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Anhedonia and Delay Discounting: Differing Patterns of Brain-Behavior Relationships in Healthy Control Participants Versus Individuals With Posttraumatic Stress Disorder

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ABSTRACT

BACKGROUND: Anhedonia may contribute to individual differences in delay discounting (DD). In prior work, we found that higher anhedonia was associated with shallower DD in healthy control (HC) participants but steeper DD in individuals with posttraumatic stress disorder (PTSD). In this study, we aimed to directly compare the relationship between anhedonia and DD across groups and to identify functional brain correlates of this interaction.

METHODS: Participants (HC group: n = 23, DSM-5 PTSD group: n = 23) completed a questionnaire assessing anhedonia (Snaith-Hamilton Pleasure Scale [SHAPS]), task-based functional magnetic resonance imaging of decision making including DD, and resting-state functional magnetic resonance imaging. Task-based activity and resting-state functional connectivity were evaluated in reward-related regions that have also been implicated in PTSD (nucleus accumbens [NAcc], right anterior insula).

RESULTS: Higher SHAPS scores were associated with steeper DD in PTSD, but there was no relationship between DD and SHAPS in the HC group. There was a significant group-by-SHAPS interaction for NAcc activity, $t_{31} = 2.92$, $p = .007$: Greater NAcc activity when immediate rewards were chosen was associated with higher SHAPS in the PTSD group but lower SHAPS in the HC group. In resting-state functional connectivity, there was a group-by-SHAPS interaction between the NAcc seed and right parietal and frontal pole clusters.

CONCLUSIONS: These results extend prior findings that anhedonia is associated with steeper DD in PTSD and demonstrate that this behavioral finding occurs in the context of NAcc hyperactivity to immediate rewards and hyperconnectivity in anhedonic individuals with PTSD.

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Alterations in reward valuation are a transdiagnostic feature of psychopathology (1,2) with critical implications for morbidity (3) and mortality (4). In the translational psychopathology literature, one important aspect of reward valuation is delay discounting (DD), or the extent to which rewards decline in subjective value as the delay to receive them increases (5). DD can be assessed by asking participants to choose between pairs of rewards (e.g., "Would you rather have $5 now or $10 in one week?"). While devaluation of future rewards is expected and likely often adaptive, there are individual differences in the discounting rate or steepness of the discounting curve that plots the decline in subjective value of rewards as the delay to receive them grows (6). Much of the extensive existing literature on steep DD has focused on its association with alcohol and substance use disorders because of their link to impulsive choice (7). Importantly, numerous studies have identified steeper DD in individuals with other forms of psychopathology including attention-deficit/hyperactivity disorder (8), schizophrenia (9), bipolar disorder (10), major depressive disorder (11), and borderline personality disorder (12). Therefore, understanding transdiagnostic processes that may contribute to steep DD across psychiatric conditions is an important goal (5).

Anhedonia is clinically defined as loss of pleasure or lack of reactivity to pleasurable stimuli (13), involves loss of reward valuation, and is a transdiagnostic process that may contribute to individual differences in DD. For example, anhedonic individuals may exhibit shallower DD because they are less motivated by immediate rewards. Indeed, one prior study found that in healthy undergraduate students, greater anhedonia was associated with shallower DD, i.e., increasing anhedonia was associated with greater willingness to wait for larger later rewards (14). In healthy adults, pharmacologically induced reduction in cortical dopamine also increases choice of delayed rewards (15). In contrast, our prior work with trauma-exposed adults found that greater anhedonia was associated with steeper DD (16). While there have been few other investigations of DD-anhedonia relationships, one recent study found that steeper DD was associated with greater

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anhedonia in individuals with alcohol use disorder (r = 0.39), but not in the healthy control (HC) group (r = 0.08) (17). These studies suggest that there is a more nuanced or complex relationship between DD and anhedonia than might be predicted based on theory alone or on findings in the HC group.

Although many studies have measured DD in clinical samples, relatively few have examined probability discounting (PD) or a decline in the subjective value of rewards with increasing odds against their receipt (18). Different relationships between DD and PD have been hypothesized. One might expect that people who impulsively choose smaller sooner rewards will also tend to engage in the risky behavior of choosing uncertain but potentially larger rewards (19). In other words, steep delay discounters may show shallow PD. Alternatively, DD and PD have been theorized to be positively related, for example because waiting for a delayed reward entails risk (20–22). However, DD and PD rates tend not to be strongly correlated (23,24), and despite robust associations between DD and psychopathology, group differences in the PD rate are rarely found (18). We are unaware of prior reports of PD-anhedonia associations, but because risky rewards tend to activate reward circuitry including the ventral striatum (19), elevated anhedonia could result in decreased attractiveness of the larger uncertain reward (i.e., steeper PD).

Posttraumatic stress disorder (PTSD) is a particularly important disorder in which to investigate relationships between anhedonia and reward-related decision making because it involves disturbances in both processes. Individuals with a history of trauma exposure and/or early-life adversity show steeper DD than non–trauma-exposed control individuals (25–27), and trauma-exposed individuals who exhibit elevated PTSD symptoms show steeper DD than trauma-exposed non-PTSD control individuals (28). Anhedonia is robustly documented in PTSD; factor analyses find that anhedonia is a core dimensional component of PTSD (29,30); patients with PTSD show abnormal performance on reward-related tasks (31,32); and neuroimaging studies have demonstrated blunting of reward-related neural circuitry in PTSD (32–34). To summarize, there are robust studies demonstrating steeper DD and elevated anhedonia in PTSD. Although we previously found that greater anhedonia was associated with steeper DD in trauma-exposed participants (16), that report needs replication, and further work explaining the nature of that relationship and its neurobiological mechanisms is needed.

