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Research paper

Using latent profile analyses to classify subjects with anhedonia based on reward-related measures obtained in the FAST-MAS study

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ABSTRACT

Background: Growing evidence indicates that anhedonia is a multifaceted construct. This study examined the possibility of identifying subgroups of people with anhedonia using multiple reward-related measures to provide greater understanding the Research Domain Criteria's Positive Valence Systems Domain and pathways for developing treatments.

Methods: Latent profile analysis of baseline data from a study that examined the effects of a novel kappa opioid receptor (KOR) antagonist drug on measures and biomarkers associated with anhedonia was used to identify subgroups. Measures included ventral striatal activation during the Monetary Incentive Delay task, response bias in the Probabilistic Reward Task, reward valuation scores from the Effort-Expenditure for Rewards Task, and scores from reward-related self-report measures.

Results: Two subgroups were identified, which differed on self-report measures of reward. Participants in the subgroup reporting more anhedonia also reported more depression and had greater illness severity and functional impairments. Graphs of change with treatment showed a trend for the less severe subgroup to demonstrate higher response to KOR antagonist treatment on the neuroimaging measure, probabilistic reward task, and ratings of functioning; the subgroup with greater severity showed a trend for higher treatment response on reward-related self-report measures.

Limitations: The main limitations include the small sample size and exploratory nature of analyses.

Conclusions: Evidence of possible dissociation between self-reported measures of anhedonia and other measures with respect to treatment response emerged. These results highlight the importance for future research to consider severity of self-reported reward-related deficits and how the relationship across measurement methods may vary with severity.

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1. Introduction

The substantial heterogeneity of psychiatric disorders is widely recognized as posing a daunting challenge to improving treatment outcomes for afflicted individuals and achieving more personalized treatments. In recognition of these challenges, the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) initiative has encouraged research focused on transdiagnostic targets and mechanisms, rather than traditionally defined psychiatric disorders (Insel et al., 2010). Research conducted within the RDoC framework seeks to better inform treatment selection using evidence stemming from basic neurobiological and behavioral science, and in particular, by targeting transdiagnostic core domains of functioning. Among such domains, anhedonia has received substantial attention as a transdiagnostic factor associated with adverse mental health problems across the lifespan (Lambert et al., 2018; Nusslock and Alloy, 2017; Whitton et al., 2015).

Anhedonia is traditionally defined as loss of pleasure or decreased reactivity to pleasurable stimuli. It has been implicated in several psychiatric diagnoses, including major depressive disorder (MDD) (Lambert et al., 2018), schizophrenia (Lambert et al., 2018), and post-traumatic stress disorder (PTSD) (Nawijn et al., 2015). Anhedonia predicts increased risk for suicide in adults, adolescents, and children (Nock and Kazdin, 2002; Spijker et al., 2010). Moreover, more severe anhedonia has been linked to greater illness severity, longer illness duration, and higher number of depressive episodes in depressed youth (Gabbay et al., 2015). In adolescents, higher levels of anhedonia have also been found to predict adult MDD (Wilcox and Anthony, 2004), and in depressed adults, worse anhedonia has been associated with poorer treatment response and a more severe disease course (Pizzagalli, 2014). Thus, identifying ways to better understand the factors which contribute to anhedonia could have broad implications for improving mental health.

Basic neurobiological and behavioral research suggests that targeting different facets of reward processing might identify different anhedonic phenotypes (Baskin-Sommers and Foti, 2015; Schlaepfer et al., 2008; Huys et al., 2013). In this context, the RDoC framework has emphasized several subdomains within the Positive Valence Systems (PVS) of reward-related functioning: reward responsiveness, reward learning, and reward valuation (RDoC Matrix, 2020). Critically, animal and human research has demonstrated that these subdomains are subserved by partially distinct neurobiological substrates and that there are aspects of anhedonia related to abnormalities in each of these subdomains (Whitton et al., 2015; Pizzagalli, 2014; Schultz, 2007; Treadway and Zald, 2011). This suggests that anhedonia should not be treated as a unitary construct; rather, research is needed to examine putative differences in reward-related components among individuals with anhedonia (Auerbach et al., 2019). For example, there may be subgroups of individuals with anhedonia who have greater deficits in reward responsiveness, whereas others may have greater deficits in reward learning. Identifying such subgroups could have important implications for enhancing treatment precision.

This paper describes secondary analyses of data collected under the NIMH Fast Mood and Anxiety Disorders Program (FAST-MAS) (Krystal et al., 2020). The FAST-MAS trial examined the potential of kappa opioid receptor (KOR) antagonism to address anhedonia cross-diagnostically. The trial probed several PVS subdomains (reward responsiveness, reward learning, and reward valuation) before and after treatment across units of analysis: circuits, physiology, behavior and self-report. The results from the original study found that the KOR antagonist significantly increased activation in the ventral straitum during reward anticipation, as measured by fMRI. The set of measures included in the FAST-MAS study represent the consensus, at the time of the original trial, of the best measures, across measurement type and subdomains, related to anhedonia. This rich clinical dataset provides the opportunity to conduct a person-centered analysis of multiple measures related to anhedonia to better understand the relationships among the PVS subdomains to guide future treatment research. The overarching goals of the current secondary analyses were to: (1) leverage these data to identify potential subgroups of individuals with distinct PVS abnormalities using data-driven approaches, and (2) evaluate whether these subgroups responded differently to KOR antagonism. The ultimate goal of this line of research is to identify subgroups of individuals with anhedonia based on different measures of reward processing that may have clinical utility (i.e., may help determine the appropriate treatment by matching based on underlying dysfunction/mechanism of change).

