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# Neural activity to reward and loss predicting treatment outcomes for adults with generalized anxiety disorder: A randomized clinical trial☆

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## Abstract

Aberrant reward processing has been predominantly associated with depressive disorders, with evidence that pre-treatment abnormalities in striatal reward responsiveness relates to treatment outcomes. Emerging research also implicates reward processing differences in anxiety disorders, particularly generalized anxiety disorder (GAD). The current study examined whether pre-treatment reward- and loss-related neural activity predicts symptom improvement with behavioral

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Appendix A. Supporting information

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activation (BA) and exposure therapy (EXP) for GAD. In this randomized clinical trial (ClinicalTrials.gov NCT02807480) conducted from 2016 to 2021, treatment-seeking adults with GAD completed the monetary incentive delay task during functional magnetic resonance imaging pre-treatment, then were randomized to 10-session EXP or BA. The primary outcome measure was the GAD-7. Of 101 participants consented, 69 completed treatment, the 46 completers with quality imaging data were included in analyses (22 EXP, 24 BA; mean 32.7 years, 10.9 % male). *A priori* region-of-interest analysis revealed that greater left caudate activity during loss receipt predicted greater symptom improvement in EXP, and did not relate to symptom change in BA ($F(1, 428)= 5.24$, $p = 0.023$), though this was not significant after correction for multiple comparisons. Whole-brain analysis further identified that greater activity during reward receipt in left frontoparietal regions and anterior insula / ventrolateral prefrontal cortex was associated with better outcomes in BA and worse outcomes in EXP. These findings highlight the role of reward and loss reactivity in GAD treatment. In particular, patients with elevated reactivity to reward salience may benefit most from BA or other reward-focused treatments. Future clinical trials are warranted to further elucidate reward-related predictors of anxiety treatment.

### Keywords

Reward; Loss; GAD; Psychotherapy; FMRI

## 1. Introduction

Generalized anxiety disorder (GAD) is a chronic and disabling mental disorder [1] that affects about 6 % of adults in the United States [2]. The individual and societal costs related to GAD are substantial, including increased healthcare costs and decreased work productivity [3]. Although pharmacotherapies (e.g., benzodiazepines and selective serotonin reuptake inhibitors) and psychotherapies (e.g., cognitive behavioral therapy (CBT)) are effective treatments for GAD [4], only 40–70 % of patients with GAD experience significant improvement with these gold-standard interventions [5,6]. A better understanding of the neural factors contributing to GAD treatment response could be useful for informing the development of novel or optimized interventions.

### 1.1. Reward in depression and anxiety

A substantial literature has associated depressive disorders with reduced reward reactivity [7]. Decreased striatal responsivity to monetary reward anticipation [8–11], reward receipt [9,11,12], and loss anticipation [10] have been observed for individuals with major depressive disorder (MDD) compared to healthy comparison participants. Depression has also been associated with increased dorsal anterior cingulate cortex (ACC) activation during monetary reward anticipation, and increased medial and dorsolateral prefrontal cortex activation during monetary reward anticipation and receipt [9,11,13]. These findings point to an imbalance of cortical and subcortical reward reactivity in depression: decreased striatal reward reactivity may indicate insufficient reward-related reinforcement learning [14], whereas increased cortical reward reactivity, particularly to reward anticipation may reflect heightened top-down executive control during reward-related processing or planning [15].

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Anxiety-related neuroimaging research has predominantly focused on threat reactivity [16,17], with results from GAD-focused studies highlighting increased amygdala, ventral and ventrolateral prefrontal cortex (PFC), and ACC reactivity to negative affective stimuli [18–20]. However, maladaptive anxiety-related avoidance often occurs in the context of approach-avoidance conflict in which rewards are relinquished in order to avoid threats [21], suggesting a potential need to understand the interplay of reward and loss reactivity that contributes to these behavioral patterns. In addition, the high overlap between depression and GAD has prompted more recent research examining the role of reward and loss reactivity in GAD specifically [22]. Results from these studies suggest that adolescents with GAD show enhanced dorsal striatal activation to reward anticipation [23], and youth with GAD, separation anxiety disorder, and/or social phobia exhibit enhanced medial PFC activation to reward receipt [24], compared to healthy comparison groups. Relatedly, in a nonclinical sample, socially anxious individuals exhibited increased activity in the precuneus, posterior cingulate cortex, and parietal cortex during reward anticipation and receipt, and decreased ventral striatal reactivity during loss anticipation [25]. Overall, the limited research to date on the neural responses to reward and loss in anxiety disorders implicates striatal and prefrontal networks, with evidence for increased reward reactivity and decreased loss reactivity.

### 1.2. Reward circuitry and treatment outcomes for depression and anxiety

The finding that anhedonia (i.e., loss of interest or pleasure in activities typically enjoyed) is a robust predictor of poor prognosis and poor treatment outcomes [26–29] sparked interest in whether neural reactivity to reward and loss might predict treatment outcome for depression. A number of neuroimaging studies have focused on behavioral activation for depression, an evidence-based behavioral therapy that focuses on re-engagement in valued and rewarding activities. These studies have found that greater pre-treatment striatal activity to reward receipt predicts greater anhedonia improvement with BA for anhedonic adolescents [30], and greater sustained activity in ACC during reward receipt predicts better response to BA for adults with MDD [31]. Findings regarding other therapeutic approaches have been mixed. Among adolescents with MDD, greater striatal activity and less medial PFC activity during reward anticipation, and lower striatal activity to reward receipt, predicted greater symptom reduction with CBT (alone or combined with pharmacotherapy) [32]. Relatedly, greater pre-treatment cortico-striatal connectivity during reward receipt has been found to predict greater symptom improvement with pharmacotherapy for MDD [33], perhaps reflecting cortical regulation of striatal reward reactivity. These findings suggest that pre-treatment striatal reward reactivity relates to treatment outcomes across a variety of treatment modalities, though the directionality may depend on the treatment and the aspect of reward processing examined.

Findings relating to reward reactivity and treatment outcomes for GAD are more sparse, and no studies to date have directly examined reward- and loss-related neural predictors of treatment outcomes with GAD. In our prior work, we have reported that increased dorsolateral PFC activation during receipt of affective decision outcomes (positive or negative images) related to greater symptom reduction with behavioral activation (BA) or exposure-based therapy for adults with GAD, and that dampened amygdala activation

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to positive affective outcomes related to better outcomes for BA than for exposure-based therapy [34]. While not directly reward-related, these findings hint at the role of neural reactivity to positive stimuli in predicting GAD treatment outcomes. In line with this, another study focused on a transdiagnostic sample of youth with GAD, separation anxiety disorder, and/or social phobia found that pre-treatment ventral striatal activation to reward receipt was higher for responders compared to non-responders (across CBT and supportive psychotherapy arms) [24]. Taken together, these studies echo findings regarding depression treatment, suggesting that greater cortical and striatal reactivity to positive or rewarding stimuli may confer superior symptom improvement in treatment for anxiety.