Core brain regions involved in subjective valuation of rewards during intertemporal choice include the ventral striatum, medial prefrontal cortex, and posterior cingulate cortex (35,36). A number of other regions also contribute to processes involved in DD, including areas involved in episodic future thinking and executive control (5,37). A meta-analysis of blood oxygen level–dependent activity during DD demonstrated that ventral striatal regions are specifically responsive to subjective value and that regions including the middle cingulate gyrus and the insula are specifically active when individuals choose larger later options (38). Consideration of possible contributions of anterior insula (AI) activity to altered DD in PTSD may be especially important for several reasons. The AI is active during selection of both smaller sooner and larger later rewards (39), and increased AI activity has been shown to be related to decisions high in ambivalence (40). In addition, via either direct connections or functional connectivity, the right AI may exert inhibitory control over the nucleus accumbens (NAcc) during decision making, thereby reducing risky choice (41–43). Individuals with PTSD typically show AI hyperresponsivity to trauma-related cues and negative emotional content (44). Our group has previously documented lower GABA (gamma-aminobutyric acid) in the right AI in PTSD, suggesting a mechanism that may contribute to AI hyperresponsivity in this disorder (45,46). Because the right AI has previously been shown to exert inhibitory control over the NAcc during decision making, we anticipated that higher right AI activity in PTSD might be associated with greater willingness to wait for delayed rewards, although this is somewhat at odds with existing insular lesion studies showing greater willingness to wait for delayed rewards and changes in delay and reward perception (47,48).

We previously found that in trauma-exposed participants, anhedonia was correlated with increased resting-state functional connectivity (rsFC) between the NAcc and the dorsomedial prefrontal cortex and with steeper DD (16). This was surprising given theoretical and prior empirical work suggesting that in HC individuals, anhedonia is associated with shallower DD (14). Therefore, the goals of the current study included 1) to replicate the relationship between anhedonia and steeper DD in PTSD and clarify whether anhedonia-DD relationships (and anhedonia-PD relationships) differ significantly between the PTSD and HC groups, 2) to determine whether there were group differences in the association between anhedonia and task-based activity during the DD task, and 3) to evaluate whether there were group differences in the association between anhedonia and rsFC. Given prior literature implicating the NAcc and right AI as particularly important and potentially opposing regions influencing reward-related decision making in PTSD, we examined activity and connectivity between these regions of interest (ROIs) and also performed whole-brain analyses.

METHODS AND MATERIALS

Participants

Participants included individuals who met DSM-5 criteria for a diagnosis of PTSD and those in the non–trauma-exposed HC group. Fifty-eight participants consented to participate. Of those, 9 were ineligible or had unusable data; for details, see the Supplement. This resulted in a final sample of 46 participants (23 DSM-5 PTSD, 23 HC). The sample was predominantly female (34 of 46); demographic characteristics of the participants are summarized in Table 1. Full inclusion/exclusion criteria are detailed in the Supplement; briefly, they included no current or lifetime psychiatric diagnoses for the HC group, head injury with loss of consciousness exceeding 5 minutes, past-month prescribed psychotropic medication use (except for the PTSD group, a stable [6-week] dose of antidepressant medication), or history of attention-deficit/hyperactivity disorder, psychotic disorder, or bipolar disorder. Past-year alcohol or substance use disorder was exclusionary for both groups (acceptable prior to that). All participants completed the Structured Clinical Interview for DSM-5 (49), and PTSD group participants completed the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) (50) for the

Table 1. Sample Demographic and Clinical Characteristics

	HC Group, n = 23	PTSD Group, n = 23	t	p Value
Age, Years, Mean (SD)	24.83 (3.89)	25.61 (5.85)	$t_{38.278} = -0.534$	.596
WASI-II FSIQ, Mean (SD)	117.00 (15.30)	109.09 (13.68)	$t_{43.459} = 1.849$	.071
SHAPS, Mean (SD)	16.39 (3.77)	26.61 (7.20)	$t_{33.253} = -6.030$	.000
DD % Later, Mean (SD)	0.53 (0.26)	0.58 (0.27)	$t_{43.858} = -0.609$	.546
PD % Uncertain, Mean (SD)	0.46 (0.17)	0.45 (0.25)	$t_{39.007} = 0.145$	.885
CAPS-5 Total, Mean (SD)		28.30 (7.63)		

CAPS-5, Clinician-Administered PTSD Scale for DSM-5; DD, delay discounting; FSIQ, Full Scale IQ; HC, healthy control; PD, probability discounting; PTSD, posttraumatic stress disorder; SHAPS, Snaith-Hamilton Pleasure Scale; WASI-II, Wechsler Abbreviated Scale of Intelligence, Second Edition.

diagnosis of DSM-5 PTSD; clinical interviews were administered by a doctoral-level licensed clinical psychologist (EAO).

Five participants with PTSD reported taking a stable dose of an antidepressant (bupropion, n = 1; sertraline, n = 2; venlafaxine, n = 1; sertraline and trazodone, n = 1). Trauma types were primarily interpersonal (additional details in Supplement).

Snaith-Hamilton Pleasure Scale

The Snaith-Hamilton Pleasure Scale (SHAPS) (51) is a 14-item self-report questionnaire of anhedonia asking participants to rate on a 4-point scale how strongly they agree with certain statements (e.g., "I would enjoy. . ."). Different approaches to scoring the SHAPS exist; we chose the dimensional scoring proposed by Franken *et al.* (52) that retains the 4-choice scoring (strongly disagree/disagree/agree/strongly agree). Therefore, scores ranged from 14 (nonanhedonic) to 56 (very anhedonic).

Wechsler Abbreviated Scale of Intelligence, Second Edition

Vocabulary and Matrix Reasoning subtests from the Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II) were used to derive a 2-subtest Full Scale IQ (FSIQ).

