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ARTICLE

Selective kappa-opioid antagonism ameliorates anhedonic behavior: evidence from the Fast-fail Trial in Mood and Anxiety Spectrum Disorders (FAST-MAS)

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Anhedonia remains a major clinical issue for which there is few effective interventions. Untreated or poorly controlled anhedonia has been linked to worse disease course and increased suicidal behavior across disorders. Taking a proof-of-mechanism approach under the auspices of the National Institute of Mental Health FAST-FAIL initiative, we were the first to show that, in a transdiagnostic sample screened for elevated self-reported anhedonia, 8 weeks of treatment with a kappa-opioid receptor (KOR) antagonist resulted in significantly higher reward-related activation in one of the core hubs of the brain reward system (the ventral striatum), better reward learning in the Probabilistic Reward Task (PRT), and lower anhedonic symptoms, relative to 8 weeks of placebo. Here, we performed secondary analyses of the PRT data to investigate the putative effects of KOR antagonism on anhedonic behavior with more precision by using trial-level model-based Bayesian computational modeling and probability analyses. We found that, relative to placebo, KOR antagonism resulted in significantly higher learning rate (i.e., ability to learn from reward feedback) and a more sustained preference toward the more frequently rewarded stimulus, but unaltered reward sensitivity (i.e., the hedonic response to reward feedback). Collectively, these findings provide novel evidence that in a transdiagnostic sample characterized by elevated anhedonia, KOR antagonism improved the ability to modulate behavior as a function of prior rewards. Together with confirmation of target engagement in the primary report (Krystal et al., Nat Med, 2020), the current findings suggest that further transdiagnostic investigation of KOR antagonism for anhedonia is warranted.

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INTRODUCTION

Despite substantial efforts, Major Depressive Disorder (MDD) remains a common, recurrent, and, for many, difficult-to-treat disorder. In the USA, large studies have shown that up to 50% of patients fail to respond to first-line antidepressant medications (e.g., selective serotonin reuptake inhibitors) [1] or evidence-based psychotherapy [2]. There are several reasons for this modest progress. First, our understanding of the etiology and pathophysiology of depression remains incomplete. Second, MDD—as defined by current nosology [3]—is highly heterogenous in its clinical presentation, which points to neurobiological heterogeneity.

To address these unmet needs, in 2010 the National Institute of Mental Health launched the Research Domain Criteria initiative [4], which proposed to focus on transdiagnostic dimensions of behavior expected to map onto neurobiological substrates more closely than psychiatric syndromes. Among such dimensions, anhedonia has attracted substantial attention, particularly since it has been implicated in numerous neuropsychiatric conditions [5–9]. Moreover, anhedonia has been linked to worse treatment response and disease course as well as increased risk for suicide [10–13].

Critically, mounting evidence indicates that anhedonia can be parsed into subdomains, which points to partially dissociable neurobiological abnormalities [10, 14, 15]. For example, findings across species indicate that reward learning, incentive motivation, and effort-based decision making strongly rely on dopaminergic signaling, whereas the experience of pleasure is more strongly related to GABA and mu opioid signaling. When probing reward learning, several laboratories have used the Probabilistic Reward Task (PRT), which provides an objective assessment of the ability to modulate behavior as a function of prior reinforcement [16–18]. Relevant here, findings across laboratories and species have shown that reward learning in the PRT was bi-directionally modulated by dopaminergic manipulations [17–19] and related to dopaminergic markers and neural functioning along mesocorticolimbic pathways [20–22]. Moreover, reward learning was inversely related to current anhedonic symptoms among (unselected) children [23] and adults [16, 24], individuals with MDD [25]

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and relatives of patients with MDD [26], and predicted future anhedonic symptoms [16, 27]. Finally, reward learning was reduced in individuals with increased depressive symptoms [16], current MDD [25, 28, 29], and past MDD [30, 31] (cf. [32]), with effects particularly pronounced in those with elevated anhedonic symptoms [29] or melancholic depression [33], and among transdiagnostic youth samples with heightened anhedonia [34].

