



Diminished reward responsiveness is associated with lower reward network GluCEST: an ultra-high field glutamate imaging study

Valerie J. Sydnor¹ · Bart Larsen¹ · Christian Kohler^{1,2} · Andrew J. D. Crow¹ · Sage L. Rush¹ · Monica E. Calkins^{1,2} · Ruben C. Gur^{1,2} · Raquel E. Gur^{1,2} · Kosha Ruparel^{1,2} · Joseph W. Kable^{3,4} · Jami F. Young^{1,2} · Sanjeev Chawla⁵ · Mark A. Elliott⁵ · Russell T. Shinohara^{6,7} · Ravi Prakash Reddy Nanga⁵ · Ravinder Reddy⁵ · Daniel H. Wolf^{1,2,7} · Theodore D. Satterthwaite^{1,2,7} · David R. Roalf^{1,2}

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Abstract

Low reward responsiveness (RR) is associated with poor psychological well-being, psychiatric disorder risk, and psychotropic treatment resistance. Functional MRI studies have reported decreased activity within the brain's reward network in individuals with RR deficits, however the neurochemistry underlying network hypofunction in those with low RR remains unclear. This study employed ultra-high field glutamate chemical exchange saturation transfer (GluCEST) imaging to investigate the hypothesis that glutamatergic deficits within the reward network contribute to low RR. GluCEST images were acquired at 7.0 T from 45 participants (ages 15–29, 30 females) including 15 healthy individuals, 11 with depression, and 19 with psychosis spectrum symptoms. The GluCEST contrast, a measure sensitive to local glutamate concentration, was quantified in a meta-analytically defined reward network comprised of cortical, subcortical, and brainstem regions. Associations between brain GluCEST contrast and Behavioral Activation System Scale RR scores were assessed using multiple linear regressions. Analyses revealed that reward network GluCEST contrast was positively and selectively associated with RR, but not other clinical features. Follow-up investigations identified that this association was driven by the subcortical reward network and network areas that encode the salience of valenced stimuli. We observed no association between RR and the GluCEST contrast within non-reward cortex. This study thus provides new evidence that reward network glutamate levels contribute to individual differences in RR. Decreased reward network excitatory neurotransmission or metabolism may be mechanisms driving reward network hypofunction and RR deficits. These findings provide a framework for understanding the efficacy of glutamate-modulating psychotropics such as ketamine for treating anhedonia.

Introduction

Reward responsiveness (RR) is a psychological construct that indexes an individual's capacity to experience pleasure

or positive affect from the anticipation or attainment of rewards, and that falls within the Research Domain Criteria (RDoC) positive valence domain of human functioning. Low RR is a symptom common to diverse psychiatric disorders, including depression and psychosis spectrum disorders, that predicts poor treatment response and prognosis [1–5]. In individuals without a diagnosable psychiatric

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✉ David R. Roalf
roalf@pennmedicine.upenn.edu

¹ Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

² Lifespan Brain Institute, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, USA

³ Department of Psychology, University of Pennsylvania, Philadelphia, PA, USA

⁴ MindCORE, University of Pennsylvania, Philadelphia, PA, USA

⁵ Department of Radiology, University of Pennsylvania, Philadelphia, PA, USA

⁶ Penn Statistics in Imaging and Visualization Endeavor, Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

⁷ Center for Biomedical Image Computing and Analytics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

disorder, low RR is furthermore associated with increased risk of developing psychopathology [6–8]. RR is thus a dimensional construct associated with psychological well-being [9] that cuts across both DSM-defined diagnostic categories and clinical versus non-clinical samples. Elucidating neural features that contribute to individual differences in RR has broad implications for understanding the neurobiology of psychiatric illness and pharmacological treatment response.

Functional MRI studies have provided insight into circuit-level correlates of RR, demonstrating that lower RR is associated with lower activity [10–15] and connectivity [10, 16] within the brain's reward network. This pattern of altered brain function has been observed both in patients with psychiatric disorders that affect RR [13, 14, 16] and in healthy individuals with non-clinical anhedonia [10–12]. Compromised reward network functioning has therefore been directly implicated in the expression of reward-related deficits. Nevertheless, the neurochemical mechanisms underlying such network hypofunction in those with lower RR remain unclear. Although dopamine is classically associated with reward, glutamate is also a major modulator of reward network functioning [17–22]. Mesolimbic reward pathway dopaminergic inputs from the ventral tegmental area to the ventral striatum are largely activated by glutamatergic neurotransmission [20, 23], hence glutamate impacts reward anticipation and incentive salience. Furthermore, large glutamatergic efferents connecting the prefrontal cortex to the striatum can influence motivation and evaluation of stimulus valence [18, 20, 24]. Given the potential for glutamatergic signaling to affect diverse aspects of reward responsivity, here we investigate the hypothesis that glutamatergic deficits within the reward network contribute to diminished RR.