2. Methods

The data used for the current analyses were collected as part of the FAST-MAS trial; detailed demographics of the sample and study procedures have been previously described (see supplement for study inclusion/exclusion criteria; 18). The current study uses data collected at baseline and post-treatment (i.e., after 8 week trial) from 89 subjects randomized to a KOR antagonist (JNJ-67953964, previously known as CERC-501 and LY2456302) (Rorick-Kehn et al., 2014) or placebo. All subjects provided written informed consent. The study was approved by the internal review boards from all participating sites (ClinicalTrials.gov Identifier: NCT02218736).

The current analyses used data from the 89 participants who met eligibility criteria, completed baseline assessments and were randomized (45 to KOR, 44 to placebo; intent-to-treat population). Please see original study for detailed eligibility criteria; the following is a brief summary. Inclusion criteria for the original study were 21–65 years old, clinically significant anhedonia, and met criteria for major depressive disorder, bipolar I or II, generalized anxiety disorder, social phobia, panic disorder, or post-traumatic stress disorder. Exclusion criteria included hospitalization during the study, history of a psychotic disorder, current manic or mixed episode, austism spectrum disorders, recently met criteria for substance abuse or dependence, history of unstable or untreated medical condition, active suicide intent or plan or recent suicide attempt, medication use with significant CNS effects or which could interfere/interact with KOR, contraindications for MRI procedures, used nicotine, or were pregnant or lactating. Reward-related measures collected at baseline were used as indicator variables for latent profile analyses (LPA). Independent variables included age, sex, self-report of depression symptoms, clinician report of cognitive and physical functioning and global severity, and quantitative EEG. Post-treatment data for reward-related measures, self-report of depression symptoms, clinician report of cognitive and physical functioning and global severity, and quantitative EEG were included for the completer population (N = 68) (Krystal et al., 2020).

2.1. Measures

2.1.1. Reward-related measures (baseline data from these used as indicator variables for LPA; Table 1 outlines the relevant RDoC subdomain for each measure as chosen for the original FAST-MAS trial)

The **Monetary Incentive Delay (MID) Task** was administered during fMRI at baseline and post-treatment to assess the neural circuitry underlying reward-related function (Admon et al., 2017). The MID task is used to parse different stages of reward processing (i.e., anticipation and consumption). We a priori selected as a neural marker of reward responsiveness activation during anticipation of reward in **ventral striatum** (VS) based on a non-thresholded nucleus accumbens mask defined by the Harvard-Oxford Subcortical Atlas. Prior research has demonstrated that striatal activation to reward-predicting cues reflects neural activity that may mediate the clinical effects related to anhedonia and such activation is also correlated with striatal dopamine release as assessed by PET (Carlezon Jr. and Krystal, 2016; Stoy et al., 2012; Schott et al., 2008). The MID was administered in five task runs that were each 24 trials. For each trial, participants were presented with one of three possible cues for 500 ms, followed by a fixation crosshair on a computer screen. These cues signaled whether the upcoming trial had the potential

Table 1
Selected self-report, behavioral, and neuroimaging variable relevant to RDoC Positive Valence Systems Sub-domains.

Construct: reward responsiveness	
Reward anticipation	VS, TEPS-A
Reward satiation	VS, TEPS-C, SHAPS, VASA
Construct: reward learning	
Probabilistic and reinforcement learning	PRT
Construct: reward valuation	
Effort	EffRT

VS = ventral striatal activation, PRT = Probabilistic Reward Task, EEfRT = Effort-Expenditure for Rewards Task, SHAPS = Snaith-Hamilton Pleasure Scale, TEPS-A = Anticipatory subscale of Temporal Experience of Pleasure Scale, TEPS-C = Consummatory subscale of Temporal Experience of Pleasure Scale, VASA = Visual Analog Scale-Anhedonia.

for monetary gain (n = 40; denoted +$), monetary loss (n = 40; denoted –$) or there was no potential for gain or loss (n = 40; denoted 0$). Participants were instructed that they could either gain or avoid losing money by pressing a button when presented with a red square target on incentive trials. On no-incentive trials, participants were instructed to press the button as soon as the target appeared. Trial types were pseudorandomly ordered within each run. The duration of fixation following presentation of the cue was jittered between 2250 and 3750 ms, and the target was displayed for a period of 150 ms; 2400–3900 ms after target offset, participants were notified of how much money they had gained or lost on that trial. Before testing, participants engaged in a training and practice run in the scanner and task difficulty (that is, maximum allowable reaction time for both gain and loss trials) was adjusted based on reaction times during the practice session. Separate gain and loss reaction time standards were established to achieve approximately 70 % success in each incentivized trial type. For the current analyses, we included the mean VS activation during anticipation of reward (reward cue minus no-incentive cue contrast); higher values correspond to greater activation to reward cues during reward anticipation.