Importantly, the observation that up to 50% of patients fail to respond to monoaminergic antidepressants and the modest success in treating anhedonia suggest that additional neurobiological abnormalities might be implicated in MDD and anhedonia. In light of their pivotal role in regulating reward processing and stress (among other functions), kappa-opioid receptors (KOR) are emerging as a promising target for MDD and, especially, anhedonia. Converging lines of evidence support this assumption (for review, see [35]). First, rodent studies show that KOR antagonists have antidepressant effects (as assessed by reduced stress-induced immobility in the forced swim test) [36, 37] and reduced learned helplessness [38], whereas KOR agonists induce depressive-like effects [39]. Second, administration of KOR antagonists in the ventral striatum (nucleus accumbens)—a region where dopaminergic and reward-related activation is often blunted in MDD [40–42]—leads to 175% increase in dopamine release in this region [43], whereas KOR agonists reduce accumbal dopamine release by 50% [43] and foster the emergence of anhedonic behavior [39].

Mechanistically, there is evidence that stress leads to a release of dynorphin, which binds to KOR receptors and inhibits the release of dopamine into the nucleus accumbens by ventral tegmental area neurons [44–48]. Accordingly, KOR antagonists may produce anti-anhedonic effects by blocking the consequences of cAMP response element binding-mediated upregulation of dynorphin function, which in turn might restore function within the mesolimbic dopaminergic system [48]. Collectively, these findings suggest that KOR antagonism may be effective at ameliorating anhedonic behavior.

To test this hypothesis, we performed secondary analyses on the recently published FAST-MAS dataset [49]. Supported by the NIMH's New Experimental Medicine Studies: Fast-Fail Trials Program (https://www.nimh.nih.gov/research-priorities/research-initiatives/fast-fast-fail-trials.shtml), the study took a "proof-of-mechanism" approach to evaluate whether KOR antagonism would have anti-anhedonic effects in a transdiagnostic sample by improving reward-related brain circuitry (specifically, ventral striatal activation to reward-predicting stimuli). This hypothesis was recently confirmed [49], along with evidence that KOR antagonism also positively affected the secondary outcome measures—self-reported anhedonia (as assessed by the Snaith Hamilton Pleasure Scale [50]) and reward learning (as assessed by the PRT [16]). In the current secondary analyses we provide novel evidence that significant group differences in posttreatment reward learning were driven by increased probability of selecting the stimulus previously paired with more frequent rewards, as well as a higher learning rate (as assessed using computational modeling), in the KOR antagonist relative to placebo group. This latter finding was hypothesized owing to prior reports that learning rate is sensitive to dopaminergic manipulations [51–54]. In line with this hypothesis, and highlighting specificity, groups did not differ in the second parameter, reward sensitivity. Collectively, these findings pinpoint precise reward subdomains that are ameliorated by KOR antagonism and further underscore the promise of KOR antagonism in alleviating anhedonia in transdiagnostic samples.

MATERIALS AND METHODS

Participants

Participants were recruited at six US centers (ClinicalTrials.gov Identifier: NCT02218736; see Supplementary Material). Participants were enrolled after providing informed written consent to a protocol approved by each local institutional review board. In total, 163 patients were screened and 94 met eligibility criteria (Supplementary Fig. 1). Among these 94, 5 did not complete baseline assessments, leaving 89 participants for randomization (45 KOR, 44 placebo). Two subjects (both in the KOR group) did not perform the PRT; among the remaining 87, 76 participants (35 KOR, 41 placebo) had usable pretreatment PRT data after quality control checks, which were performed blindly to treatment arm using predefined cutoff scores (Supplementary Material); among these 76, 16 participants (9 KOR, 7 placebo) did not perform the PRT at posttreatment and 5 (2 KOR, 3 placebo) failed QC evaluations at posttreatment. As a result, 55 participants (24 KOR, 31 placebo) had both pre- and posttreatment PRT data that passed QC and were included in the analyses. Highlighting the translational nature of the sample, DSM diagnoses included MDD, bipolar disorder, generalized anxiety disorder, social anxiety disorder, panic disorder, and posttraumatic stress disorder (Table 1).