This hypothesis is motivated in part by results from preclinical and clinical studies that pharmacologically manipulate the glutamatergic system. In rodents and non-human primates, antagonism of AMPA and group 1 metabotropic glutamate receptors decreases the rewarding effects of drugs and food [25–28]. In humans, ketamine—which indirectly drives glutamatergic activation of AMPA receptors on excitatory neurons via interneuron NMDA blockade [29, 30]—is capable of rapidly reducing anhedonia [31, 32]. Though convergent evidence from preclinical and clinical studies indicates that glutamate availability in reward-associated regions may be a critical modulator of RR, validation in humans remains elusive. This noteworthy gap in the literature exists in part due to limitations in our ability to study glutamate in the brain *in vivo*.

To date, proton magnetic resonance spectroscopy (¹HMRS) has been the method most commonly used to study

glutamate *in vivo* [33]. A main benefit of ¹HMRS is that it can simultaneously measure the concentration of diverse neurochemicals, including glutamate, creatine, choline, myo-inositol, glutathione, and N-acetylaspartate, providing important insight into brain biochemistry and relationships amongst neurometabolites. Its utility in measuring glutamate, however, is principally limited by the low concentration of glutamate in the brain compared to water, as well as by resonance overlap with glutamine and GABA [34, 35]. This study therefore harnesses a complementary approach to imaging brain glutamate at ultra-high field (7.0 T): glutamate chemical exchange saturation transfer (GluCEST) imaging [36, 37]. GluCEST is a magnetization transfer-based method that measures glutamate levels via a water pool-dependent imaging contrast, thus largely overcoming the concentration limitations of ¹HMRS. Critically, the magnitude of the contrast effect observed, quantified as the GluCEST contrast, is proportional to the local concentration of glutamate [36]. While both ¹HMRS and GluCEST have inherent pros and cons, key advantages of GluCEST include a substantial increase in sensitivity to glutamate [36] and the ability to more directly mitigate effects of cerebrospinal fluid contamination on glutamate quantification. Moreover, GluCEST produces a high-resolution image that covers a large expanse of the brain with small voxel sizes (a 5 mm thick sagittal slice with complete in-plane brain coverage), thereby providing enhanced spatial coverage and spatial resolution [34].

Here, we quantified the GluCEST contrast in a meta-analytic reward network in individuals with and without diagnosable psychopathologies to test the overarching hypothesis that individual variation in RR is affected by brain glutamate. Based on aforementioned results from functional MRI studies and trials of glutamate-modulating psychotropics, we predicted that reduced RR would be associated with lower levels of reward network GluCEST. Further, because the total reward network is a neuroanatomically expansive network encompassing areas that respond to rewards, areas that respond to negative outcomes, and areas that encode the magnitude of both rewarding and negative outcomes, we undertook analyses designed to provide anatomical and valence specificity regarding the relationship between brain GluCEST and RR.

Methods

Participants

To sample a broad range of RR, we studied healthy individuals and individuals with psychiatric conditions that can affect RR. The final study sample ($N = 45$, ages 15–29, 30 female) thus included a typically developing group (no axis

I diagnoses or subthreshold psychosis symptomatology, no history of psychotropic medication use, $N=15$) and a clinical group comprised of individuals classified by doctoral-level clinician scientists (TDS, CK, MEC) as having depressive disorders ($N=11$) or psychosis spectrum disorders ($N=19$ total, including 12 with clinical high risk symptoms and 7 with a diagnosed psychotic disorder). Study exclusion criteria and participant medication information are reported in Supplementary Information (SI). All procedures were approved by the Institutional Review Boards of the University of Pennsylvania and/or the Children's Hospital of Philadelphia. All participants over the age of 18 provided written informed consent prior to study participation. For minors, informed assent and written parental consent were obtained.

Clinical questionnaires

To assess RR, participants completed the Behavioral Activation System (BAS) Scale [38]. Factor analyses have identified three independent, empirically derived BAS subscales, which have been validated in both non-clinical and psychiatric samples [16, 38–40]: BAS RR, BAS Drive, and BAS Fun Seeking. The five BAS RR items were reverse scored and summed to produce a dimensional, trait-like measure of RR [38, 41] ranging from 5 (low RR) to 20 (high RR). Participants additionally completed the Patient-Reported Outcomes Measurement Information System (PROMIS) depression scale and the PRIME Screen-Revised (PS-R) [42, 43]. These scales were used to generate graded measures of depression severity and subthreshold positive psychosis symptom severity, respectively.