### 1.3. The current study

In the current study, we utilized data collected as part of a randomized clinical fMRI study to examine whether pre-treatment neural responses to reward and loss anticipation and receipt (a) are predictive of the effectiveness of behavioral therapy outcome among adults with GAD and (b) may be useful for informing precision medicine approaches to therapy, differentiating the type of behavioral therapy best suited for an individual. In the study, two treatment arms were employed: behavioral activation (BA) and exposure-based therapy (EXP). BA is an evidence-based treatment widely used as a treatment for depression [35, 36], whereas EXP is considered a gold-standard behavioral approach to treating anxiety. Both of these interventions focused on modifying behavioral patterns and reducing avoidance as well as monitoring emotional reactions to the new behaviors or activities, but through the use of unique strategies; EXP emphasizes reducing distress and negative expectancy in feared situations [37], and BA encourages patients to increase engagement in activities that are rewarding or meaningful [38]. Given the differential focus of BA and EXP, and findings from prior studies, we hypothesized that BA would serve to capitalize on existing reward reactivity, such that greater striatal activity during reward would be associated with better symptom improvement in BA. If supported, this would suggest that individuals with greater baseline striatal reward reactivity might have a stronger neural response to the rewarding activities assigned in BA, resulting in a greater likelihood of continuing to engage in rewarding activities outside of treatment, and thus greater symptom improvement. Similarly, we hypothesized that EXP would serve to capitalize on both reward and loss reactivity, such that greater striatal activity during reward and loss would be associated with better symptom improvement in EXP. If supported, this would suggest that individuals with greater baseline reward and loss reactivity might more adequately process the positive and negative outcomes of assigned exposure exercises, thereby increasing the likelihood of continued adherence to exposures and symptom improvement.

## 2. Method

### 2.1. Study design and participants

The study was a randomized clinical trial conducted in [removed for masked review] examining how pre-treatment neural responses predicts the effectiveness of behavioral therapy outcome among adults with GAD. The study protocol was registered in advance with Clinical Trials. gov (NCT 02807480). Participants underwent fMRI while performing the monetary incentive delay (MID) task at pre-treatment, followed by 10 weeks of

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manualized EXP or BA therapy. Participants provided consent to participate in the study and received monetary compensation according to the guidelines set by the Western Institutional Review Board, which approved the study protocol. Research was conducted in accordance with the World Medical Association Declaration of Helsinki.

Participants were recruited from local community mental health clinics as well as online and print advertisements. Participants were eligible for the study if they were 18–55 years old, had sufficient proficiency in English to complete measures, met the criteria for GAD per the Mini International Neuropsychiatric Interview (MINI, version 6.0.0 for DSM-IV-TR or version 7.0.2 for DSM-5, administered by trained clinicians) and scored higher than 7 on the Overall Anxiety Severity and Impairment Scale [39]. Comorbid MDD was allowed, but severe depressive symptoms (Patient Health Questionnaire-9 score >17) and comorbid psychotic, bipolar, or obsessive-compulsive disorders were exclusion criteria; full inclusion and exclusion criteria are described in the Supplement. Participants completed self-report assessments at pre-treatment, on the day of their weekly treatment sessions, and at post-treatment. The primary outcome measure was GAD-7 [40]. A Bonferroni-corrected $p$ threshold of 0.0125 was used to correct across the set of four regions of interest for each analysis.

Only participants who completed at least 7 of the 10 sessions of treatment were included in the present analyses, to enable prediction of symptom outcomes for an adequate dose of treatment. Of the 101 participants who met the study criteria and consented to participate (54 BA, 47 EXP), 69 completed at least 7 sessions of treatment. Of these, 19 (11 BA, 8 EXP) had incomplete or missing MID task fMRI data, and an additional 2 participants (both BA) were excluded from fMRI analysis due to poor fMRI data quality (e.g., excess motion defined as an average Euclidean norm value of 0.30 or greater, artifacts), and 2 participants (1 BA, 1 EXP) were excluded for extreme outlier behavior during the task (number of hits or misses less than 2 SD below the mean). As a result, the final analysis included fMRI data from a total of 46 (24 BA, 22 EXP) participants (Fig. 1, Table 1).

### 2.2. Interventions

The therapies are described in detail in our published protocol paper [41]. EXP and BA both included ten manualized sessions. Both interventions focused on behavioral techniques such as identifying maladaptive behavioral patterns, assigning weekly behavioral homework, and planning for behavioral modification, without involving any cognitive techniques (e.g., cognitive restructuring). EXP focused on testing out one's negative expectancies concerning anxiety-provoking events by having individuals be exposed to feared situations in a controlled and safe environment. BA focused on increasing opportunities for reinforcement or reward by having individuals behaviorally engage in activities in line with their values or goals. Further information about the interventions, providers, and fidelity measures are provided in the Supplement and in our prior report of clinical outcomes associated with these interventions [42].

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### 2.3. Experimental paradigm

Participants completed two runs of the MID task, a validated paradigm designed to elicit neural responses to monetary reward and loss [43], during fMRI at pre-treatment (Fig. 2). Each trial of the task begins with an "anticipation" cue (250 ms) signaling potential reward (+$1 or +$5), loss (-$1 or -$5), or no reward/loss. After a delay, participants then view a target shape. The participant must respond to the target by pressing a button quickly enough in order to gain the reward or prevent the loss. The feedback appeared immediately after the response (1650 ms) conveying "receipt" of reward or loss. A total of 30 trials per condition were presented across two runs. Trial order was pseudo-randomized, and all participants completed the runs in the same order. Task difficulty was adjusted based on participants' pre-scan reaction times so that each participant would succeed on approximately 66 % of the target responses and earn $0–40 [13,43,44].

### 2.4. Neuroimaging

Acquisition parameters for fMRI are described in the Supplement. Neural activity was examined during anticipation and receipt for the contrasts 'loss vs. non-loss' and 'gain vs. non-gain' in the whole brain as well as in *a priori* regions of interest (ROIs) from the Brainnetome atlas [45] in left and right caudate and nucleus accumbens, based on our hypotheses regarding striatal responding to reward and loss.