The **Probabilistic Reward Task (PRT)** was designed to assess participants' propensity to modulate behavior as a function of reinforcement history (i.e., a measure of the PVS reward learning subdomain). Participants completed two blocks of 100 trials where they determined whether a briefly presented mouth on a cartoon face was 'long' or 'short' and reported their decision by pressing one of two corresponding keys (z or /). The brief presentation time (100 ms) and the minimal difference in length between the two target stimuli (11.5 versus 13 mm) made it difficult for participants to distinguish the stimuli. An asymmetrical reinforcement ratio was implemented across the two blocks so that one of the two stimuli was rewarded ('Correct!! You Won 20 Cents') three times more frequently than the other (30 versus 10 times per block). Reinforcement allocation and key assignments were counterbalanced across participants. Participants were instructed to respond as quickly and accurately as possible to maximize monetary rewards and that not all correct responses were followed by rewards. This behavioral measure has been validated in multiple independent samples (Pizzagalli et al., 2005; Pizzagalli et al., 2008; Barr et al., 2008; Bogdan and Pizzagalli, 2006; Vrieze et al., 2013). We used the same pre-defined quality control check that was performed for the primary analyses (Krystal et al., 2020). Analyses for the original trial examined change in two PRT variables: change across trial block and the total response bias across the two blocks. For the current analyses, we used the total response bias score, which demonstrated a significant change with treatment; higher scores are indicative of higher reward learning.

The **Effort-Expenditure for Rewards Task** (EEfRT; 29) is intended to assess an individual's willingness to expend effort in order to obtain rewards of increasing probability and value, and relates to the PVS reward valuation subdomain. It is a multi-trial game where participants are given an opportunity on each trial to choose between two different task difficulty levels to obtain monetary rewards. For all trials participants make repeated manual button presses; each press raises the level of a virtual "bar". Participants are eligible to win the money allotted for each trial if they raise the bar to the "top" within the prescribed time period. Each trial presents the participant with a choice between two levels of task difficulty, a 'hard task' and an 'easy task.' Each trial presents a choice between a difficult task (100 button presses within 21 s) with higher potential monetary reward ($1.24–$4.30 per trial) and an easier task (30 button presses within 7 s) with lower potential monetary reward ($1 per trial). Further, participants are not guaranteed to win the reward for each task completion as some trials are "win" trials, in which the participant receive the stated reward amount, and others are "no win" trials, in which the participant receives no money for that trial. Participants are provided with accurate probability cues ("high" 88 % probability of being a win trial, "medium" 50 % and "low" 12 %) at the beginning of each trial to help them determine which trials are likely to be "win" trials. Probability levels always apply to both the hard task and easy task, and there are equal proportions of each probability level across the experiment. Each level of probability appears once in conjunction with each level of reward value for the hard task. All participants receive trials presented in randomized order. Research using the EEfRT has shown that reduced willingness to expend effort to obtain high-probability, high-value rewards, is associated with greater levels of depression and anhedonia (Treadway et al., 2009; Treadway et al., 2012). We used the proportion of hard tasks completed as a behavioral measure of reward valuation; higher scores indicate higher reward valuation.

The **Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995)** is a 14-item self-report questionnaire used to assess anhedonia. It asks participants to agree or disagree with statements of hedonic response in pleasurable situations (e.g., "I would enjoy my favorite television or radio program"). Responses include Strongly disagree (4), Disagree (3), Agree (2), or Strongly agree (1), with a total score derived by summing the responses to each item. Scores on the SHAPS range from 14 to 56, with higher scores corresponding to higher levels of anhedonia. Note that, for ease of interpreting the results, the SHAPS scores were reverse scored such that the higher scores indicate lower anhedonia, which corresponds to the direction of the other reward-related measures.

The **Temporal Experience of Pleasure Scale** (TEPS) is an 18-item self-report measurement of anticipatory (10 items; TEPS-A subscale, 'wanting') and consummatory (8 items; TEPS-C subscale, 'liking') pleasure (Gard et al., 2006). The subscale scores were examined separately; for both, lower scores indicate higher anhedonia.

The **Visual Analog Scale-Anhedonia** (VASA) is a brief, self-report assessment of anhedonia severity that provides a global anhedonia indicator (Martinotti et al., 2011). The assessment consists of making a rating on a 100-mm scale in response to the instructions: "Make a mark on the line below that indicates how much pleasure you experience from food, sexual behavior, and meeting friends". At the left end of the scale is the anchor "No Pleasure" and at the right end of the scale is the anchor "Extreme Pleasure." Lower scores indicate higher anhedonia.

2.1.2. Other baseline and post-treatment variables used to characterize latent profiles

Age and **sex** are two of the demographic variables collected during the initial recruitment and screening process that were used to characterize LPA results.