The two groups did not differ in any sociodemographic variable or baseline depression severity (Table 1). However, relative to patients eventually randomized to placebo, the KOR group unexpectedly had higher baseline SHAPS scores (mean ± SD: 37.29 ± 8.89 vs. 33.03 ± 5.54, $t(53) = 2.18$, $p = 0.034$). Owing to prior PRT findings showing that anhedonic symptoms negatively correlated with response bias [16, 23, 24, 26, 29], all analyses included baseline (pretreatment) SHAPS score as a covariate.

Note that in the original analysis [49] we did not control for baseline anhedonia because (1) SHAPS scores did not significantly differ between treatment groups in the overall sample, and (2) it was not part of our prespecified analysis plan. Accordingly, the prespecified three-way interaction analysis (*Treatment Arm* × *Time* × *Block*) was repeated by controlling for baseline SHAPS scores to confirm the original findings. In addition, we performed novel analyses (computational modeling and probability analyses) to probe putative dysfunction in more depth.

Randomized clinical trial

A full description of the randomized clinical trial has been provided [49]. Briefly, eligibility was determined using the Mini-International Neuropsychiatric Interview for DSM 4 [55, 56], and clinical scales, including the SHAPS to assess anhedonia. Eligible patients scoring ≥20 on the SHAPS [57] returned for a baseline visit, which included: a second administration of the SHAPS and other clinical scales (Hamilton Depression Rating Scale [58], Hamilton Rating Scale for Anxiety [59]); an MRI session; an EEG recording; and the PRT. Next, patients were randomized to a KOR antagonist or placebo (1:1 ratio) for 8 weeks. After 8 weeks, patients were re-assessed with the same procedures. For the active condition, we selected JNJ-67953964 (Aticaprant) (formerly, CERC-501 and LY2456302), a high-affinity, selective KOR antagonist with favorable pharmacologic and safety profiles. A 10-mg dose was selected based on preclinical toxicology and human single ascending dose and multiple ascending dose studies [60, 61] as well as positron emission tomography evidence of robust KOR engagement at this dose [62].

Probabilistic reward task

The PRT is a computerized task rooted in signal detection theory [16, 19, 25]. On each trial, participants are asked to determine, via key press, whether one of two difficult-to-differentiate stimuli had been presented. Unlike earlier PRT papers [16, 19, 25], this study used two blocks of 100 trials to limit task duration. For each trial, participants had to decide whether a brief visual stimulus (a mouth presented on a cartoon face for 100 ms) was "long" or "short", by pressing one of two computer keys ("*z*" or "/", counterbalanced). Per design, the brief stimulus presentation time (100 ms) and small physical difference between the mouth stimuli (11.5 vs. 13 mm) make

Table 1. Clinical and sociodemographic variables.