### 2.5. Data analysis

To identify predictors of symptom trajectory, LMEs were conducted with symptom score as the outcome variable, and time (linear effect of time as a numeric variable: Week 1 of treatment = 1 through post-treatment = 11), treatment-arm, and pre-treatment MID neural response, and the interactions among these, as predictors. For those without post-treatment symptom scores, the last available symptom score was used; i.e., "last one carried forward". The pre-treatment symptom score was included as a covariate, to ensure that modeled effects did not reflect baseline differences. Baseline motion was included as an additional covariate, and participant ID were included as random effects. An autocorrelation structure of order 1 was included. Effects of interest included the time x treatment-arm x brain activation. Whole-brain analyses were conducted using 3dLMEr in AFNI, with models taking the same form as the ROI analyses: participant- and timepoint-specific "volumes" of clinical scores were entered as the outcome variable, and volumes of voxelwise pre-treatment task-related coefficients were entered as predictor variables (see Supplement). Although MDD did not have significant effects on symptom change in prior analyses [42], to examine potential effects of MDD on reward-related prediction of symptom change, ROI analyses were repeated with major depressive disorder status as a covariate. This did not substantially change results; therefore, results from models without MDD as a covariate are reported here. Data and analysis scripts are available at https://osf.io/nfj5v/?view_only=dd3c8710697c4d1e847b9c37a6261a6c.

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# 3. Results

## 3.1. Differential predictors of treatment outcomes

Greater activity in the left caudate during loss receipt predicted greater GAD symptom reductions in EXP but not in BA ($F(1, 428)= 5.24$, $\eta^2p = .012$, $p = 0.023$) (Fig. 3), although this finding did not meet the Bonferroni-corrected threshold. We conducted an exploratory post-hoc analysis to determine the direction of this effect, which revealed that in EXP, greater levels of pre-treatment left caudate activation corresponded to better outcomes ($p = 0.017$), in contrast to comparably favorable symptom declines across levels of pre-treatment left caudate activation in BA ($p = 0.479$). Post-hoc correlation indicated that pre-treatment left caudate activity during loss receipt did not correlate with pre-treatment GAD-7 scores ($p = .646$). Other *a priori* regions of interest for other contrasts were not predictive of GAD symptom trajectory (activation * time and activation * time * treatment-arm effects: $p$s > .08).

Whole-brain analyses revealed differential prediction of treatment outcomes in left cortical regions. Specifically, activation in the left dorsolateral PFC, left anterior insula / operculum, and left temporo-parieto-occipital junction to reward receipt was associated with differential outcomes across treatment-arms. Post-hoc analyses revealed that greater activation in these regions was associated with better outcomes in BA and worse outcomes in EXP, such that treatment outcomes differed across treatment-arms for those with higher levels of left cortical activation (Table S3, Fig. 4). Time x activation effects (i.e., common predictors) were not significant.

# 4. Discussion

This study examined reward- and loss-related predictors of behavioral activation and exposure therapy outcomes for adults with GAD. We hypothesized that EXP would capitalize on pre-treatment striatal reward and loss reactivity. Our findings that lower pre-treatment activation of left caudate to loss receipt related to poorer outcomes for EXP (but not BA) partially supported this hypothesis. We also hypothesized that BA would capitalize on pre-treatment striatal reward reactivity; while this was not supported, we did find that greater *cortical* reward reactivity was associated with better BA. These findings shed light on the role of reward and loss reactivity in GAD and its treatment.

Our findings revealed that caudate reactivity to loss was differentially related to treatment outcome, with greater activation relating to better outcomes for EXP but not for BA. While this finding did not meet Bonferroni thresholds, it is worth considering for replication in future studies given its potential theoretical relevance to treatment. Caudate activity during reward / loss receipt may reflect learning or updating of action-outcome contingencies [46,47], given evidence for its role in reward learning [48–51]. Caudate reactivity to the task may therefore relate to encoding of the relationship between the target response and the associated outcomes, which may enable learning from the outcomes of exposure exercises. For example, when an exposure exercise results in a negative outcome, caudate activation may serve to update the set of expectancies associated with the activity (e.g., comparing severity of negative outcome with prior negative expectancy, processing concurrent negative

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and positive outcomes). While BA undoubtedly also involves learning from experience, perhaps it is less reliant on caudate-based learning to negative outcomes. In light of this, the present finding suggests that strategies or tools that enhance caudate activation when processing outcomes may serve to enhance response to exposure-based therapy specifically. Future studies corroborating this finding could support the use of cognitive-behavioral strategies (e.g., to enhance awareness of action-outcome contingencies) [47] or neuromodulation techniques [52,53] to enhance caudate activation when processing exposure outcomes.

Through exploratory whole-brain analyses, we also identified poorer symptom improvements in EXP among those with greater activation within executive control and salience regions during reward receipt, specifically in left frontoparietal regions and anterior insula. One possibility is that activity in these regions reflects greater orienting and attention during reward receipt, given the role of the anterior insula in salience detection [54] and the role of frontoparietal networks in attention regulation and cognitive control [55–57]. The anterior insula cluster we identified also extends into the left ventrolateral prefrontal cortex (Brodmann area 45), which has specifically been implicated as a reward-related salience network node [58] with relevance for psychopathology [59,60]. Heightened frontoparietal, anterior insula, and vlPFC activity to reward receipt in the present study could therefore reflect greater orienting toward the rewarding stimulus, up- or down-regulation of positive emotion, and/or recruitment of cognitive resources, when processing positive or rewarding outcomes. Our findings suggest that for individuals with heightened baseline cortical reward reactivity, BA's focus on rewarding activities serves to capitalize on this tendency, whereas EXP's focus on anxiety reduction does not. Of note, previous cross-sectional studies identified increased dlPFC activation during reward receipt in populations with depression [9,11], modulation of dlPFC circuitry with repetitive transcranial magnetic stimulation (rTMS) has been effective in the treatment of depression [61], and there is some evidence that dlPFC rTMS may enhance reward sensitivity [62,63]. Further experimental investigations are needed to examine how modulation of these circuits during reward processing influences behavior, symptoms, and/or treatment outcome for individuals with depression or GAD.

The present study comes with some limitations. First, we did not include a comparison intervention condition such as an attentional control or waitlist, limiting our ability to draw conclusions about whether identified predictors are specific to behavioral therapy effects. In addition, we focused on striatal regions of interest, given prior literature on the role of the striatum in reward reactivity. However, this focus may have been limiting, especially in light of our whole-brain results which highlight the relevance of prefrontal reward reactivity in predicting treatment outcomes. Finally, our finding in the left caudate *a priori* region of interest was not significant after correcting for multiple comparisons, perhaps due to our limited power to detect differential predictors. Future studies with larger samples and additional comparison conditions will be well-suited to further assess the conclusions suggested by the present findings.

All in all, the present findings highlight the role of reward and loss reactivity in predicting response to behavior therapy for GAD. A crucial next step will be identifying specific

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behavioral or neuromodulation strategies that can be paired with EXP or BA to improve treatment outcomes, such as enhancing awareness of action-outcome contingencies or modulating engagement of executive control or striatal regions in the context of reward and loss.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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### Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Robin Aupperle reports financial support was provided by National Institute of Mental Health. Christopher Martell reports receiving royalties for four books on the topic of behavioral activation. Martin Paulus has received royalties for an article about methamphetamine published in UpToDate. The other authors have no conflicts of interest to declare.