The **Hamilton Rating Scale for Depression** (HAM—D) 17-item version (Hamilton, 1967) is an interviewer-administered semi-structured interview of depression symptoms. The HAM-D was used in the current analyses to characterize LPA results with regard to depressive symptoms independent of anhedonia severity. Thus, HAM-D scores excluded item 7, which assesses anhedonia. The scores on the remaining 16 items were summed, with higher scores indicating more depressive

Table 2
Bivariate correlation matrix of reward variables at baseline.

	VS	PRT	EEfRT	SHAPS	TEPS-A	TEPS-C	VASA
VS	–	0.08	0.11	−0.01	−0.03	−0.08	0.07
PRT	–	–	−0.10	−0.07	−0.20	−0.10	0.05
EEfRT	–	–	–	0.24*	0.22*	0.20	0.10
SHAPS	–	–	–	–	0.68**	0.70**	0.65**
TEPS-A	–	–	–	–	–	0.69**	0.63**
TEPS-C	–	–	–	–	–	–	0.51**
VASA	–	–	–	–	–	–	–

Note: all variables were coded such that higher scores indicate greater reward/lower anhedonia. VS = ventral striatal activation, PRT = Probabilistic Reward Task, EEfRT = Effort-Expenditure for Rewards Task, SHAPS = Snaith-Hamilton Pleasure Scale, TEPS-A = Anticipatory subscale of Temporal Experience of Pleasure Scale, TEPS-C = Consummatory subscale of Temporal Experience of Pleasure Scale, VASA = Visual Analog Scale-Anhedonia.
* Significant at 0.05 level (2-tailed).
** Significant at 0.01 level (2-tailed).

symptoms.

The **Cognitive and Physical Functioning Questionnaire** (CPFQ) is a 7-item self-report instrument assessing cognitive and executive dysfunction in patients with mood and anxiety disorders (Fava et al., 2009).

The **Clinical Global Impression - Severity** (CGI—S) is a widely administered clinician-rated global measure of subject overall illness severity (Guy, 1976). Subjects are rated on a scale from 1 ("Normal, Not at All Ill") to 7 ("Among the Most Extremely Ill Patients"). Thus, a lower score indicates less illness.

Quantitative EEG (QEEG). Resting state, eyes-closed EEG data were collected to provide an additional circuit-based measure related to hedonic functioning. Based on prior research showing that higher delta (1.5–6 Hz) current density (i.e., lower brain activity) in the rostral anterior cingulate correlated with higher anhedonia among healthy controls (Wacker et al., 2009) and characterized the melancholic subtype of depression (Pizzagalli et al., 2004), we a priori focused on rACC delta current density. EEG data were obtained from at least 32 channels with electrodes located according to the Modified International 10–20 System. Estimates of resting state EEG delta current density in the rostral anterior cingulate were computed using Low Resolution Electromagnetic Magnetic Tomography (LORETA).

2.2. Statistical analyses

Bivariate Pearson correlation coefficients were used to characterize the relationship among all indicator (i.e., reward-related) variables at baseline using IBM SPSS Statistics for Windows, Version 26. Missing data were handled with listwise deletion for correlations. Mplus version 8 was used for latent variable modeling (Muthén and Muthén, 1998-2017). Alpha was set at $p < 0.05$ for all analyses unless otherwise indicated. Latent profile analyses were implemented to identify subgroups of responders based on multiple reward measures collected at baseline using maximum likelihood estimation. Since the reward-related variables used as indicators (VS, PRT, EEfRT, SHAPS, TEPS-A, TEPS-C, VASA) used different scales all indicator variables were first converted to z scores prior to latent profile analyses. Models of 2–4 profiles were fit to the data; each analysis was replicated by doubling the number of random starts. The best fitting solution was chosen based on multiple fit indices: (1) the lowest Bayesian Information Criterion (BIC; (Schwarz, 1978)), (2) a significant Lo, Mendel, and Rubin (LMR) likelihood ratio test ($p < 0.05$), (3) entropy values approaching 1, and (4) >2 individuals in each latent profile (Lo et al., 2001). We compared participant age, sex, and scores on additional baseline measures, which were not used to identify the latent profiles, across profiles using the auxiliary function in Mplus. This test is similar to a chi-square test while accounting for uncertainty inherent in classifying individuals. We employed the Benjamini & Hochberg correction for multiple testing for these analyses (Benjamini and Hochberg, 1995).

To evaluate whether the subgroups demonstrated different responses to treatment, we first calculated change in reward-related and other outcome variables by subtracting post-scores from pre-scores. We then analyzed a mixture model to estimate the interaction between distal outcome variables (i.e., change scores for reward-related variables, HAMD, CGI—S, CPFQ, and QEEG) and treatment assignment (i.e., treatment vs. placebo) across subgroups. We used the BCH 3-step method using a maximum likelihood estimation, which is the recommended method, to model how subgroup membership relates to distal outcomes (Nylund-Gibson et al., 2019). This modeling approach takes into account the uncertainty inherent in classifying individuals. The models were estimated separately for each distal outcome variable due to the exploratory nature of the study; distal outcomes (i.e., treatment response variables) examined were change scores for all reward-related variables as well as change scores for HAM—D, CGI—S, CPFQ, and QEEG.