MRI acquisition

MRI data were acquired on a 7.0 T Siemens Terra at the University of Pennsylvania. Acquisition of GluCEST images and B_0 and B_1 maps was completed as described in previous studies [36, 44], and as detailed extensively in SI. Briefly, GluCEST images were acquired in a 5 mm sagittal slice (slice number: 1, slice thickness: 5 mm) positioned in the right hemisphere to cover key reward network regions. This GluCEST field of view (FOV) offers full in-plane brain coverage (matrix size: 224×224) with $1 \times 1 \text{ mm}^2$ in-plane resolution [36, 44]. Structural images including T1-weighted uniform (UNI) images and corresponding INV1 and INV2 images were acquired with a magnetization prepared 2 rapid acquisition gradient echoes (MP2RAGE) sequence (acquisition details in SI) [45]. GluCEST and MP2RAGE data were originally acquired from a total of 53 participants. Raw and processed UNI images, GluCEST images, B_0 maps, and B_1 maps from all 53 participants underwent stringent visual quality control procedures. Overall, 8 of the 53 participants

were ultimately excluded from the study due to identifiable motion in GluCEST images or the presence of large inhomogeneity artifacts in B_0 maps, resulting in the final analytic study sample of $N=45$ individuals from which all reported results were obtained.

MR image processing

Figure 1 provides an overview of the image analysis pipeline.

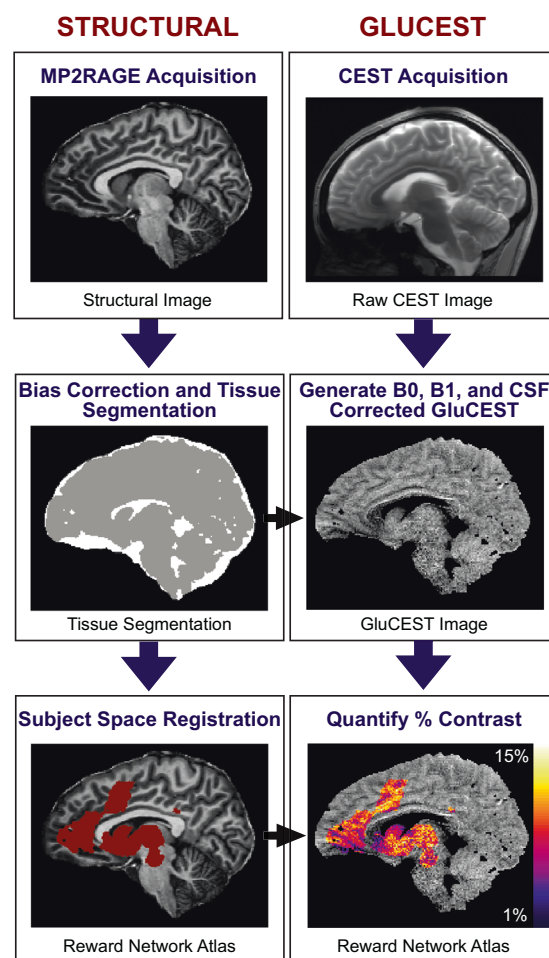


Fig. 1 Overview of structural and GluCEST processing. Structural: Structural images acquired as part of the 7.0 T magnetization prepared 2 rapid acquisition gradient echoes (MP2RAGE) sequence were bias field corrected and used to generate tissue segmentation maps (cerebrospinal fluid voxels shown in white, brain tissue in gray). Atlases were registered from MNI space to participant images. GluCEST: B_0 and B_1 inhomogeneity-corrected GluCEST images were generated from raw chemical exchange saturation transfer (CEST) images, and voxels labeled as cerebrospinal fluid (CSF) by tissue segmentation maps were removed from final GluCEST images. The GluCEST contrast was then estimated in the meta-analytic reward network. The color bar (bottom right) represents the average GluCEST contrast in each $1 \times 1 \times 5 \text{ mm}^3$ GluCEST voxel, scaled from 1% contrast (dark blue) to 15% contrast (light yellow).

Structural image processing

INV2 and UNI images were bias field corrected using advanced normalization tools (ANTs) N4 [46], and used for tissue segmentation and atlas registration, respectively. FSL FAST [47] was employed to generate three tissue segmentation maps and gray matter density maps. In order to register atlases from MNI space to participant images, UNI images were first nonlinearly registered to the MNI152 nonlinear T1 template using ANTs symmetric diffeomorphic image normalization [48].

GluCEST image processing

GluCEST images represent the GluCEST contrast (%) in each voxel (equation in SI). GluCEST images were first corrected for B_0 and B_1 inhomogeneity effects using in-house Matlab software, as previously described [36, 44]. As prior, voxels that had a B_0 offset of greater than ± 1 ppm and voxels with relative B_1 values outside of the 0.3–1.3 range were excluded [44], as were voxels labeled as cerebrospinal fluid by tissue segmentation maps.