## References

[1]. Baldwin DS, Polkinghorn C. Evidence-based pharmacotherapy of generalized anxiety disorder. Int J Neuropsychopharmacol 2005;8:293–302. 10.1017/S1461145704004870. [PubMed: 15576000]

[2]. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen H-U. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int J Methods Psychiatr Res 2012;21:169–84. 10.1002/mpr.1359. [PubMed: 22865617]

[3]. Wittchen H-U. Generalized anxiety disorder: prevalence, burden, and cost to society. Depress Anxiety 2002;16:162–71. 10.1002/da.10065. [PubMed: 12497648]

[4]. Hoge EA, Oppenheimer JE, Simon NM. Generalized anxiety disorder. Focus 2004; 2:346–59. 10.1176/foc.2.3.346.

[5]. Koen N, Stein DJ. Pharmacotherapy of anxiety disorders: a critical review. Dialog-Clin Neurosci 2011;13:423–37. 10.31887/DCNS.2011.13.4/nkoen.

[6]. Olatunji BO, Cisler JM, Deacon BJ. Efficacy of cognitive behavioral therapy for anxiety disorders: a review of meta-analytic findings. Psychiatr Clin North Am 2010;33:557–77. 10.1016/j.psc.2010.04.002. [PubMed: 20599133]

[7]. Admon R, Pizzagalli DA. Dysfunctional reward processing in depression. Curr Opin Psychol 2015;4:114–8. 10.1016/j.copsyc.2014.12.011. [PubMed: 26258159]

[8]. Arrondo G, Segarra N, Metastasio A, Ziauddeen H, Spencer J, Reinders NR, et al. Reduction in ventral striatal activity when anticipating a reward in depression and schizophrenia: a replicated cross-diagnostic finding. Front Psychol 2015;6:1280. 10.3389/fpsyg.2015.01280. [PubMed: 26379600]

[9]. Forbes EE, Hariri AR, Martin SL, Silk JS, Moyles DL, Fisher PM, et al. Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. Am J Psychiatry 2009;166:64–73. 10.1176/appi.ajp.2008.07081336. [PubMed: 19047324]

[10]. Stoy M, Schlagenhauf F, Sterzer P, Bermpohl F, Hägele C, Suchotzki K, et al. Hyporeactivity of ventral striatum towards incentive stimuli in unmedicated depressed patients

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normalizes after treatment with escitalopram. J Psychopharmacol (Oxf) 2012;26:677–88. 10.1177/0269881111416686.

[11]. Zhang W-N, Chang S-H, Guo L-Y, Zhang K-L, Wang J The neural correlates of reward-related processing in major depressive disorder: a meta-analysis of functional magnetic resonance imaging studies. J Affect Disord 2013;151:531–9. 10.1016/j.jad.2013.06.039. [PubMed: 23856280]

[12]. Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, et al. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am J Psychiatry 2009;166:702–10. 10.1176/appi.ajp.2008.08081201. [PubMed: 19411368]

[13]. Knutson B, Bhanji JP, Cooney RE, Atlas LY, Gotlib IH. Neural responses to monetary incentives in major depression. Biol Psychiatry 2008;63:686–92. 10.1016/j.biopsych.2007.07.023. [PubMed: 17916330]

[14]. Cox J, Witten IB. Striatal circuits for reward learning and decision-making. Nat Rev Neurosci 2019;20:482. 10.1038/s41583-019-0189-2. [PubMed: 31171839]

[15]. Friedman NP, Robbins TW. The role of prefrontal cortex in cognitive control and executive function. Neuropsychopharmacology 2022;47:72–89. 10.1038/s41386-021-01132-0. [PubMed: 34408280]

[16]. Cisler JM, Koster EHW. Mechanisms of attentional biases towards threat in anxiety disorders: an integrative review. Clin Psychol Rev 2010;30:203–16. 10.1016/j.cpr.2009.11.003. [PubMed: 20005616]

[17]. Eldar S, Yankelevitch R, Lamy D, Bar-Haim Y. Enhanced neural reactivity and selective attention to threat in anxiety. Biol Psychol 2010;85:252–7. 10.1016/j.biopsycho.2010.07.010. [PubMed: 20655976]

[18]. McClure EB, Monk CS, Nelson EE, Parrish JM, Adler A, Blair RJR, et al. Abnormal attention modulation of fear circuit function in pediatric generalized anxiety disorder. Arch Gen Psychiatry 2007;64:97–106. 10.1001/archpsyc.64.1.97. [PubMed: 17199059]

[19]. Monk CS, Nelson EE, McClure EB, Mogg K, Bradley BP, Leibenluft E, et al. Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. Am J Psychiatry 2006;163:1091–7. 10.1176/ajp.2006.163.6.1091. [PubMed: 16741211]

[20]. Monk CS, Telzer EH, Mogg K, Bradley BP, Mai X, Louro HMC, et al. Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. Arch Gen Psychiatry 2008;65:568–76. 10.1001/archpsyc.65.5.568. [PubMed: 18458208]

[21]. Aupperle RL, Sullivan S, Melrose AJ, Paulus MP, Stein MB. A reverse translational approach to quantify approach-avoidance conflict in humans. Behav Brain Res 2011;225:455–63. 10.1016/j.bbr.2011.08.003. [PubMed: 21843556]

[22]. Carter RM, Wittchen HU, Pfister H, Kessler RC. One-year prevalence of subthreshold and threshold DSM-IV generalized anxiety disorder in a nationally representative sample. Depress Anxiety 2001;13:78–88. 10.1002/da.1020. [PubMed: 11301924]

[23]. Guyer AE, Choate VR, Detloff A, Benson B, Nelson EE, Perez-Edgar K, et al. Striatal functional alteration during incentive anticipation in pediatric anxiety disorders. Am J Psychiatry 2012;169:205–12. 10.1176/appi.ajp.2011.11010006. [PubMed: 22423352]

[24]. Sequeira SL, Silk JS, Ladouceur CD, Hanson JL, Ryan ND, Morgan JK, et al. Association of neural reward circuitry function with response to psychotherapy in youths with anxiety disorders. Am J Psychiatry 2021;178:343–51. 10.1176/appi.ajp.2020.20010094. [PubMed: 33472390]

[25]. Maresh EL, Allen JP, Coan JA. Increased default mode network activity in socially anxious individuals during reward processing. Biol Mood Anxiety Disord 2014;4:7. 10.1186/2045-5380-4-7. [PubMed: 25075275]

[26]. Uher R, Farmer A, Maier W, Rietschel M, Hauser J, Marusic A, et al. Measuring depression: comparison and integration of three scales in the GENDEP study. Psychol Med 2008;38:289–300. 10.1017/S0033291707001730. [PubMed: 17922940]

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[27]. Uher R, Perlis RH, Henigsberg N, Zobel A, Rietschel M, Mors O, et al. Depression symptom dimensions as predictors of antidepressant treatment outcome: replicable evidence for interest-activity symptoms. Psychol Med 2012;42:967–80. 10.1017/S0033291711001905. [PubMed: 21929846]

[28]. Vinckier F, Gourion D, Mouchabac S. Anhedonia predicts poor psychosocial functioning: Results from a large cohort of patients treated for major depressive disorder by general practitioners. Eur Psychiatry J Assoc Eur Psychiatr 2017;44:1–8. 10.1016/j.eurpsy.2017.02.485.