3. Results

3.1. Between measure correlations

The bivariate correlation matrix from baseline reward-related variables is presented in Table 2. Significant correlations were present and in the expected direction for all self-report measures (SHAPS, TEPS-A, TEPS-C, VASA). The EEfRT, but not the PRT, also demonstrated significant correlations in the expected direction with the SHAPS, and the TEPS-A. However, no significant correlations were observed between the neurobiological measure (mean VS during anticipation of reward) and the behavioral measures (PRT and EEfRT) or self-report measures.

3.2. Latent profile analyses

The 2-profile model was the best fitting solution for the reward-related baseline data; while the BIC slightly decreased and entropy slightly increased for the 3- and 4-profile solutions, the LMR test was not significant for the 3- or 4-profile model and both models had very small group sizes (see Table 3 for fit statistics and class size). Thus, the 2-class solution was retained for further analyses. To examine the differences between the 2 subgroups, the mean of the z-scores for each subgroup was calculated by assigning each person to their most likely profile. Across the variables, higher scores indicate less anhedonia or increased anticipation/effort/response bias to reward. Profiles differed in self-report measures (i.e., SHAPS, TEPS-A and —C, and VASA) but not neural and behavioral measures (VS, PRT, EEfRT), such that subgroup 1 reported less anhedonia/more responsiveness to reward and average reward responsiveness based on neural and behavioral measures (Fig. 1).

3.3. Subgroup differences at baseline

Alpha of 0.03 was used to adjust for multiple testing. The subgroups did not significantly differ by sex ($X^2 = 2.92$ df = 1, p = 0.09) or age (approximate $X^2 = 0.002$, df = 1, p = 0.96). Significant differences between the subgroups were observed for baseline HAM-D (*approximate* $X^2 = 22.08$, df = 1, $p < 0.001$), CGI-S (*approximate* $X^2 = 6.46$, df = 1, p = 0.011), and CPFQ scores (*approximate* $X^2 = 20.48$, df = 1, $p < 0.001$). Specifically, subgroup 1 was less depressed (HAM—D; mean = 11.03, SD = 6.66), had lower clinician-rated severity (lower CGI—S; mean = 3.78, SD = 0.79), and better cognitive and physical functioning (lower CPFQ; mean = 23.39, SD = 8.38) compared to subgroup 2 (HAM-D mean = 15.31, SD = 5.42; CGI-S mean = 4.60, SD = 0.69; CPFQ mean = 28.70, SD = 7.15).

3.4. Preliminary analyses of subgroup differences in treatment response

The BCH modeling did not converge, likely due to small sample size.

Table 3
Fit statistics and subgroup size for latent profile models of reward-related baseline data.

	BIC[1]	Entropy[2]	LMR adjusted p-value[3]	Number of subjects in subgroup 1	Number of subjects in subgroup 2	Number of subjects in subgroup 3	Number of subjects in subgroup 4
2 group model	1579.50	0.872	0.0005	39	50	–	–
3 group model	1579.11	0.887	0.49	7	47	35	–
4 group model	1577.92	0.893	0.07	6	43	8	32

[1] BIC = Bayesian Information Criterion; lower BIC indicates better model fit.
[2] Entropy values approaching 1 indicate clear delineation of groups.
[3] A significant Lo, Mendel, and Rubin (LMR) likelihood ratio test ($p < 0.05$) indicates better model fit.

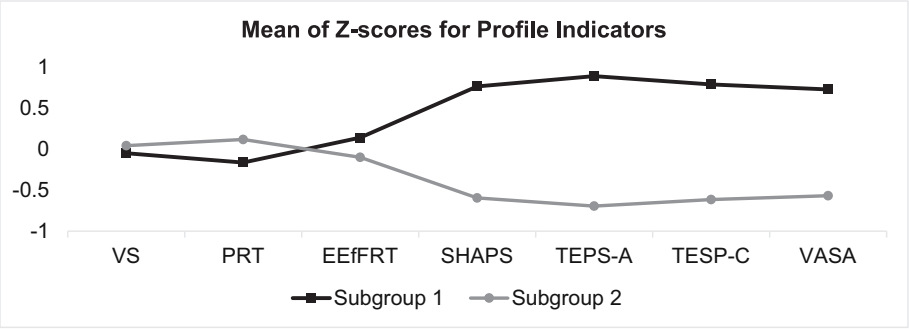

Fig. 1. Note: for all measures, higher scores indicate more reward/less anhedonia.
Corresponding raw score means(standard deviations) for subgroup 1 are VS 0.6(1.0), PRT 0.1 (0.1), EEfRT 0.4(0.2), SHAPS 40.8(5.7), TEPS-A 39.8(6.9), TEPS-C 32.8 (5.5), VASA 4.8(2.1). Means and standard deviations for subgroup 2 are VS 0.7(0.7), PRT 0.2(0.1), EEfRT 0.3(0.2), SHAPS 30.6 (5.3), TEPS-A 22.2(6.5), TEPS-C 21.4(5.7), and VASA 2.0(1.3).