	Kappa-opioid receptor $N = 24$		Placebo $N = 31$		t value	p value
	Mean	SD	Mean	SD		
Age	39.17	13.87	40.81	13.68	−0.44	>0.66
Baseline						
HRSD	15.13	5.04	14.32	5.91	0.54	>0.93
SHAPS	37.29	8.89	33.03	5.54	2.18	0.034
CGI i	3.96	0.36	3.97	0.48	−0.10	>0.93
CGI s	3.79	0.51	3.84	0.52	−0.34	>0.73
Posttreatment						
HRSD	11.96	7.89	10.42	7.46	0.74	>0.46
SHAPS	32.86	8.13	30.76	6.75	1.01	>0.31
CGI i	3.50	0.96	3.21	1.11	0.99	>0.32
CGI s	3.23	0.87	3.21	1.01	0.08	>0.94
	N (%)		*N* (%)		χ^2 value	p value
Sex					0.049	>0.80
Females	14		19			
Males	10		12			
DSM diagnosis					7.98	>0.24
MDD[a]	16 (66.7%)		18 (58.1%)			
Bipolar I[b]	2 (8.3%)		2 (6.5%)			
Bipolar II[b]	0 (0%)		4 (12.9%)			
GAD	2 (8.3%)		5 (16.1%)			
SAD	2 (8.3%)		0 (0%)			
Panic disorder	1 (4.2%)		2 (6.5%)			
PTSD	1 (4.2%)		0 (0%)			
Race					2.34	>0.66
White	18 (75%)		19 (61.3%)			
African American	3 (12.5%)		5 (16.1%)			
Asian	0 (0%)		2 (6.5%)			
More than 1 race	2 (8.3%)		4 (12.9%)			
Unknown	1 (4.2%)		1 (3.2%)			

The table summarizes primary diagnosis. Fourteen of the 25 patients randomized to the KOR and 18 of the 31 patients randomized to placebo had at least a secondary DSM diagnosis ($\chi^2(1) = 0.02$, ns). For control analyses of the PRT data within the MDD subsample, see Supplementary.
HRSD Hamilton Rating Scale for depression, *SHAPS* Snaith Hamilton Pleasure Scale. *CGI i* Clinical Global Impression—improvement scale, *CGI s* Clinical Global Impression—severity scale, *GAD* generalized anxiety disorder, *SAD* social anxiety disorder, *PTSD* Posttraumatic stress disorder.
[a]Major Depressive Disorder (MDD) current 2 weeks or recurrent.
[b]Bipolar disorder current or past.

discrimination challenging. Critically, and unbeknownst to participants, the task includes an asymmetrical reinforcement schedule such that one of the two stimuli (the "rich" stimulus) is rewarded ("Correct!! You Won 20 Cents") three times more frequently than the "lean" stimulus (30 vs. 10 times per block). Participants were instructed that not all correct responses would be followed by rewards and to respond as quickly and accurately as possible in order to maximize task earnings.

Data reduction

Following established procedures [16, 19, 25], PRT data were analyzed using signal detection theory. First, QC evaluations were performed using a priori defined criteria and blind to treatment arm (Supplementary Material). Next, response bias (log *b*) and discriminability (log *d*) were computed as:

$$\log b = 0.5 \times \log\left(\frac{(Rich_{Correct} + 0.5) \times (Lean_{Incorrect} + 0.5)}{(Rich_{Incorrect} + 0.5) \times (Lean_{Correct} + 0.5)}\right),$$

$$\log d = 0.5 * \log\left(\frac{(Rich_{Correct} + 0.5) * (Lean_{Correct} + 0.5)}{(Rich_{Incorrect} + 0.5) * (Lean_{Incorrect} + 0.5)}\right).$$

In secondary analyses, accuracy and reaction time in response to the rich and lean stimulus were computed for each block.

Statistics

The main variable of interest was response bias, which was analyzed using a mixed analysis of covariance (ANCOVA) with the between-subject factor of *Treatment Arm* (KOR, placebo) and the repeated measures of *Time* (pre-, posttreatment) and *Block* (1, 2), with pretreatment SHAPS scores entered as covariate. To evaluate with more precision response bias differences, two additional analyses were performed. In the first, we computed the probability of a given response (e.g., "rich") as a function of whether the preceding trial (rich vs. lean) had been rewarded or not. Specifically, ANCOVA analyses were performed on the probability of both a *rich hit* (i.e., a rich stimulus was presented, and the participant responded "rich") and a lean miss (i.e., a lean stimulus was presented, and the participant responded "rich"), as a function of whether the immediately preceding trial had been rich or lean, and had been rewarded or not.