Reward network delineation

To study the relationship between reward network GluCEST and RR, we delineated the reward network using a recent meta-analysis of 206 functional MRI studies [49] (further meta-analysis details are provided in SI). The meta-analytic reward network atlas was aligned from MNI space to GluCEST images by applying the inverse of pre-computed composite UNI-to-MNI transforms, and extracting the portion of the atlas that corresponded to a participant's GluCEST FOV. It should be noted that the GluCEST FOV did not provide complete coverage of the reward network. Accordingly, the percent of the network included in each participant's GluCEST acquisition was calculated to provide an estimate of network spatial coverage, and included as a model covariate in a sensitivity analysis.

Given that the reward network is inherently heterogeneous in both regional anatomy and valence encoding, we furthermore subdivided the meta-analytic reward network both structurally and functionally for analyses designed to enhance the anatomical and functional precision of our primary results. Specifically, we independently evaluated cortical and subcortical regions of the network, defined using Harvard–Oxford [50] cortical and subcortical atlases. We additionally partitioned the network into three valence-specific components based on the original meta-analysis [49], including an appetitive/positive valence encoding component, an aversive/negative valence encoding component, and a salience component.

Statistical analysis

Statistical analyses were performed in R 4.0.2. We investigated associations between GluCEST contrast and BAS RR scores across the entire sample using multiple linear regressions. All regressions reported controlled for age and sex and met linearity, homoscedasticity, and normality assumptions. For each multiple regression analysis, the individual predictor t value quantifying the association between GluCEST and BAS RR scores was used to calculate a partial r value (r_{PARTIAL}): an estimate of the association effect size. False discovery rate correction (FDR; p_{FDR}) was employed to correct for multiple comparisons within anatomical and valence-specific follow-up analyses. Following the main analyses, we conducted a series of rigorous sensitivity and specificity analyses to ensure that observed effects were not being driven by reward network gray matter density, reward network coverage, depression symptoms, psychosis symptoms, or scores on other BAS domains. Each of these variables was included as a model covariate in a multiple linear regression.

Results

BAS Reward Responsiveness indexes RR across typically developing and clinical groups

Sample demographics and clinical information are presented in Table 1. BAS RR scores were variable across the entire sample (min = 12, max = 20, mean = 17.4, SD = 1.9), reflecting the dimensional nature of this measure, and more variable in the clinical than the typically developing group (Table 1). There was a trend for BAS RR scores to be higher in females than males ($t = 1.79$, $p = 0.081$).

Reward network GluCEST does not differ between typically developing and clinical groups

Reward network GluCEST contrast did not significantly differ between the typically developing and clinical group in an ANCOVA controlled for age and sex, indicating that diagnostic status did not influence reward network glutamate level. Diagnostic status was, however, related to the GluCEST signal within specific, anatomically defined regions of interest, in a manner that largely replicated previously published 7.0 T ^1H MRS case–control studies (see SI for full results and comparisons to previous ^1H MRS studies).

Reward network GluCEST is dimensionally associated with RR

To investigate relationships between the dimensional construct of RR and glutamate within brain regions that do

Table 1 Sample demographics and clinical characteristics.

Demographic and clinical variables	Study sample <i>N</i> = 45	Typically developing <i>N</i> = 15	Clinical <i>N</i> = 30	<i>t</i> -test or Pearson's chi-squared test
Age	22.78 (2.8)	22.60 (2.9)	22.87 (2.8)	<i>p</i> = 0.770
Sex				
Male	15	5	10	<i>p</i> = 1.000
Female	30	10	20	
Race				
Asian	1	0	1	<i>p</i> = 0.442
Black	24	6	18	
White	17	8	9	
>1 race	3	1	2	
BAS reward responsiveness score	17.36 (1.9)	17.53 (1.4)	17.27 (2.1)	<i>p</i> = 0.658
PROMIS depression symptom score	12.84 (6.3)	9.73 (1.8)	14.40 (7.1)	<i>p</i> = 0.002 ^a
PS-R positive psychosis symptom score	5.98 (9.7)	0.53 (1.1)	8.70 (10.9)	<i>p</i> < 0.001 ^a

Age, sex, race, and clinical questionnaire score means are presented for the study sample, as well as for the typically developing and clinical groups that make up the sample. Differences between typically developing and clinical groups (right column) were evaluated using two-sided independent samples *t*-tests (for age and clinical scores) and Pearson's chi-squared tests (for sex and race).