Since the BCH modeling approach is current best practice for modeling the interactions across subgroups, we opted to examine differences by subgroup graphically rather than choosing an alternative statistical modeling approach. Participants were assigned to their most likely subgroup. Of those who received the KOR antagonist, 13 were assigned to subgroup 1 and 20 were assigned to subgroup 2; of those who received placebo, 15 were assigned to subgroup 1 and 20 were assigned to subgroup 2. Change scores for reward-related measures, HAM—D, CPFQ, CGI—S, and QEEG were converted to z-scores and graphed to facilitate comparisons and explore trends (see Fig. 2). Greater change with KOR antagonist treatment was observed for subgroup 2 on self-report reward related measures whereas subgroup 1 demonstrated greater change with KOR antagonist therapy on the VS, PRT, and CPFQ.

4. Discussion

This study evaluated whether a data-driven approach could identify subgroups of individuals with anhedonia based on the relationship between biological, behavioral, and self-report measures related to the RDoC PVS. A 2-subgroup latent profile model was found to best fit the baseline data of reward-related measures; these subgroups were characterized by differences in severity across the self-report measures but did not differ based on the neural or behavioral measures. Of note, the latent subgroups also differed in depression severity, clinician-rated severity, and cognitive and physical functioning. These findings provide a preliminary indication that self-reported reward measures might be indicators of anhedonia patient types that could be explored for possible treatment tailoring.

Consideration of our findings in the context of the design of the original FAST-MAS study is important. Individuals were included in the study based on severity of anhedonia, assessed by the SHAPS and the sample was transdiagnostic (i.e., not all subjects met criteria for MDD). While MDD is associated with substantial functional impairment, our findings with subgroup 1 having less symptom severity and better functioning suggest that subgroup 1 may be a subset of individuals who are experiencing anhedonia outside of the context of significant MDD. It is important to appreciate that it would be premature for researchers to use cutoffs that correspond to the mean latent profile differences from the current analyses for research studies. Replicating the current analyses to evaluate whether the subgroups emerging from this study are stable is a necessary next step as the current analyses may be under powered to detect the correct number of groups. Power in LPAs depends on multiple factors, including number of true subgroups, effect size, sample size, and number of indicators. We used multiple fit indices to select the final model, including those demonstrating more power to detect the true number of subgroups across different conditions (i.e., BIC and adjusted LMR). It should be noted that both the BIC and adjusted LMR may indicate fewer subgroups than the true number of subgroups (Tein et al., 2013); future research should examine solutions with >2 subgroups. Entropy, which may be interpreted as effect size, was high for the current analysis (Granado, 2015). While the effect of sample size on power to detect the correct number of subgroups is minimal compared to other factors (Tein et al., 2013), additional work with a larger sample size is needed to better understand the nature of these measures of reward and to evaluate whether the subgroups emerging here are stable.

It is also premature to rule-out the utility of neural and behavioral measures of reward based on the current secondary analyses. The tasks used for the neural and behavioral measures in the current study all employed monetary rewards. There is emerging evidence that the type of reward used impacts reward processing (Sescousse et al., 2013). It may be that using tasks with rewards that are more closely related to natural reinforcement of engagement in daily living may show more utility.

If these subgroups are found to be robust, one important area for future work will be to assess the differential treatment responsiveness of these subgroups. Graphs of standardized change scores provided preliminary evidence that the subgroups might differ with respect to treatment response. There was a non-significant tendency for subgroup 1 to manifest greater benefit from KOR antagonist treatment on the neuroimaging VS measure, PRT, and CPFQ, while subgroup 2 tended to have more improvement on the reward-related self-report measures.