Clinician-Administered PTSD Scale for DSM-5

The CAPS-5 is a 30-item semistructured interview that assesses symptoms of DSM-5 PTSD; 20 items contribute to the CAPS-5 total score. These items assess DSM-5 PTSD symptom severity and are scored from 0 (absent) to 4 (extreme/incapacitating); thus, CAPS-5 total scores can range from 0 to 80, with higher scores indicating greater PTSD severity. Total scores in the 31 to 33 range indicate probable PTSD, although for this study there was no total score cutoff. Item scores of $\geq$2 (moderate/threshold) counted as endorsement; PTSD group participants were included if they met diagnostic criteria.

DD and PD

Participants completed an incentive-compatible, in-scanner version of the DD/PD task (53), with 4 task blocks consisting of 30 trials per block. The first and third blocks for each participant were DD blocks; the second and fourth blocks were PD blocks. On each DD trial, participants chose between a larger amount of money available after a delay or $20 available the same day. Similarly, on each PD trial, participants chose between a larger amount of money available with a lower probability or $20 available with a 100% chance. Participants completed practice trials for task familiarization out of the scanner.

We used the percentage of trials on which the participant chose the (larger) later option as the measure of DD and the percentage of trials on which the participant chose the (larger) uncertain option as the measure of PD (54,55). This type of metric has advantages over methods such as fitting discounting parameters because it avoids the theoretical assumptions of model-based metrics (24,55). In addition, the k parameter typically needs to be log-transformed prior to use, while percentage later chosen tends to be normally distributed, which simplifies interpretation. In this study, DD percentage later chosen was strongly correlated with the natural log of the DD k parameter, $r_{44} = -0.97$, and PD percentage uncertain chosen was strongly correlated with the natural log of the PD k parameter, $r_{44} = -0.94$.

Magnetic Resonance Imaging Scan

Scans were collected on a 3T Siemens Prisma scanner (Siemens Corp.) using a 64-channel head coil. Structural T1-weighted 3-dimensional magnetization-prepared rapid acquisition gradient-echo multi-echo images were collected over 176 sagittal slices with voxel size = 1.0 $\times$ 1.0 $\times$ 1.0 mm^3. For the resting-state scan, 180 T2*-weighted echoplanar images were collected over 84 transverse interleaved slices with voxel size = 1.5 $\times$ 1.5 $\times$ 1.5 mm^3. Scans for the task-based scans were identical to the resting-state scan except that 159 images were collected per block (rather than 180). For additional scan details, see the Supplement.

Imaging Data Preprocessing

Imaging data were preprocessed using a standard pipeline (fMRIPrep version 1.5.8) (56). Briefly, standard processing of the T1-weighted images included correction for intensity nonuniformity, skull stripping, segmentation, and spatial normalization to Montreal Neurological Institute space. Processing of each blood oxygen level–dependent run included generation of a reference volume, susceptibility distortion correction using the fieldmap-less approach, registration to the T1 reference, slice-time correction, resampling into standard space, and smoothing at 6-mm full width at half maximum. For the task-based data, automatic removal of motion artifacts using independent component analysis was used. Frames that exceeded 0.5-mm framewise displacement or 1.5 standardized derivative of root mean square variance over voxels were annotated as motion outliers. For complete details, see the Supplement.

Task-Based Functional Magnetic Resonance Imaging Data Analysis

Task-based functional magnetic resonance imaging (fMRI) data were analyzed using SPM12. At the first level, regressors included onset times for the following events: choosing the delayed option, choosing the immediate option, choosing the certain option, choosing the uncertain option, and failing to choose in time. At the group level, we used whole-brain as well as ROI-based approaches to investigate the relationship between self-reported anhedonia (SHAPS score) and group status in relation to task performance. A priori ROIs included the NAcc and right AI. Results with a significant group-by-SHAPS interaction were followed by analysis of the relationship between blood oxygen level–dependent activity and SHAPS in each group separately to clarify the nature of the interaction. All analyses controlled for WASI-II FSIQ (see explanation below); whole-brain analyses also controlled for age and sex (57).

RESULTS

Behavioral Results: DD and PD and Anhedonia (SHAPS Scores)

Across the full sample, the percentage of delayed rewards chosen was correlated with the percentage of uncertain rewards chosen, $r_{44} = 0.315$, $p = .033$. Higher SHAPS scores (i.e., higher anhedonia) were associated with lower WASI-II FSIQ, $r_{44} = -0.409$, $p = .005$; there were no other significant associations between demographic variables (age, sex, FSIQ) and anhedonia or DD or PD. Therefore, we controlled for WASI-II FSIQ in all subsequent analyses.

To examine the effect of anhedonia on DD and PD, we ran separate regression models predicting the percentage of delayed (or uncertain) rewards chosen, with group, SHAPS, WASI-II FSIQ, and the group-by-SHAPS interaction as predictors. For DD, the overall model was significant ($F_{4,41} = 3.54$, $p = .014$), and there were significant main effects of group ($t_{41} = 2.51$, $p = .016$) and WASI-II FSIQ ($t_{41} = 2.04$, $p = .048$); the group-by-SHAPS interaction ($t_{41} = -1.888$, $p = .0661$) was not significant (Figure 1). Within the PTSD group, after controlling for WASI-II FSIQ, there was a significant relationship between SHAPS and DD ($t_{20} = -2.586$, $p = .018$). This relationship was not significant in the HC group ($t_{20} = 0.483$, $p = .635$). Importantly, within the PTSD group, the relationship between SHAPS scores and DD remained significant after controlling for overall PTSD symptom severity (CAPS-5 scores) ($t_{19} = -2.642$, $p = .0161$), a particularly rigorous correction because the CAPS-5 includes some items related to loss of interest/pleasure.

For PD, the overall model was not significant ($F_{4,41} = 1.291$, $p = .290$), nor were any of the predictors; therefore, subsequent analyses focused on DD only.