[29]. McMakin DL, Olino TM, Porta G, Dietz LJ, Emslie G, Clarke G, et al. Anhedonia predicts poorer recovery among youth with selective serotonin reuptake inhibitor treatment-resistant depression. J Am Acad Child Adolesc Psychiatry 2012;51:404–11. 10.1016/j.jaac.2012.01.011. [PubMed: 22449646]

[30]. Webb CA, Murray L, Tierney AO, Forbes EE, Pizzagalli DA. Reward-related predictors of symptom change in behavioral activation therapy for anhedonic adolescents: a multimodal approach. Neuropsychopharmacol Publ Am Coll Neuropsychopharmacol 2023;48:623–32. 10.1038/s41386-022-01481-4.

[31]. Carl H, Walsh E, Eisenlohr-Moul T, Minkel J, Crowther A, Moore T, et al. Sustained anterior cingulate cortex activation during reward processing predicts response to psychotherapy in major depressive disorder. J Affect Disord 2016;203:204–12. 10.1016/j.jad.2016.06.005. [PubMed: 27295377]

[32]. Forbes EE, Olino TM, Ryan ND, Birmaher B, Axelson D, Moyles DL, et al. Reward-related brain function as a predictor of treatment response in adolescents with major depressive disorder. Cogn Affect Behav Neurosci 2010;10:107–18. 10.3758/CABN.10.1.107. [PubMed: 20233959]

[33]. Admon R, Nickerson LD, Dillon DG, Holmes AJ, Bogdan R, Kumar P, et al. Dissociable cortico-striatal connectivity abnormalities in major depression in response to monetary gains and penalties. Psychol Med 2015;45:121–31. 10.1017/S0033291714001123. [PubMed: 25055809]

[34]. Berg H, McDermott TJ, Kuplicki R, Yeh H-W, Thompson WK, Smith R, et al. (2023, December). Neural activations to approach-avoidance conflict predict response to behavioral therapy for adults with GAD. Poster presented at the annual meeting of the American College of Neuropsychopharmacology (ACNP), Tampa, FL.

[35]. Lejuez CW, Hopko DR, Hopko SD. A brief behavioral activation treatment for depression. Treatment manual. Behav Modif 2001;25:255–86. 10.1177/0145445501252005. [PubMed: 11317637]

[36]. Sturmey P Behavioral activation is an evidence-based treatment for depression. Behav Modif 2009;33:818–29. 10.1177/0145445509350094. [PubMed: 19933444]

[37]. Craske MG, Kircanski K, Zelikowsky M, Mystkowski J, Chowdhury N, Baker A. Optimizing inhibitory learning during exposure therapy. Behav Res Ther 2008;46:5–27. 10.1016/j.brat.2007.10.003. [PubMed: 18005936]

[38]. Martell CR, Dimidjian S, Herman-Dunn R. Behavioral Activation for Depression: A Clinician's Guide. Guilford Publications; 2021.

[39]. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(20):22–33. quiz 34–57.

[40]. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166:1092–7. 10.1001/archinte.166.10.1092. [PubMed: 16717171]

[41]. Santiago J, Akeman E, Kirlic N, Clausen AN, Cosgrove KT, McDermott TJ, et al. Protocol for a randomized controlled trial examining multilevel prediction of response to behavioral activation and exposure-based therapy for generalized anxiety disorder. Trials 2020;21:17. 10.1186/s13063-019-3802-9. [PubMed: 31907032]

[42]. Berg H, Akeman E, McDermott TJ, Cosgrove KT, Kirlic N, Clausen A, et al. A randomized clinical trial of behavioral activation and exposure-based therapy for adults with generalized anxiety disorder. J Mood Anxiety Disord 2023;1:100004. 10.1016/j.xjmad.2023.100004.

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[43]. Knutson B, Westdorp A, Kaiser E, Hommer D. FMRI visualization of brain activity during a monetary incentive delay task. NeuroImage 2000;12:20–7. 10.1006/nimg.2000.0593. [PubMed: 10875899]

[44]. Knutson B, Adams CM, Fong GW, Hommer D. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J Neurosci J Soc Neurosci 2001;21: RC159. 10.1523/JNEUROSCI.21-16-j0002.2001.

[45]. Fan L, Li H, Zhuo J, Zhang Y, Wang J, Chen L, et al. The human brainnetome atlas: a new brain atlas based on connectional architecture. Cereb Cortex N Y N 1991 2016;26:3508–26. 10.1093/cercor/bhw157.

[46]. Morris RW, Dezfouli A, Griffiths KR, Le Pelley ME, Balleine BW. The neural bases of action-outcome learning in humans. J Neurosci 2022;42:3636–47. 10.1523/JNEUROSCI.1079-21.2022. [PubMed: 35296548]

[47]. Tricomi EM, Delgado MR, Fiez JA. Modulation of caudate activity by action contingency. Neuron 2004;41:281–92. 10.1016/S0896-6273(03)00848-1. [PubMed: 14741108]

[48]. Patterson TK, Knowlton BJ. Subregional specificity in human striatal habit learning: a meta-analytic review of the fMRI literature. Curr Opin Behav Sci 2018; 20:75–82. 10.1016/j.cobeha.2017.10.005.

[49]. Tricomi E, Delgado MR, McCandliss BD, McClelland JL, Fiez JA. Performance feedback drives caudate activation in a phonological learning task. J Cogn Neurosci 2006;18:1029–43. 10.1162/jocn.2006.18.6.1029. [PubMed: 16839308]

[50]. Haruno M, Kawato M. Different neural correlates of reward expectation and reward expectation error in the putamen and caudate nucleus during stimulus-action-reward association learning. J Neurophysiol 2006;95:948–59. 10.1152/jn.00382.2005. [PubMed: 16192338]

[51]. Bick SK, Patel SR, Katnani HA, Peled N, Widge A, Cash SS, et al. Caudate stimulation enhances learning. Brain J Neurol 2019;142:2930–7. 10.1093/brain/awz254.

[52]. Legon W, Mueller J, Tyler W. The use of transcranial focused ultrasound for fmri bold response in humans. Brain Stimul 2017;10:e5–6. 10.1016/j.brs.2016.11.034.