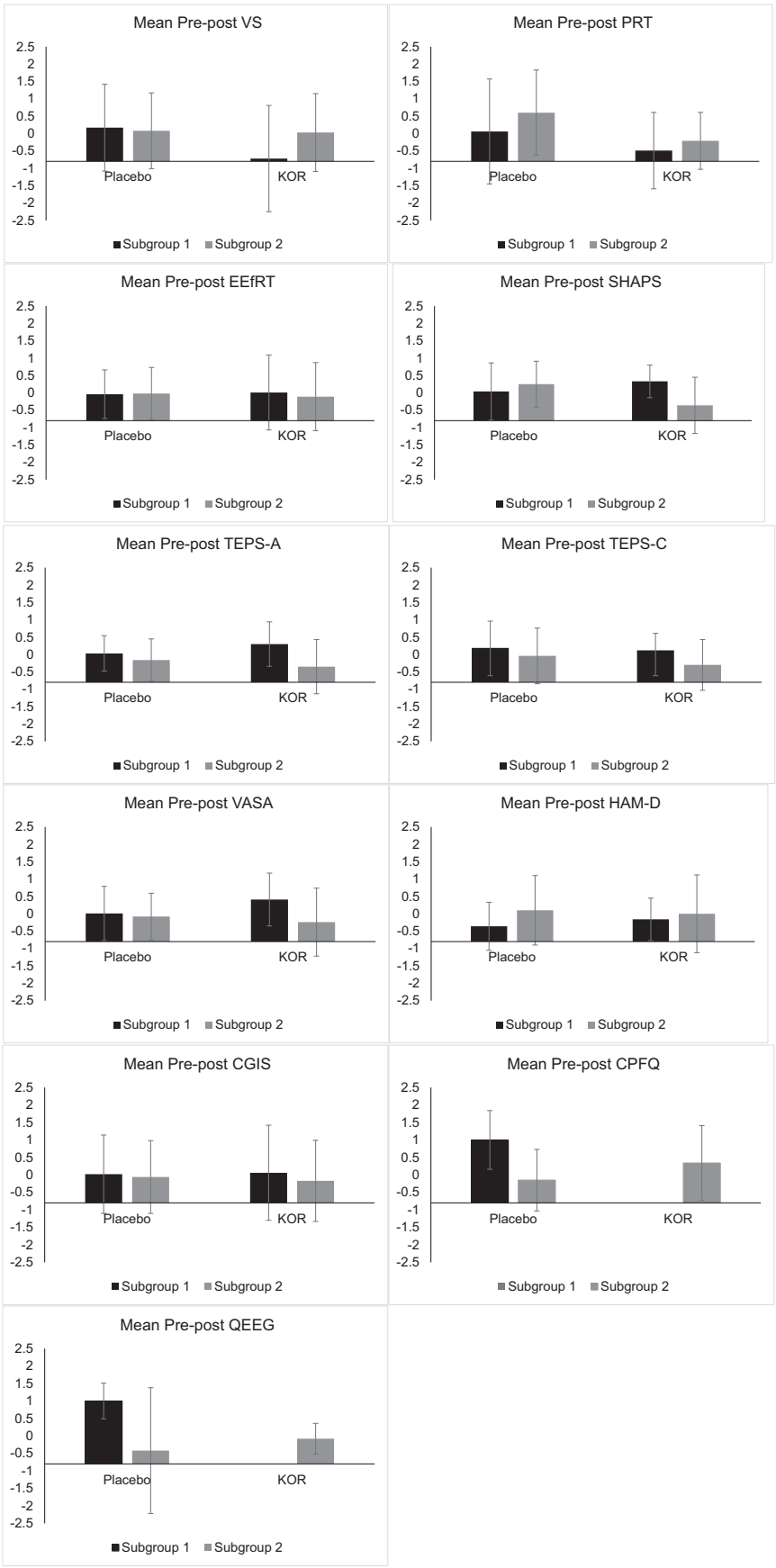

Fig. 2. Standardized pre-post change scores by treatment arm and latent profile.

The latter could reflect the greater potential for improvement in those with greater measure severity.

Consistent with the finding that self-report measures differentiated the subgroups, robust significant correlations (e.g., SHAPS vs. TEPS $r = 0.68–0.70$) were observed among the reward-related self-report measures. Only two cross-measure domain correlations were observed and only at a modest level, between the EEfRT (behavioral measure) and the SHAPS and TEPS-A (self-report measures; $r = 0.22–0.24$). Notably, both the TEPS-A and EEfRT are related to the reward valuation PVS subdomain so some degree of correlation is to be expected. Conversely, we did not find a significant relationship of clinical measures with the neural measure (VS) and the other behavioral measure (PRT), with the latter probing reward learning which is not assessed within the self-report measures included in the current study. This contrasts with the findings seen with analysis of the changes in these variables with treatment that were previously reported, where the change in VS was significantly correlated with the change on the SHAPS (Krystal et al., 2020). This may reflect a difference in studying baseline and assessing the effects of KOR antagonism. Moreover, it highlights that the clinical severity measures employed have a complex and poorly understood relationship to a physiological measure selected to reflect activation of reward circuitry. Since reward circuitry identification was initially based on "reward" paradigms in rodents it is not surprising that the broad clinical concept of anhedonia might not track well with a measure of reward circuit activation. Our findings are consistent with the literature demonstrating larger correlations within measurement method compared to across measurement method. This pattern of correlations may also have led to spurious identification of subgroups; the correlation among self-report measures might be have driven the separation of profiles into a high and low group, rather than profiles that demonstrate differences across reward-domains (Hallquist and Wright, 2014). Larger studies are needed to better understand the relationship among measurement methods, given differences in how different methods account for situational and temporal variability of reward-related processes (Lilienfeld, 2014).

The main limitations of the current study are the small sample size and exploratory nature of the analyses. While the results are preliminary, this study is a meaningful step forward and leverages the rich dataset from the first Fast-Fail trial, which established proof of mechanism for a KOR antagonist targeting anhedonia. This study highlights the need to determine the severity of reward-reward related deficits that correspond with impairment and that will be helped by targeted treatment. Future research is needed to better understand how different measurement approaches relate and how these relationships may vary with the severity of reward deficits.

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CRediT authorship contribution statement

Darrow: contributed to data analyses and finding interpretation, drafted first draft and revisions, approved the final article.