Task-Based fMRI

ROI-Based Analysis: Anhedonia (SHAPS scores), Choosing Immediate Versus Delayed Rewards, and Activity in the NAcc and Right AI. To examine the effect of anhedonia on brain activity during DD, we ran regression models for activity when choosing immediate versus delayed rewards in the NAcc and right AI ROIs as dependent variables and group, SHAPS, WASI-II FSIQ, and the group-by-SHAPS interaction as independent variables. For the NAcc, the overall model was significant ($F_{4,31} = 3.287$, $p = .023$), and there were significant effects of group (lower in PTSD, $t_{31} = -2.580$, $p = .015$) and SHAPS scores (lower at higher SHAPS scores, $t_{31} = -2.712$, $p = .011$), qualified by a significant group-by-SHAPS interaction ($t_{31} = 2.916$, $p = .007$). In the PTSD group, participants with higher SHAPS scores had higher activity in the NAcc when choosing immediate versus delayed rewards than those with lower SHAPS scores, while in the HC group, participants with higher SHAPS scores had lower activity in the NAcc when choosing immediate versus delayed rewards than those with lower SHAPS scores (Figure 2); while the interaction was significant, these slopes did not significantly differ from 0 in either group. A supplemental parametric modulation analysis (see the Supplement, pp S6–S8) similarly found that on immediate reward trials, as the subjective value of the delayed reward increased, anhedonic PTSD participants showed greater NAcc activity than nonanhedonic participants. For the right AI, the overall model was not significant ($F_{4,31} = 1.469$, $p = .235$), and there were no significant main effects or interactions.

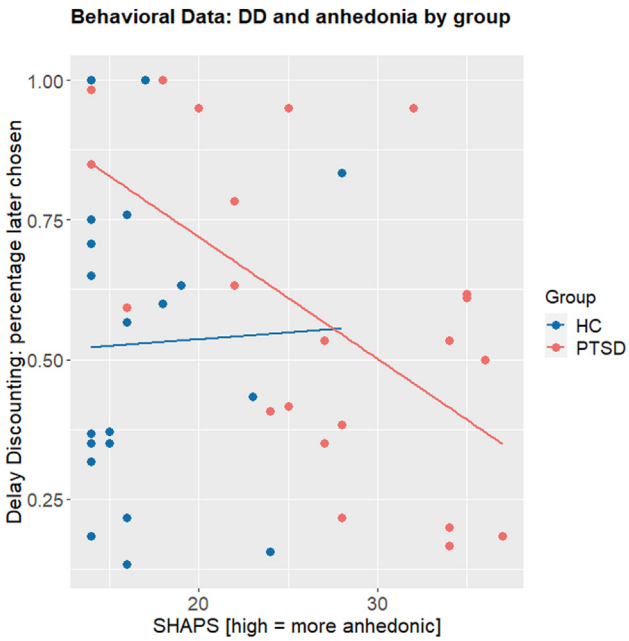

Figure 1. The relationship between anhedonia and delay discounting (DD) by group. HC, healthy control; PTSD, posttraumatic stress disorder; SHAPS, Snaith-Hamilton Pleasure Scale.

Whole-Brain Analysis: Anhedonia (SHAPS Scores) and Choosing Immediate Versus Delayed Rewards. Whole-brain analyses indicated a significant interaction between group and SHAPS scores when participants chose immediate versus delayed rewards, with 2 significant clusters in the right superior temporal lobe extending to the right insula that showed a stronger association between SHAPS scores and activity when choosing immediate rewards in the HC group (Table 2 and Figures 3A, B) and 1 significant cluster in the left frontal lobe that showed a stronger

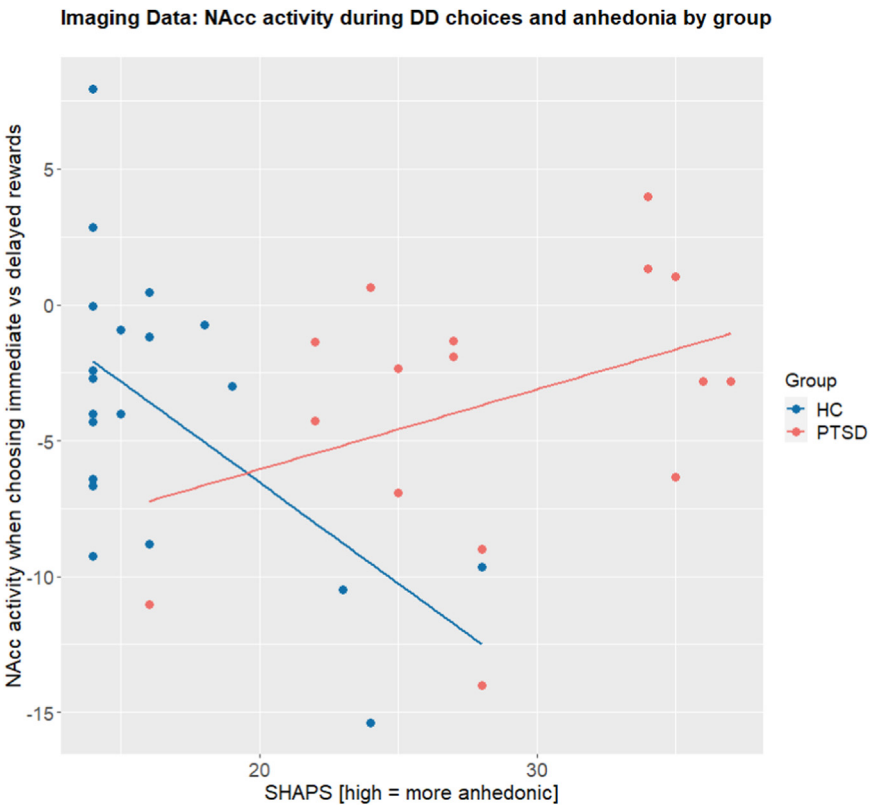

Figure 2. The relationship between anhedonia and nucleus accumbens (NAcc) region-of-interest activity when choosing immediate vs. delayed rewards on the delay discounting (DD) task differed across groups. HC, healthy control; PTSD, posttraumatic stress disorder; SHAPS, Snaith-Hamilton Pleasure Scale.

association between SHAPS scores and activity when choosing immediate rewards in the PTSD group (Table 3 and Figure 4). Therefore, relationships with SHAPS scores were examined separately for each group.