[53]. Munoz F, Meaney A, Gross A, Liu K, Pouliopoulos AN, Liu D, et al. Long term study of motivational and cognitive effects of low-intensity focused ultrasound neuromodulation in the dorsal striatum of nonhuman primates. Brain Stimul 2022;15:360–72. 10.1016/j.brs.2022.01.014. [PubMed: 35092823]

[54]. Gu X, Hof PR, Friston KJ, Fan J. Anterior insular cortex and emotional awareness. J Comp Neurol 2013;521:3371–88. 10.1002/cne.23368. [PubMed: 23749500]

[55]. Bramson B, Meijer S, van Nuland A, Toni I, Roelofs K. Anxious individuals shift emotion control from lateral frontal pole to dorsolateral prefrontal cortex. Nat Commun 2023;14:4880. 10.1038/s41467-023-40666-3. [PubMed: 37573436]

[56]. Nejati V, Majdi R, Salehinejad MA, Nitsche MA. The role of dorsolateral and ventromedial prefrontal cortex in the processing of emotional dimensions. Sci Rep 2021;11:1971. 10.1038/s41598-021-81454-7. [PubMed: 33479323]

[57]. Roelofs K, Bramson B, Toni I. A neurocognitive theory of flexible emotion control: the role of the lateral frontal pole in emotion regulation. Ann N Y Acad Sci 2023;1525:28–40. 10.1111/nyas.15003. [PubMed: 37170478]

[58]. Trambaiolli LR, Peng X, Lehman JF, Linn G, Russ BE, Schroeder CE, et al. Anatomical and functional connectivity support the existence of a salience network node within the caudal ventrolateral prefrontal cortex. eLife 2022;11:e76334. 10.7554/eLife.76334.

[59]. Edmiston EK, Fournier JC, Chase HW, Aslam HA, Lockovich J, Graur S, et al. Left ventrolateral prefrontal cortical activity during reward expectancy predicts mania risk up to one year post scan. J Affect Disord 2022;319:325–8. 10.1016/j.jad.2022.08.081. [PubMed: 36087789]

[60]. Chase HW, Nusslock R, Almeida JR, Forbes EE, LaBarbara EJ, Phillips ML. Dissociable patterns of abnormal frontal cortical activation during anticipation of an uncertain reward or loss in bipolar versus major depression. Bipolar Disord 2013;15:839–54. 10.1111/bdi.12132. [PubMed: 24148027]

[61]. Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS)

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for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol Med 2014;44:225–39. 10.1017/S0033291713000512. [PubMed: 23507264]

[62]. Mas-Herrero E, Dagher A, Zatorre RJ. Modulating musical reward sensitivity up and down with transcranial magnetic stimulation. Nat Hum Behav 2017;2:27–32. 10.1038/s41562-017-0241-z. [PubMed: 30980048]

[63]. Wang X, He K, Chen T, Shi B, Yang J, Geng W, et al. Therapeutic efficacy of connectivity-directed transcranial magnetic stimulation on anticipatory anhedonia. Depress Anxiety 2021;38:972–84. 10.1002/da.23188. [PubMed: 34157193]

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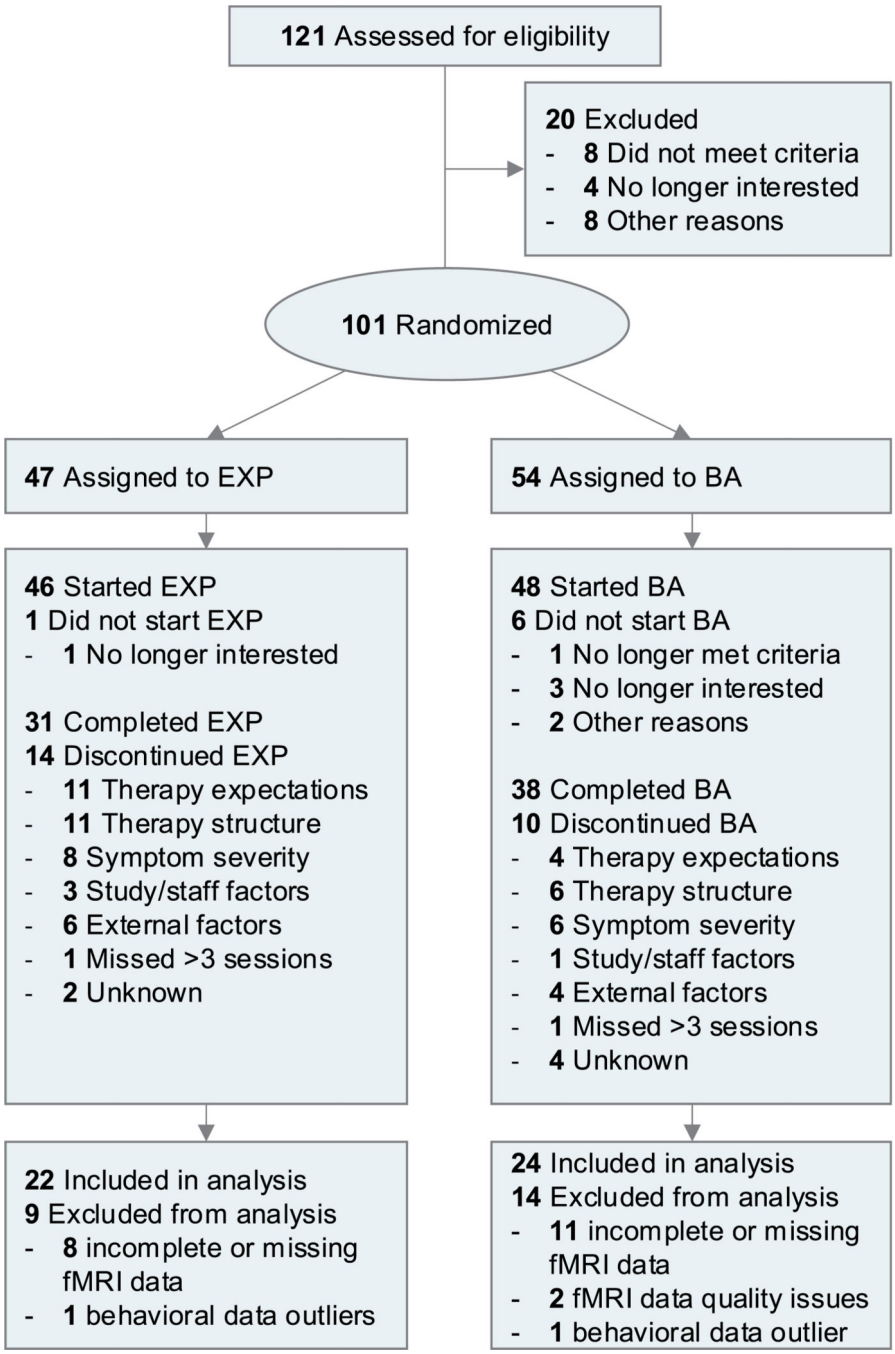


**Fig. 1.**

Participant flow diagram. Participants who discontinued treatment were asked to remotely complete a survey assessing reasons for discontinuation, which included ratings of various potential reasons as well as a space to provide free text. Participants were allowed to indicate as many reasons for discontinuation as applicable. Responses were summarized using the categories shown above.