In the second analysis, a computational model of trial-level performance was implemented (Supplementary Methods). This model-based Bayesian modeling [51] allows parsing of the

contribution of two subconstructs on PRT performance: *reward sensitivity* (which operationalizes consummatory pleasure) and *learning rate* (which operationalizes participants' ability to learn from reward feedback). For each parameter, a *Time* (pre-, posttreatment) × *Treatment Arm* (KOR, placebo) ANCOVA was run (covariate: pretreatment SHAPS scores). Relations among variables are summarized in the Supplementary Table 1 (see also Supplementary Fig. 2).

Finally, control analyses comparing groups in their rich-to-lean reward ratio and discriminability scores were performed to confirm that possible differences in response bias were not affected by group differences in the reinforcement schedule received, or by overall task difficulty. For these analyses, a *Time* × *Block* × *Treatment Arm* ANCOVA was run. Analyses on accuracy and reaction time were performed to confirm that the task elicited the intended behavioral effects, and results are reported in the Supplementary Results (see Supplementary Fig. 3). Across all analyses, variables were normally distributed, pretreatment SHAPS scores were entered as covariates, and significant ANCOVA effects were followed up with Bonferroni-corrected post-hoc tests of simple effects.

RESULTS

Response bias

The *Time* (pre-, posttreatment) × *Block* (1, 2) × *Treatment Arm* (KOR, placebo) ANCOVA on response bias revealed a significant *Time* × *Treatment Arm* interaction, $F(1, 52) = 4.69$, $p = 0.035$, $\eta p^2 = 0.083$ (Fig. 1a). Bonferroni-corrected post-hoc tests of simple effects indicated that this interaction was driven by significantly higher posttreatment response bias in the KOR relative to placebo group ($p = 0.017$; Cohen's $d = 0.69$), whereas groups did not differ pretreatment ($p > 0.60$). Moreover, the KOR group ($p = 0.074$) showed a trend for an increase in response bias from pre- to posttreatment (placebo: $p > 0.17$). At an individual level, 16 of the 24 patients randomized to KOR group (66.7%) showed an increase in response bias from pre- to posttreatment (binomial $p(16/24) = 0.044$), whereas only 13 of the 31 patients randomized to placebo (41.4%) showed this pattern (binomial $p(13/31) > 0.09$; $\chi^2 = 7.73$, $df = 1$, $p < 0.005$). As summarized in the Supplementary Results, secondary analyses on accuracy scores clarified that the KOR group had significantly higher rich accuracy at posttreatment relative to the placebo group ($p = 0.002$; Cohen's $d = 0.88$), whereas groups did not differ in their pretreatment rich accuracy ($p = 0.50$) nor in their pre- or posttreatment lean accuracy. Moreover, the KOR and placebo groups showed a significant increase ($p = 0.026$) and decrease ($p = 0.003$), respectively, in rich accuracy from pre- to posttreatment (Supplementary Fig. 3).

Probability analyses

Rich hit rates. A *Preceding Trial* (rich, lean) × *Rewarded* (yes, no) × *Time* (pre, post) × *Treatment Arm* ANCOVAs was run on the probability of a rich hit (i.e., the next trial was rich and the subject responded "rich"). The only significant findings involving *Treatment Arm* were the *Time* × *Treatment Arm* interaction, $F(1, 52) = 13.13$, $p < 0.001$, $\eta p^2 = 0.202$, as well as the four-way interaction, $F(1, 52) = 5.41$, $p = 0.024$, $\eta p^2 = 0.202$. Post-hoc tests indicated that the *Time* × *Treatment Arm* interaction was driven by significantly higher posttreatment rich hits for the KOR relative to the placebo group (Fig. 1b; $p < 0.001$; Cohen's $d = 1.03$), whereas groups did not differ in their pretreatment scores ($p > 0.35$). Moreover, the KOR group showed significantly higher rich hits at postrelative to pretreatment ($p = 0.017$), whereas the placebo group showed a significant reduction from pre- to posttreatment in rich hit rates ($p = 0.007$).