Pizzagalli: contributed to study design, data analyses, and finding interpretation; contribute to first draft; provided final review; approved the final article.

Smoski: contributed to data analyses, and finding interpretation; provided manuscript review; approved the final article.

Mathew: contributed to study design, data collection, finding interpretation; provided manuscript review; approved the final article.

Nurnberger: contributed to study design, data collection, finding interpretation; provided manuscript review; approved the final article.

Lisanby: contributed to study design, data collection, finding interpretation; provided manuscript review; approved the final article.

Iosifescu: contributed to data collection, finding interpretation; provided manuscript review; approved the final article.

Murrough: contributed to data collection, finding interpretation; provided manuscript review; approved the final article.

Yang: contributed to study design, data analyses, and finding interpretation; provided manuscript review; approved the final article.

Weiner: contributed to data collection, finding interpretation; provided manuscript review; approved the final article.

Sanacora: contributed to study design, data collection, finding interpretation; provided manuscript review; approved the final article.

Keefe: contributed to study design, data analyses, and finding interpretation; provided manuscript review; approved the final article.

Song: contributed to study design, data analyses, and finding interpretation; provided manuscript review; approved the final article.

Goodman: contributed to study design, data collection, finding interpretation; provided manuscript review; approved the final article.

Whitton: contributed to data collection, data analyses, finding interpretation; provided manuscript review; approved the final article.

Potter: contributed to study design, finding interpretation; provided manuscript review; approved the final article.

Krystal: obtained funding, provided overall study oversight, contributed to study design, data collection, data analyses, finding interpretation; contributed to first draft, provided manuscript review; approved the final article.

Declaration of competing interest

Darrow: reports no financial relationship with commercial interests.

Pizzagalli: Over the past 3 years, Dr. Pizzagalli has received consulting fees from Albright Stonebridge Group, Boehringer Ingelheim, Compass Pathways, Engrail Therapeutics, Neumora Therapeutics (formerly BlackThorn Therapeutics), Neurocrine Biosciences, Neuroscience Software, Otsuka, Sunovion, and Takeda; he has received honoraria from the Psychonomic Society and American Psychological Association (for editorial work) and from Alkermes; he has received research funding from the Brain and Behavior Research Foundation, Dana Foundation, Wellcome Leap, Millennium Pharmaceuticals, and NIMH; he has received stock options from Compass Pathways, Engrail Therapeutics, Neumora Therapeutics, and Neuroscience Software; he has a financial interest in Neumora Therapeutics, which has licensed the copyright to the human version of the probabilistic reward task through Harvard University. No funding from these entities was used to support the current work, and all views expressed are solely those of the authors.

Smoski: reports no financial relationships with commercial interests.

Mathew: Dr. Mathew has been a consultant for Allergan, Alkermes, Axsome Therapeutics, BioXcel Therapeutics, Clexio Biosciences, Eleusis, EMA Wellness, Engrail Therapeutics, Intra-Cellular Therapies, Greenwich Biosciences, Janssen, Levo Therapeutics, Neurocrine, Perception Neuroscience, Praxis Precision Medicines, Relmada Therapeutics, Sage Therapeutics, Signant Health and Seelos Therapeutics, and received research support from Biohaven, Janssen, Merck, NIH, NeuroRx, PCORI, Sage Therapeutics, VA, and VistaGen Therapeutics, drug from Biohaven for NIMH-funded study, and support from the Michael E. Debakey VA Medical Center (Houston, TX) for use of resources and facilities and The Menninger Clinic, Houston, Texas.

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Iosifescu: In the past 5 years, Dr. Iosifescu has received consulting fees from Alkermes, Axsome, Allergan, Biogen, the Centers for Psychiatric Excellence, Global Medical Education, MyndAnalytics (CNS Response), Jazz, Lundbeck, Otsuka, Precision Neuroscience, Sage, Sunovion; and he has received research grant support (through his academic institutions) from Alkermes, AstraZeneca, Brainsway, LiteCure, NeoSync, Roche, and Shire.

Murrough: In the past 5 years, Dr. Murrough has served as a consultant to Allergan, Boehreinger Ingelheim, Clexio Biosciences, Global Medical Education (GME), Otsuka, Sage Therapeutics, and Engrail Therapeutics. Dr. Murrough is named on a patent pending for neuropeptide Y as a treatment for mood and anxiety disorders and on a patent pending for the use of KCNQ channel openers to treat depression and related conditions. The Icahn School of Medicine (employer of Dr. Murrough) is named on a patent and has entered into a licensing agreement and will receive payments related to the use of ketamine or esketamine for the treatment of depression. The Icahn School of Medicine is also named on a patent related to the use of ketamine for the treatment of PTSD. Dr. Murrough is not named on these patents and will not receive any payments.

Yang: reports no financial relationship with commercial interests.

Weiner: reports no financial relationship with commercial interests.

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Keefe: During the period that work was conducted on this study, R.S. E.K. was the owner of VeraSci, a for-profit company that provides clinical trial support and other services for over 100 pharmaceutical companies and other institutions.

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