BAS Behavioral Activation System, PROMIS Patient-Reported Outcomes Measurement Information System, PS-R PRIME Screen-Revised.

^aSignificant difference between groups in a two-sided independent samples *t*-test with unequal variances.

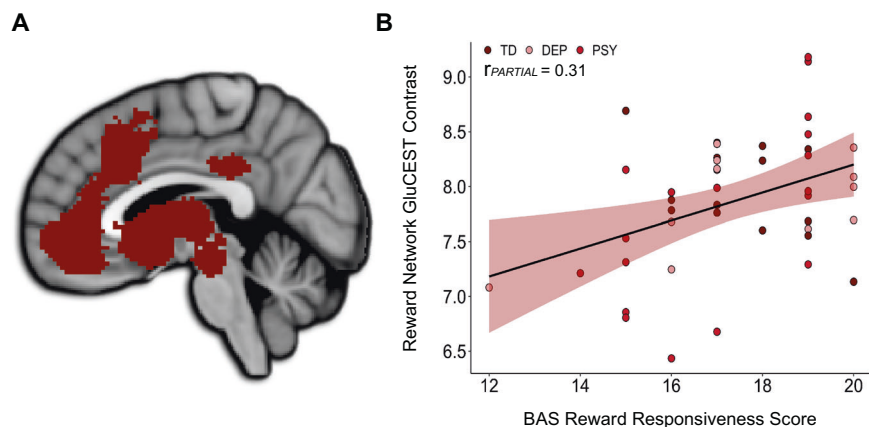


Fig. 2 Association between dimensional reward responsiveness and reward network GluCEST. **A** The meta-analytically defined reward network comprised of cortical, subcortical, and upper brainstem regions. **B** Reward network GluCEST contrast was positively associated with BAS Reward Responsiveness scores across typically

developing and clinical groups. Data points are differently colored for typically developing (TD) individuals, individuals with a depressive disorder (DEP), and individuals with a psychosis spectrum disorder (PSY).

and do not subserve reward-related functions, we conducted a multiple regression with reward network GluCEST and non-reward network GluCEST as predictors of BAS RR. BAS RR scores were significantly positively associated with reward network GluCEST contrast in this model (estimate = 1.01, $r_{\text{PARTIAL}} = 0.31$, $p = 0.048$; Fig. 2). Highlighting the specificity of this association, BAS RR scores were not significantly associated with non-reward network GluCEST contrast, i.e., with GluCEST in regions not included in the meta-analytic reward network (estimate = 0.11, $r_{\text{PARTIAL}} = 0.03$, $p = 0.864$).

The association between BAS RR scores and reward network GluCEST contrast did not differ between males and females, as indicated by a non-significant interaction term ($p = 0.693$) between sex and GluCEST contrast for predicting BAS RR.

Association between reward network GluCEST and RR is driven by subcortical regions

Anatomical division of the total reward network into cortical and subcortical components (Fig. 3A) revealed a

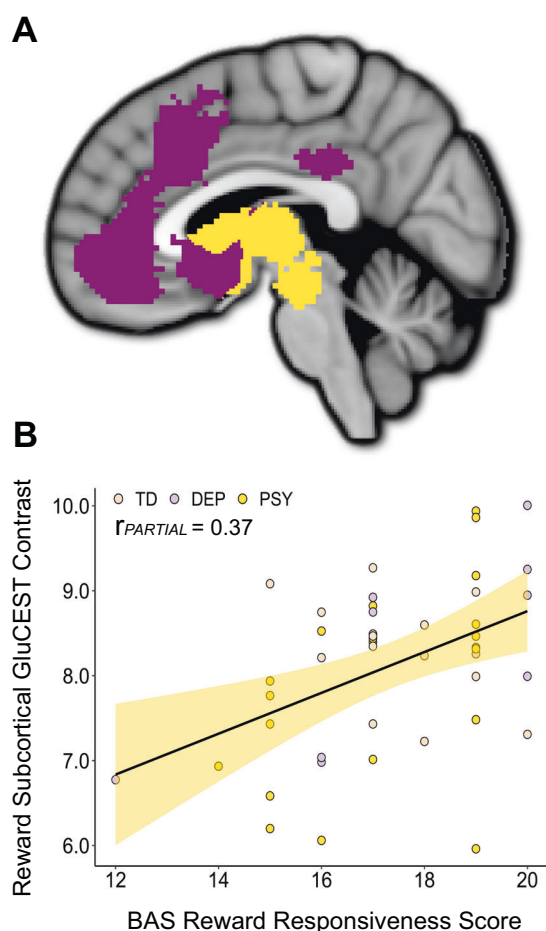


Fig. 3 Association between dimensional reward responsiveness and subcortical reward network GluCEST. **A** Cortical (purple) and subcortical (yellow) components of the reward network. **B** GluCEST imaging revealed a significant association between BAS Reward Responsiveness scores and the GluCEST contrast in the subcortical reward network. Individual data points are colored based on diagnosis; *TD* typically developing, *DEP* depressive disorder, *PSY* psychosis spectrum disorder.