In the PTSD group, SHAPS scores were associated with activity in multiple clusters when participants chose immediate versus delayed rewards; in all of these, participants with higher SHAPS scores showed more activity than those with lower SHAPS scores when choosing immediate versus delayed rewards. This included clusters in the right superior temporal gyrus and right insula, anterior cingulate cortex, thalamus, left postcentral gyrus, right supramarginal gyrus, and left superior temporal lobe (Table 4). Critically, in the PTSD group, 2 clusters remained significant after additionally controlling for total CAPS-5 scores in the whole-brain analysis; these were the clusters in the right superior temporal gyrus and the thalamus.

In the HC group, there were no significant clusters where SHAPS was associated (positively or negatively) with activity when choosing immediate or delayed rewards.

Resting State

Forty-five participants had usable resting-state data. From a seed in the bilateral NAcc, there was a significant group-by-SHAPS interaction at rest in clusters in the right parietal lobe (supramarginal gyrus/angular gyrus) and the right frontal pole (Table 5). Therefore, relationships with SHAPS scores were examined separately for each group. Within the HC group, there were no significant regions where rsFC from the NAcc seed was associated with SHAPS scores; there also were no significant clusters within the PTSD group. In terms of the directionality of the group-by-SHAPS interaction, in the HC group, higher SHAPS scores were associated with

Table 2. Significant Clusters Where the Slope of the Interaction Between SHAPS Scores and Activity When Choosing Immediate vs. Delayed Rewards Was Higher in the PTSD Group Than in the HC Group

Brain Region	Cluster Size	MNI (x, y, z)	*z* Score	p_{FWE}
Right Superior Temporal Gyrus/Heschl's Gyrus/Right Middle Temporal Gyrus/Right Insula	84	(60, 10, −2)	4.96	.009
Right Superior Temporal Gyrus/Right Middle Temporal Gyrus/Heschl's Gyrus/Right Insula	71	(50, −32, 0)	4.12	.023

Results are from whole-brain analysis in all participants (n = 36 with usable task-based fMRI data) that were significant at voxelwise $p < .001$ uncorrected followed by $p < .05$ familywise error (FWE)–corrected. Analysis controlled for age, sex, and Full Scale IQ (Wechsler Abbreviated Scale of Intelligence, Second Edition).

HC, healthy control; MNI, Montreal Neurological Institute; PTSD, posttraumatic stress disorder; SHAPS, Snaith-Hamilton Pleasure Scale.