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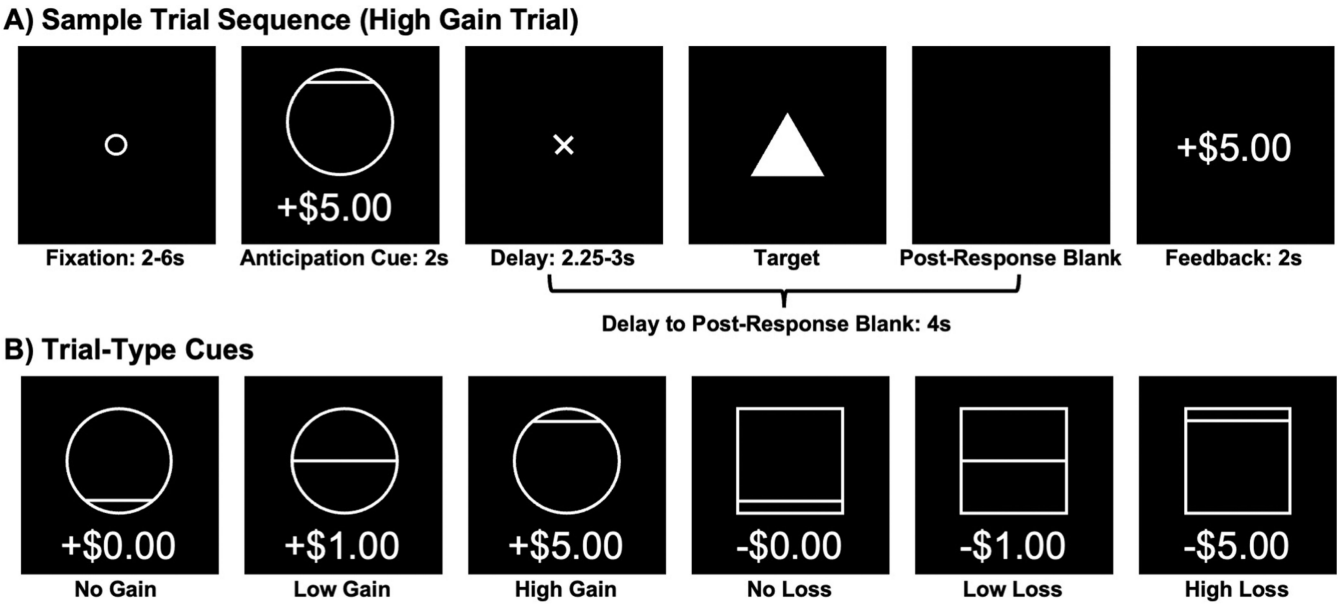


**Fig. 2.**

The monetary incentive delay task. Events of interest for fMRI analysis are anticipation (4 s including the anticipation cue and the subsequent delay) and receipt (2 s). Reward-related contrasts were +$1 and +$5 trials minus $0 trials, loss-related contrasts were -$1 and -$5 trials minus $0 trials.

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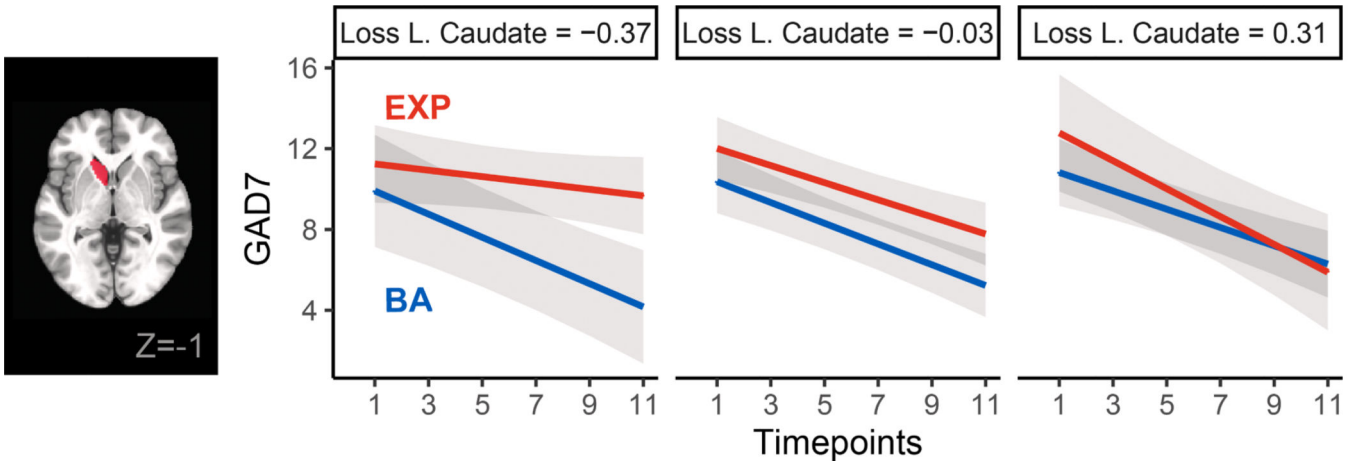


**Fig. 3.**

Neural activation to loss receipt in the left caudate, an *a priori* region of interest, differentially predicts GAD-7 symptom change. Lower levels of left caudate activation corresponded to poorer symptom improvement in EXP (leftmost panel). Estimated marginal means are shown from model with the form *symptom ~ time * treatment * neural activity + pre-treatment symptom + head motion,* with random effects for participant. Estimated values are shown for left caudate activity at the sample mean + /−1 SD. 95 % confidence intervals are shown. Timepoints on the *x* axis reflect timepoints from Week 1 of treatment (1) through post-treatment timepoint (11). L: left; BA: behavioral activation, EXP: exposure.