non-significant association between BAS RR scores and cortical reward network GluCEST contrast. There was, however, a significant association between BAS RR scores and subcortical reward network GluCEST (estimate = 0.69, $r_{\text{PARTIAL}} = 0.37$, $p_{\text{FDR}} = 0.027$; Fig. 3B), suggesting that the main result was driven by subcortical reward regions. In an exploratory analysis designed to provide enhanced anatomical resolution, we further divided the reward network into 11 distinct anatomical regions. Region-specific multiple regressions revealed the strongest associations between BAS RR scores and the GluCEST contrast within the caudate, posterior cingulate, and thalamus, followed by the brainstem (midbrain/upper pons) and the nucleus accumbens (Supplementary Fig. 1), though results of these regional analyses did not survive FDR correction.

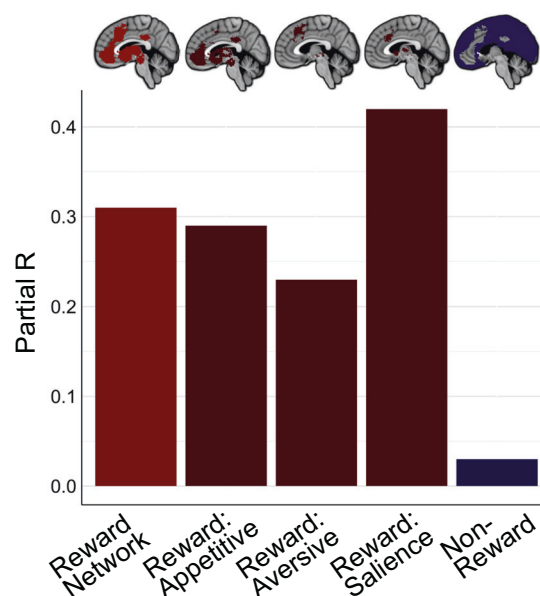


Fig. 4 Effect size determined by valence encoding. Effect sizes for the association between brain GluCEST contrast and BAS Reward Responsiveness scores for the total reward network, appetitive-encoding reward network regions, aversive-encoding reward network regions, salience-encoding reward network regions, and non-reward regions (left to right). Partial r values were derived from independent multiple linear regressions, as reported in the text.

Reward network GluCEST findings are influenced by valence encoding

The reward network was next functionally subdivided into (1) areas that are activated by appetitive stimuli only, (2) areas that are activated by aversive stimuli only, and (3) areas that respond to both appetitive and aversive stimuli, and are thus understood to encode the salience of valenced stimuli [49]. Independent, valence-specific multiple regressions revealed that the association between BAS RR scores and GluCEST contrast was significant in reward network regions responsive to stimulus salience (estimate = 0.95, $r_{\text{PARTIAL}} = 0.42$, $p_{\text{FDR}} = 0.014$) and trend level in appetitive-encoding regions (estimate = 0.76, $r_{\text{PARTIAL}} = 0.29$, $p_{\text{FDR}} = 0.083$), but not significant in aversive-encoding regions (Fig. 4).

Sensitivity analyses provide convergent results

A series of sensitivity analyses (all controlled for age and sex) confirmed that the association observed between total reward network GluCEST contrast and RR was not attributable to other brain features, methodological considerations, or comorbid psychiatric symptoms. Specifically, the association between reward network GluCEST and BAS RR scores remained significant when controlling for reward network gray matter density (estimate = 1.06,

$r_{\text{PARTIAL}} = 0.36$, $p = 0.020$), indicating that differences in network tissue composition were not driving results. Given that the GluCEST FOV did not encompass the entirety of the reward network, we confirmed that controlling for percent coverage of the total reward network did not alter our findings (estimate = 1.05, $r_{\text{PARTIAL}} = 0.35$, $p = 0.022$). To further confirm that differential network coverage was not impacting results, we performed an exploratory analysis that only included reward network voxels for which greater than 50% of participants had GluCEST data. This did not impact significance (estimate = 0.90, $r_{\text{PARTIAL}} = 0.35$, $p = 0.022$). Finally, the association between reward network GluCEST and BAS RR scores remained significant when controlling for typically developing versus clinical group (estimate = 1.04, $r_{\text{PARTIAL}} = 0.35$, $p = 0.024$).