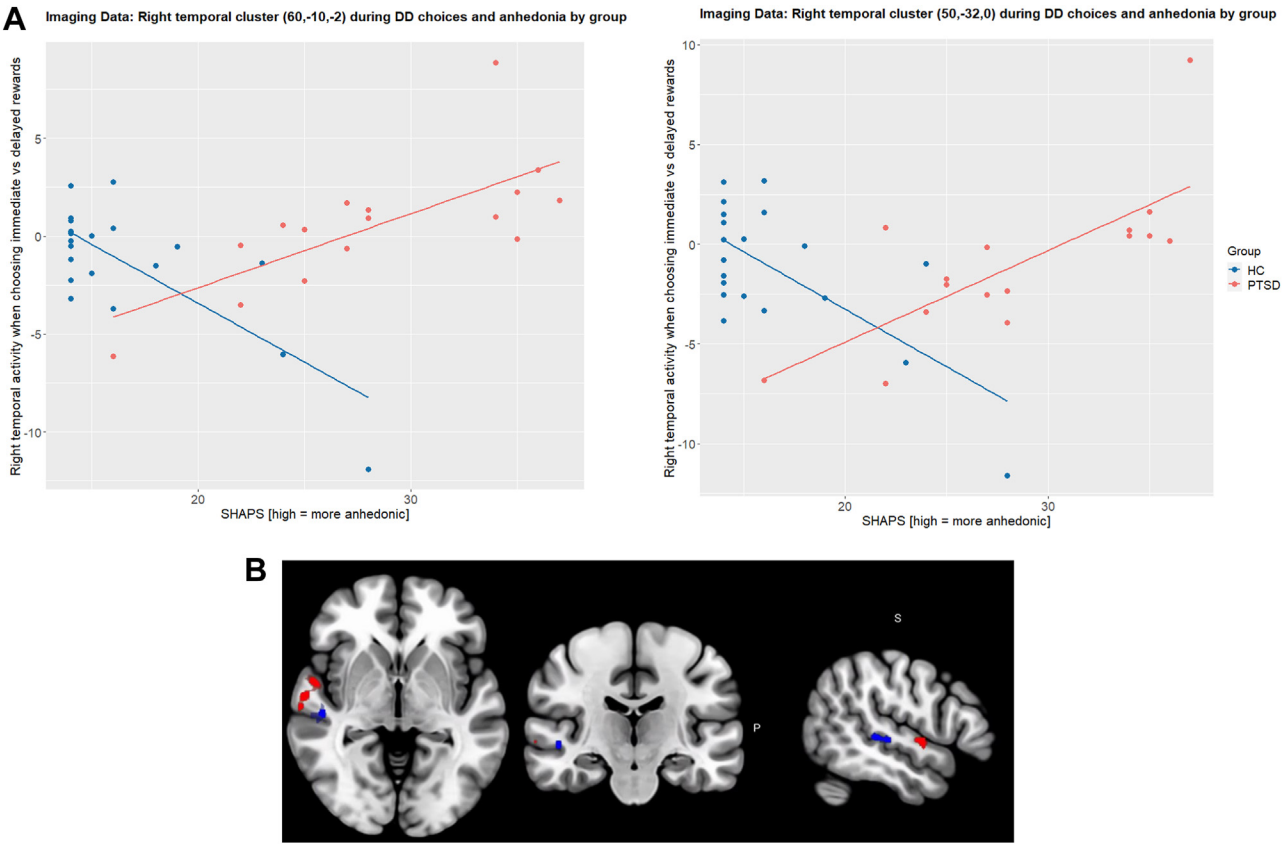

Figure 3. **(A)** The relationship between anhedonia and activity in right temporal clusters when choosing immediate vs. delayed rewards on the delay discounting (DD) task differed across groups. **(B)** Location of temporal clusters where there was a significant interaction between group and anhedonia on activity when choosing immediate vs. delayed rewards. Clusters overlaid on Montreal Neurological Institute (MNI) space brain. Red: first cluster from Table 2 (peak coordinates: 60, 10, −2). Blue: second cluster from Table 2 (peak coordinates: 50, −32, 0). HC, healthy control; PTSD, posttraumatic stress disorder; SHAPS, Snaith-Hamilton Pleasure Scale.

(nonsignificantly) less NAcc rsFC with a cluster in the right supramarginal gyrus and with (nonsignificantly) greater rsFC between the NAcc and the right frontal pole; these results were attenuated in PTSD (Figures 5 and 6). Finally, in an analysis from a seed in the right AI, there were no significant clusters characterized by a group-by-SHAPS interaction at rest.

DISCUSSION

In this study, we examined behavioral and brain correlates of anhedonia in individuals with PTSD versus HC individuals. Given prior literature and our own prior work suggesting differences in associations between self-reported anhedonia and DD in individuals with PTSD versus HC individuals, we were particularly interested in evaluating group differences in the relationship of anhedonia with behavior and with the neural circuitry supporting reward processing (i.e., in detecting group-by-anhedonia interactions). From a behavioral standpoint, self-reported anhedonia (SHAPS score) was associated with steeper DD in the PTSD group and was not related to DD in the HC group. That is, anhedonic individuals with PTSD preferred smaller sooner rewards. In addition, during decision making, self-reported anhedonia was associated with less NAcc activity for immediate versus delayed rewards in the HC group and with greater NAcc activity for immediate versus delayed rewards in the PTSD group. Furthermore, whole-brain analysis indicated that greater self-reported anhedonia in PTSD was

Table 3. Significant Clusters Where the Slope of the Interaction Between SHAPS Scores and Activity When Choosing Immediate vs. Delayed Rewards Was Higher in the HC Group Than in the PTSD Group

Brain Region	Cluster Size	MNI (x, y, z)	z Score	p_{FWE}
Left Middle Frontal Gyrus/Left Superior Frontal Gyrus/Left Lateral OFC	76	(−38, 56, −4)	3.93	.016

Results are from whole-brain analysis in all participants (n = 36 with usable task-based fMRI data) that were significant at voxelwise $p < .001$ uncorrected followed by $p < .05$ familywise error (FWE)–corrected. Analysis controlled for age, sex, and Full Scale IQ (Wechsler Abbreviated Scale of Intelligence, Second Edition).

HC, healthy control; MNI, Montreal Neurological Institute; OFC, orbitofrontal cortex; PTSD, posttraumatic stress disorder; SHAPS, Snaith-Hamilton Pleasure Scale.

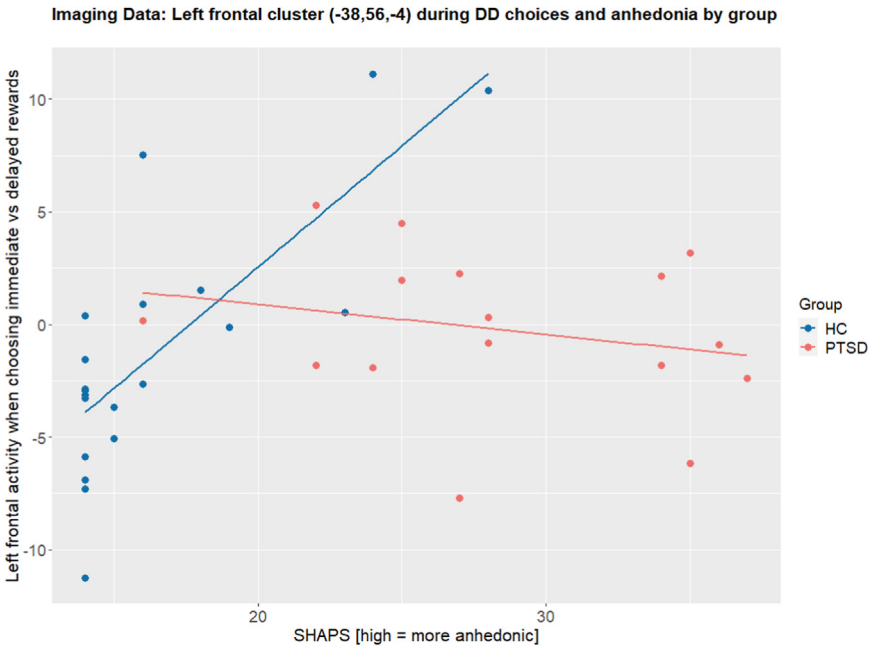

Figure 4. The relationship between anhedonia and activity in a left frontal cluster when choosing immediate vs. delayed rewards on the delay discounting (DD) task differed across groups. HC, healthy control; PTSD, posttraumatic stress disorder; SHAPS, Snaith-Hamilton Pleasure Scale.

associated with greater activity for immediate versus delayed rewards in a broadly distributed, predominantly frontotemporal network. There were also group differences in the association between anhedonia and rsFC: Self-reported anhedonia was associated with less connectivity between the NAcc and the right frontal pole in the PTSD group and with greater rsFC between the NAcc and the right frontal pole in the HC group. Finally, NAcc-supramarginal gyrus rsFC was associated with anhedonia in the HC group, but not in the PTSD group. Despite a moderate positive correlation between DD and PD, behavioral models predicting PD from clinical characteristics were not significant, consistent with overwhelming literature suggesting that DD is more strongly related to clinically relevant phenomena. To summarize, our results provide initial evidence that self-reported anhedonia is associated with a different, and at times opposing, set of neural correlates of DD in the PTSD group than in the HC group.