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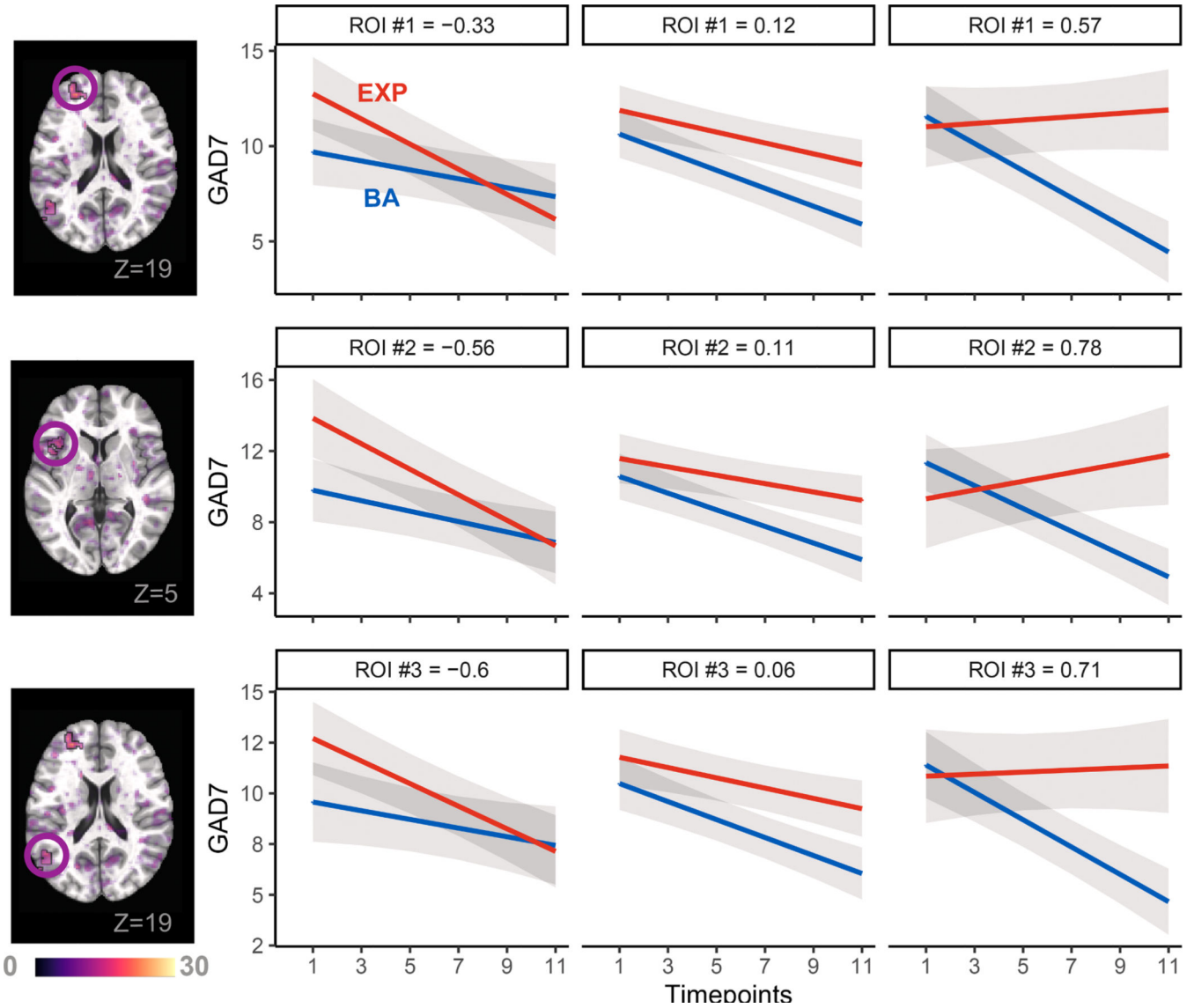


**Fig. 4.**

Whole-brain analysis revealed clusters in which neural activation to reward receipt differentially predicts GAD-7 symptom change. Estimated marginal means are shown from models with the form *symptom ~ time * treatment *** neural activity + *pre-treatment symptom* + *head motion,* with random effects for participant. ROI #1: left dlPFC; ROI #2: left anterior insula / ventrolateral prefrontal cortex; ROI #3: left temporo-parieto-occipital junction. Estimated values are shown for whole-brain ROI activity at the sample mean + / −1 SD. 95 % confidence intervals are shown. Timepoints on the *x* axis reflect timepoints from Week 1 of treatment (1) through post-treatment timepoint (11). ROI: region of interest (defined by whole-brain analysis); BA: behavioral activation, EXP: exposure.

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**Table 1**

Demographic and Clinical Characteristics.

| | BA | EXP | *p* |
|---|---|---|---|
| *n* | 24 | 22 | |
| Age (mean (SD)) | 35.12 (11.30) | 29.95 (8.21) | 0.085 |
| Gender = Male (%) | 5 (20.8) | 0 (0.0) | 0.05† |
| Income (%) | | | 0.185† |
| Not provided | 0 (0.0) | 1 (4.5) | |
| Less than 50,000 | 12 (50.0) | 6 (27.3) | |
| 50,000 to 100,000 | 3 (12.5) | 7 (31.8) | |
| 100,000 to 150,000 | 8 (33.3) | 5 (22.7) | |
| over 150,000 | 1 (4.2) | 3 (13.6) | |
| Race (%) | | | 0.472† |
| American Indian | 8 (34.8) | 3 (15.0) | |
| Asian | 0 (0.0) | 1 (5.0) | |
| Black | 2 (8.7) | 1 (5.0) | |
| Hispanic | 1 (4.3) | 1 (5.0) | |
| Multi | 0 (0.0) | 0 (0.0) | |
| White | 12 (52.2) | 14 (70.0) | |
| Race = White (%) | 12 (50.0) | 14 (63.6) | 0.526 |
| Education (%) | | | 0.307† |
| Less than high school | 1 (4.2) | 0 (0.0) | |
| High school or GED | 0 (0.0) | 2 (9.1) | |
| Some college, no degree | 7 (29.2) | 4 (18.2) | |
| Bachelor’s degree | 9 (37.5) | 7 (31.8) | |
| Associate’s degree | 3 (12.5) | 1 (4.5) | |
| Master’s degree | 4 (16.7) | 8 (36.4) | |
| Professional/doctoral degree | 0 (0.0) | 0 (0.0) | |
| GAD7 (mean (SD)) | 11.88 (3.57) | 12.00 (4.92) | 0.921 |
| PROMIS Anxiety (mean (SD)) | 65.25 (4.38) | 64.64 (4.57) | 0.644 |
| PROMIS Depression (mean (SD)) | 58.79 (5.78) | 54.51 (7.30) | 0.032 |
| SDS (mean (SD)) | 13.83 (4.89) | 11.09 (5.18) | 0.071 |
| Psychiatric medications (%) | 9 (37.5) | 8 (36.4) | > 0.99† |
| Current MDE (%) | 11 (45.8) | 4 (18.2) | 0.092 |
| Social Anxiety Disorder (%) | 5 (20.8) | 9 (40.9) | 0.247 |
| Agoraphobia (%) | 0 (0.0) | 3 (13.6) | 0.101† |
| Panic Disorder (%) | 0 (0.0) | 2 (9.1) | 0.223 |
| Suicidality (%) | 10 (41.7) | 5 (22.7) | 0.292 |
| PTSD (%) | 0 (0.0) | 0 (0.0) | > 0.99† |
| Binge Eating Disorder (%) | 1 (4.2) | 1 (4.5) | > 0.99† |
| Sessions Attended (mean (SD)) | 8.96 (1.04) | 8.86 (0.99) | 0.754 |

[†]Fisher's exact test.

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