Reward network GluCEST associations are specific to the construct of RR

To confirm the specificity of the association between reward network GluCEST contrast and RR, we conducted specificity analyses using multiple regressions that included additional measures of clinical features. All models included age, sex, and BAS RR scores as predictors. Notably, in these models we did not find any significant associations between reward network GluCEST contrast and PS-R scores ($p = 0.267$), PROMIS depression scores ($p = 0.383$), BAS Drive scores ($p = 0.685$), or BAS Fun Seeking scores ($p = 0.371$). Conversely, BAS RR remained significant or trend level significant in all of these models ($p = 0.016$ covarying for PS-R, $p = 0.081$ covarying for PROMIS depression, $p = 0.022$ covarying for BAS Drive, $p = 0.085$ covarying for BAS Fun Seeking).

GluCEST and single voxel $^1\text{HMRS}$ demonstrate cross-method agreement

Finally, to compare results between GluCEST and $^1\text{HMRS}$, the method most frequently employed to measure brain glutamate in vivo, $^1\text{HMRS}$ data were collected from a subsample of the 45 study participants (final $N = 20$ following quality control procedures). $^1\text{HMRS}$ data were collected from a single voxel of interest (VOI) positioned in the right anterior cingulate cortex, a frequently studied $^1\text{HMRS}$ VOI in psychiatry [51–56]. Independent multiple regression analyses revealed that associations of BAS RR scores with both (1) $^1\text{HMRS}$ -derived glutamate concentration within the VOI and (2) mean GluCEST within the VOI were similar in strength, suggesting cross-method convergence. Moreover, $^1\text{HMRS}$ - and GluCEST-derived measures of glutamate were positively correlated within the VOI. The strength of this correlation was dependent on the degree of anatomical overlap between the $^1\text{HMRS}$ VOI and the GluCEST FOV,

and ranged from $r_{\text{PARTIAL}} = 0.26$ in all participants to $r_{\text{PARTIAL}} = 0.36$ in those with $> 50\%$ anatomical overlap, and to $r_{\text{PARTIAL}} = 0.60$ in those with $> 90\%$ anatomical overlap. Extended results and corresponding methods are available in SI.

Discussion

Using a clinically diverse sample and the novel 7.0 T glutamate imaging method GluCEST, we found that a lower GluCEST contrast in the brain's reward network was dimensionally related to diminished RR. This finding links individual differences in RR to differences in neurochemistry within brain regions involved in reward encoding, incentive salience, and valence evaluation. The association observed here between GluCEST and RR was specific to the reward network, and selective for RR but not for other clinical features. This work therefore provides evidence of a neuroanatomically- and construct-specific relationship between reward network glutamate and RR, implicating a main excitatory neurotransmitter and neurometabolite in reward sensitivity and anhedonia.

Glutamate-modulating psychotropics have recently demonstrated efficacy for treating anhedonia [31, 32], motivating clinical interest in parsing relationships between glutamate and reward functioning. Yet, to our knowledge, this is the first study to demonstrate that an in vivo measure of glutamate quantified in cortical, subcortical, and brain-stem reward regions relates to RR. A handful of previous investigations examined associations between anhedonia severity and brain glutamate using $^1\text{HMRS}$, yet these studies predominantly reported null results [51–54, 57, 58]. This discrepancy between past $^1\text{HMRS}$ findings and this report is likely attributable to the following technical and conceptual advances offered by the present study: (1) in contrast to previous $^1\text{HMRS}$ anhedonia studies, which assessed metabolites within the anterior cingulate cortex [51–54, 57] or striatum [58] only, we quantified the GluCEST contrast across a neuroanatomically expansive portion of the reward network; (2) we acquired GluCEST data at 7.0 T (rather than at 3.0 T [52–54, 58]), thus capitalizing on improvements in sensitivity and signal-to-noise ratio obtainable at higher field strengths [59]; and (3) we studied a transdiagnostic sample using a dimensional measure of RR—an approach distinct from past efforts focused on patients with major depression and severe clinical anhedonia [51–54, 57, 58]. Considered in conjunction with prior studies relating low RR to reduced reward network BOLD activity [10–15], these GluCEST results provide novel evidence that reward region glutamatergic deficits may in part drive the association between reward network hypo-function and low RR.

The circuitry of the reward network has been extensively delineated in rodents and non-human primates, and the importance of glutamatergic projections within this network has been described [17–22, 24]. Cortical reward glutamatergic efferents converge in the midbrain and striatum, two key regions for reward anticipation and responding, likely explaining the stronger association between GluCEST and RR observed in the subcortical reward network. The relationship between GluCEST and RR was additionally influenced by regional valence-related functioning, as it was stronger in brain areas that encode appetitive stimuli or the salience of valenced stimuli than in those that preferentially respond to aversive stimuli. This finding is consistent with the RDoC classification of RR within the positive valence domain, as well as with theories positing that glutamatergic signaling in brain regions subserving reward mediates stimulus and incentive salience [60, 61].