In contrast to findings in the NAcc, we did not find relationships between right AI activity or connectivity and altered DD in PTSD. Although the right AI ROI did not show a significant group-by-anhedonia interaction, a whole-brain analysis identified additional regions involved in the group-by-anhedonia interaction on activity when choosing immediate versus delayed rewards. More specifically, in right temporal

Table 4. Significant Clusters Within the PTSD Group (n = 16) Where Greater Anhedonia Was Associated With Increased Activity When Choosing Immediate vs. Delayed Rewards

Brain Region	Cluster Size	MNI (x, y, z)	z Score	p_{FWE}
Rolandic Operculum/Right Superior Temporal Lobe/Right Postcentral Gyrus/Right Heschl's Gyrus/Right Insula	133[a]	(60, 0, 10)	5.13	<.001
Right and Left Frontal Superior Medial Cortex/Right and Left Pre ACC/Right and Left Frontal Medial Orbital Cortex	80	(8, 54, 18)	4.91	.001
Left Superior Temporal Gyrus/Left Middle Temporal Gyrus/Left Supramarginal Gyrus	74	(−58, −32, 14)	4.22	.002
Right Postcentral Gyrus/Right Superior Temporal Gyrus/Right Rolandic Operculum/Right Supramarginal Gyrus	69	(64, −14, 14)	3.69	.004
Right Supramarginal Gyrus/Right Rolandic Operculum/Right Temporal Gyrus/Right Postcentral Gyrus	52	(50, −30, 26)	4.13	.020
Left Rolandic Operculum/Left Postcentral Gyrus/Left Precentral Gyrus/Left Frontal Inferior Operculum/Left Superior Temporal Gyrus/Left Heschl's Gyrus	48	(−58, −2, 14)	4.49	.030
Right and Left Thalamus	45[a]	(0, −20, 2)	4.22	.002

Results are from whole-brain analysis that were significant at voxelwise $p < .001$ uncorrected followed by $p < .05$ familywise error (FWE)–corrected. Analysis controlled for age, sex, and Full Scale IQ (Wechsler Abbreviated Scale of Intelligence, Second Edition).

ACC, anterior cingulate cortex; CAPS-5, Clinician-Administered PTSD Scale for DSM-5; PTSD, posttraumatic stress disorder.

[a]Cluster also survives whole-brain correction for CAPS-5 total score.

Table 5. Significant Clusters Where There Was a Significant Group-by-Anhedonia Interaction on Resting-State Functional Connectivity From the Bilateral Nucleus Accumbens

Brain Region	Cluster Size	MNI (x, y, z)	p_{FDR}
Right Supramarginal Gyrus/Angular Gyrus	63	(64, −40, 32)	.046
Right Frontal Pole	63	(20, 64, −2)	.046

Results are from whole-brain analysis of resting-state data in all participants that were significant at voxelwise $p < .001$ uncorrected followed by $p < .05$ false discovery rate–corrected (FDR). Analysis controlled for age, sex, and Full Scale IQ (Wechsler Abbreviated Scale of Intelligence, Second Edition).

MNI, Montreal Neurological Institute.

clusters extending to the right insula (adjacent to the right AI), greater anhedonia was associated with more activity when choosing immediate versus delayed rewards in the PTSD group. In contrast, anhedonia was associated with less activity when choosing immediate versus delayed rewards in the HC group. These results are similar to those seen in the NAcc and are consistent with a broader picture of relative overactivity in reward-related regions when choosing immediate versus delayed rewards in anhedonic individuals with PTSD. In fact, analysis within the PTSD group showed several frontotemporal areas where the magnitude of activity when processing immediate versus delayed rewards scaled with increasing anhedonia. While the ROI-based analysis for the NAcc was significant, there were no significant clusters involving the NAcc in the whole-brain analysis, suggesting that frontotemporal regions may be most strongly relevant to DD-related alternations in PTSD.

The findings of the current study are consistent with prior literature showing that anhedonia is associated with steeper DD rates in PTSD but not in HC adults. Here, we begin to identify some possible neural underpinnings of that difference: Anhedonic individuals with PTSD have hyperactivity in the NAcc when choosing immediate rewards. One possible explanation for this unexpected relationship comes from existing translational literature showing that developmental stress affects relationships between anhedonia and reward seeking. In male rats exposed to a limited bedding and nesting model of early-life adversity, increased anhedonia occurs in tandem with accelerated acquisition of cocaine self-administration (58). These (anhedonic) rats also show hyperactivity in reward-related regions including the NAcc core after cocaine administration (59). Individuals with PTSD, including those in this sample, report elevated exposure to childhood maltreatment. Therefore, there is intriguing overlap between our results and this existing preclinical literature, suggesting that early-life adversity may flip the expected relationship between anhedonia and DD. Although speculative, it is possible that developmental stress could be the driver for these unexpected relationships with anhedonia, including steeper DD (as in our data), facilitated acquisition of drug use behavior (in the preclinical data), and NAcc hyperactivity (in both datasets).

