiences (i.e., emotions, thoughts, events) and therefore away from negative experiences (i.e., emotional reactions to an imminent, anticipated, or remembered negative event). Loss anticipation contexts in the MID may involve redirection of attention from anticipating possible monetary loss (negative experience) toward an opportunity to retain a reward (positive experience), thereby facilitating behavioral engagement to achieve desired outcomes. Thus, increased connectivity of reward related regions with occipital areas may map onto pre-to-post-AMP shifts in attentional deployment toward the desired anticipated event (i.e., avoidance of loss) and away from the possibility of loss.

We also observed increased anterior cingulate connectivity with the bilateral precuneus during loss anticipation. Parietal regions such as the precuneus are thought to be involved in generating semantic representations of cues in the environment (Messina et al., 2016) and increased connectivity with the anterior cingulate post-AMP may indicate that AMP also works via changes in semantic connections—for example, changes in the perceived meaning of anticipating loss to an opportunity to retain what was gained.

4.4. Anterior insula connectivity changes with the middle frontal gyrus and ventral striatum

We also found that individuals who completed AMP relative to waitlist had increased pre-to-post anterior insula connectivity with the middle frontal gyrus and ventral striatum. The anterior insula is known to have connections to frontal and parietal areas involved in cognitive processes as well as to limbic areas involved in affective processes (Uddin et al., 2017). These networks have shown aberrant patterns in depression (Hamilton et al., 2012) and anxiety (Etkin et al., 2009). More specifically, the insula is involved in risky decision-making (Von Siebenthal et al., 2017) and loss aversion (Markett et al., 2016). Increased post-AMP connectivity within insula networks in the context of loss anticipation may therefore be associated with decreased loss aversion and contribute to symptom improvement. We also observed one cluster of insula connectivity with the middle frontal gyrus in the context of gain anticipation. The specific region of this middle frontal gyrus cluster overlaps with the premotor cortex involved in motor preparation. Given the insula's involvement in detecting stimulus salience and initiating switches between default mode and central executive networks (Uddin, 2015), increased connectivity in the context of gain anticipation post-AMP may be related to increased readiness to engage in the task upon detecting a salient stimulus signaling a potentially rewarding outcome (i.e., monetary gain cue).

4.5. Anterior cingulate connectivity changes with the ventral striatum and with lateral prefrontal cortex

Anterior cingulate connectivity with the ventral striatum and with lateral prefrontal cortex regions during loss anticipation also emerged among AMP from pre-to post-treatment, relative to waitlist. The anterior cingulate is thought to regulate limbic regions such as the ventral striatum which are involved in generating emotional responses (Etkin et al., 2011). It has also been hypothesized to play an important role in cognitive control by engaging the lateral prefrontal cortex to resolve conflict (Carter et al., 2007) including in the context of anticipatory preparation for conflict (Sohn et al., 2007). Furthermore, the anterior cingulate seed region used in the present study is in an area of overlap thought to be related to both voluntary and automatic emotion regulation (Phillips et al., 2008). Taken together, increased anterior cingulate connectivity with the ventral striatum and lateral prefrontal areas among individuals who underwent AMP may mediate improved voluntary and automatic emotion regulation in face of a potential loss. This aligns with theoretical frameworks suggesting that positive activity interventions may work by improving emotion regulation (Quoidbach et al., 2015). CBT (Goldin et al., 2013; Sandman et al., 2020) and behavioral activation (Dichter et al., 2010; Mori et al., 2016) have also demonstrated neural treatment-related changes in limbic and prefrontal circuits that underlie emotion regulation suggesting possible common mechanisms between AMP and other psychosocial treatments.

4.6. Limitations

We would like to note several limitations of the present study. First, this study was powered a priori to detect only large treatment effects given the small planned sample size ($N = 30$). This prevented us from being able to detect medium or smaller treatment effects that may be clinically meaningful (Cuijpers et al., 2014). We are also underpowered to examine whether connectivity changes relate to changes in positive affect and symptoms. Relatedly, although the overall trend of increased connectivity among AMP was consistent across clusters, it is important to note that in a subset of clusters at the post-hoc level these increases were no longer significant after correcting for multiple comparisons. It will be important to replicate our findings in larger samples that have enough power to examine the relation between brain and symptoms changes. The interpretations offered in this paper should until then be evaluated with caution. Second, we focused on reward anticipation. Future work could examine other phases of the reward processing cycle. Third, due to inherent limitations of pre-post designs it is unclear if the observed brain connectivity changes preceded clinical change. More frequent assessments of neural functioning and symptoms will be needed to establish the time course of changes. Finally, the present sample was selected based on meeting criteria for depression and/or anxiety disorders rather than dysfunctions in the PVS, such as anhedonia or neural response to reward. Examining neural changes following AMP in a sample with evidence of PVS dysfunction at baseline may shed further insight into specific treatment mechanisms. Overall, replication in larger samples is important and will facilitate examination of the relationship between brain and symptom changes as well as moderation effects with respect to baseline deficits.

5. Conclusion

Our findings contribute to a growing literature documenting neural mechanisms of treatment change in depression and anxiety disorders (Young et al., 2018) and answer calls for research to examine interventions that target the positive valence system specifically (Craske et al., 2016; Dunn et al., 2020; Layout et al., 2014). Although no significant activation differences emerged in our a priori analyses, exploratory seed-based connectivity analyses revealed increased connectivity in neural networks related to reward-processing, attention, and

emotion regulation following AMP. The present study is the first to examine potential neural mechanisms of an intervention that targets the PVS through positive activity interventions and sets the stage for future work to further explore these mechanisms and predictors of response in larger samples. This work may eventually contribute to more fine-tuned, individualized treatments for target populations.

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CRediT authorship contribution statement

Maria Kryza-Lacombe: Conceptualization, Methodology, Software, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Nana Pearson:** Formal analysis, Visualization, Writing – review & editing. **Sonja Lyubomirsky:** Resources, Writing – review & editing. **Murray B. Stein:** Resources, Writing – review & editing. **Jillian Lee Wiggins:** Supervision, Writing – review & editing. **Charles T. Taylor:** Conceptualization, Writing – original draft, Writing – review & editing, Resources, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Maria Kryza-Lacombe, Nana Pearson, and Jillian Lee Wiggins declare that they have no conflicts of interest. Charles T. Taylor declares that in the past 3 years he has been a paid consultant for Homewood Health, and receives payment for editorial work for UpToDate. Murray B. Stein declares that in the past 3 years he has been a paid consultant for Acadia Pharmaceuticals, Aptinyx, Biomimics, Genentech/Roche, GW Pharma, and Janssen, and receives payment for editorial work for UpToDate and the journals *Biological Psychiatry* and *Depression and Anxiety*. Sonja Lyubomirsky declares that in the past 3 years she has been a paid lecturer for the University of Arizona Center for Integrative Medicine and the Laureate Institute for Brain Research.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brat.2021.103860>.

Author contributions

CTT, SL, and MBS developed the study concept and design. MKL developed the analytic plan with critical input from CTT and JLW. MKL

and NP conducted data analysis. MKL and CTT interpreted the findings with input from all other authors. MKL took the lead in writing the paper with critical feedback and revisions provided by CTT, SL, MBS, and JLW. All authors approved the manuscript for publication and agreed with the order of authorship.

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