The central role that glutamatergic neurotransmission plays in reward-associated processes provides a direct mechanism—decreased excitatory neural communication—by which lower glutamate levels in reward network regions could lead to network dysfunction and diminished RR. This interpretation accords with preclinical findings that glutamate receptor pharmacological blockade decreases responding to rewards [25–28], whereas optogenetic activation of reward network glutamatergic afferents is rewarding and reinforcing [62–64]. Moreover, this interpretation is supported by the fact that the CEST acquisition employed in this study is sensitive to glutamate at the pH found within glutamate-containing synaptic vesicles (pH 5–6) and synaptic and extrasynaptic spaces (pH 7–7.5) [36, 65, 66]. Still, GluCEST's sensitivity to glutamate at a pH of ~7 ensures it additionally measures intracellular glutamate present within both neurons and astrocytes. Glutamate located within these cellular compartments plays a vital role not only in neurotransmission, but also in neurometabolism [67]. Accordingly, both decreased excitatory signaling and altered network metabolism could contribute to the association observed between lower reward network GluCEST contrast and lower RR.

Deficits in RR frequently emerge during adolescence [68] and following periods of chronic stress [8, 69]. Notably, these are two timeframes characterized by overall reductions in glutamatergic synapses and signaling [70, 71]. Our GluCEST results thus provide a framework for understanding the link between the onset of diminished RR and neurobiological changes that occur during neurodevelopment or stress-induced neurodegeneration, i.e., during two vulnerable periods for glutamate perturbations. Given that diminished RR is furthermore a risk factor for development of mood disorders [6, 68, 72] and suicidality [73–75], we speculate that low reward network

glutamate may partially mediate the association between low RR and development of these psychopathologies.

For individuals with diagnosed psychopathologies, anhedonia is a consistent predictor of poor psychotropic treatment response [1–5]. The present work suggests that some patients with anhedonia may have a glutamate-based disruption, potentially explaining why such individuals do not respond to conventional antidepressants, which target monoamines, or conventional antipsychotics, which are dopamine antagonists. Clinical trials that harness 7.0 T GluCEST to assess the role of reward network glutamate level in treatment resistance would thus be highly informative. These trials could provide insight into the utility of ultra-high field neurochemical imaging for predicting treatment response, potentially paving the way to neurochemistry-informed treatment stratification in psychiatry. Currently, clinical translation of 7.0 T GluCEST is limited by a lack of widely available 7.0 T MRIs, the high cost of scanning, and insufficient data available for defining normative versus low ranges of the GluCEST contrast. However, increased integration of 7.0 T imaging into routine clinical care and collection of GluCEST data from large healthy and patient samples would enable the use of objective, evidence-based, neurobiological CEST imaging measures in psychiatric patient care.

GluCEST has inherent limitations [36, 44], including the acquisition FOV, which limited analysis to a portion of the reward network. Regarding the GluCEST contrast, it must be noted that while at least 70% of the CEST effect is directly attributable to magnetization transfer from glutamate to water, up to 30% of the signal can come from exchangeable protons on other macromolecules (e.g., creatine), though notably none of the signal is from glutamine [36]. Unlike ¹HMRS, GluCEST does not provide information about other neurochemicals (e.g., myo-inositol or N-acetylaspartate). Future studies may thus consider acquiring both GluCEST and ¹HMRS data in a complementary manner. This would simultaneously capitalize on the enhanced spatial coverage and resolution provided by GluCEST and the localized measurement of multiple metabolites enabled by ¹HMRS. Last, we did not exclude individuals taking psychotropic medications given our clinical study sample, though medications may impact brain neurochemicals. Adjustment for medication did not, however, alter our results: partial correlations between BAS RR scores and reward network GluCEST, subcortical reward GluCEST, and salience reward GluCEST all remained significant (p s < 0.05) when controlling for psychotropic medication use (yes/no).

In conclusion, by harnessing the ultra-high field glutamate imaging method GluCEST, we identified a significant and selective relationship between RR and the GluCEST contrast in the brain's reward network, implicating reward

network glutamatergic deficiencies in diminished reward sensitivity. Future longitudinal studies designed to parse relationships between brain glutamate, RR deficits, and progression to psychopathology are warranted. More broadly, this study demonstrates the utility of in vivo neurochemical imaging, highlighting its potential to identify druggable targets for ameliorating psychiatric symptoms that are frequently treatment-resistant.

Code availability

All analytic code is available at https://github.com/PennLINC/sydnor_glucest_rewardresponsiveness_2020.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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