Unlike in the translational literature, where anhedonia is assessed directly via measuring actual consumption of pleasurable rewards, we assessed anhedonia using a widely used self-report questionnaire, the SHAPS. An alternate possible explanation for these findings is that rather than being associated with an altered relationship between anhedonia and DD, PTSD may be associated with an alteration in the way that

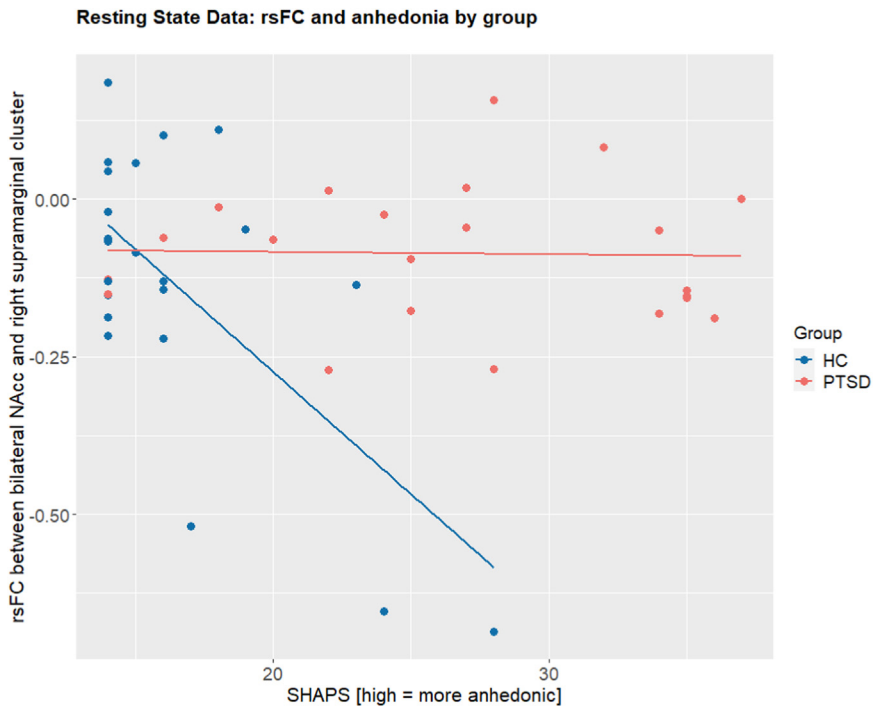

Figure 5. The relationship between anhedonia and resting-state functional connectivity (rsFC) between the nucleus accumbens (NAcc) and a right supramarginal gyrus cluster differed between groups. HC, healthy control; PTSD, posttraumatic stress disorder; SHAPS, Snaith-Hamilton Pleasure Scale.

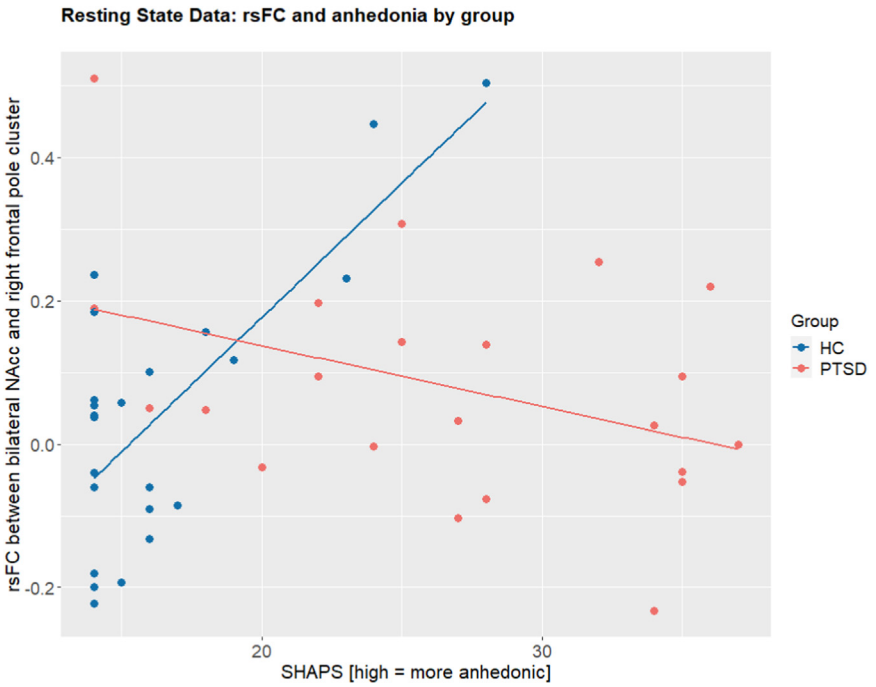

Figure 6. The relationship between anhedonia and resting-state functional connectivity (rsFC) between the nucleus accumbens (NAcc) and a right frontal pole cluster differed between groups. HC, healthy control; PTSD, posttraumatic stress disorder; SHAPS, Snaith-Hamilton Pleasure Scale.

participants evaluate or report on their own hedonic experiences. At the broadest level, these results raise a note of caution about drawing conclusions about psychopathology by examining relationships between dimensional constructs in healthy samples; there may be circumstances in which established associations in healthy individuals are disrupted or reversed in samples with psychopathology.

This study has several limitations. The small sample size is a significant limitation. The current findings should be treated with caution, particularly because significant findings in small samples are at higher risk for failure to replicate. Due to the small sample size, we also cannot perform subgroup analyses, including analyzing for possible sex differences or effects of trauma type or age of exposure. In addition, we excluded based on past-year alcohol or substance use disorder, which may have truncated the distribution of DD rates and/or anhedonia in the PTSD sample. Finally, there are many aspects of anhedonia and reward functioning that are not addressed herein but may contribute to differences in discounting; for example, future research could address how individual differences in reward learning, reward memory, and/or reward motivation could affect evaluation of and decision making regarding delayed rewards (60,61).

Conclusions

The results of the current study suggest that contrary to established relationships in healthy participants, anhedonia in PTSD is associated with steeper DD and with greater NAcc activity to immediate versus delayed rewards. These findings contribute to an emerging literature demonstrating reward processing abnormalities in PTSD.

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