To follow-up the four-way interaction, we ran a *Preceding Trial* (rich, lean) × *Time* (pre, post) × *Treatment Arm* ANCOVA on the probability of a rich hit separately depending on whether the preceding trials had been rewarded or not. For both analyses, the *Time* × *Treatment Arm* interaction was significant (rewarded preceding trial: $F(1, 52) = 8.13$, $p = 0.006$, $\eta p^2 = 0.135$; nonrewarded preceding trial: $F(1, 52) = 8.05$, $p = 0.006$, $\eta p^2 = 0.134$). Post-hoc tests confirmed that, irrespective of whether the preceding trial had been rewarded or not, the KOR group had significantly higher rich hit rates relative to the placebo group at posttreatment (both $ps < 0.011$), whereas groups did not differ at pretreatment (both $ps > 0.44$).

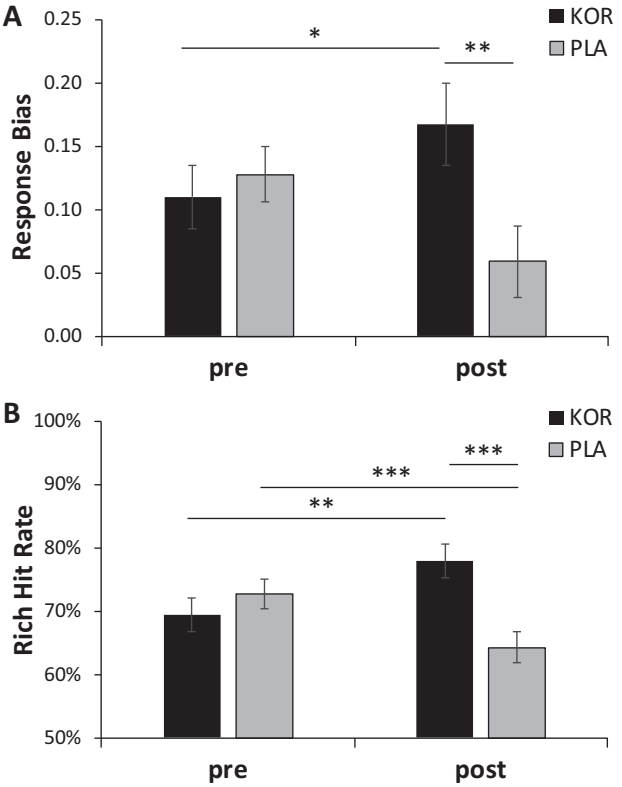

Fig. 1 Pre- to Post-treatment changes in Response Bias and Rich Hit Rates as a Function of Treatment. a Response bias and **b** probability of Rich Hits in the KOR ($n = 24$) and Placebo ($N = 31$) group pre- and posttreatment. Error bars denote standard errors. Estimated means are plotted (covariate: pretreatment SHAPS scores). ***$p < 0.01$, **$p < 0.05$, *$p < 0.10$.

Lean miss rates. An identical ANCOVA was run on the probability of a lean miss (i.e., the next trial was lean and the subject responded "rich"). No effects involving *Treatment Arm* emerged (all $Fs < 1.63$, $ps > 0.20$).

Computational model

Learning rate

A *Time* × *Treatment Arm* ANCOVA on the learning rate parameter indicated that the *Time* × *Treatment Arm* interaction was significant, $F(1, 52) = 7.52$, $p < 0.008$, $\eta p^2 = 0.126$. Post-hoc tests revealed that, relative to the placebo group, the KOR group had significantly higher posttreatment learning rate ($p < 0.005$; Cohen's $d = 0.81$), whereas groups did not differ at pretreatment ($p > 0.20$) (Fig. 2a). For the placebo group ($p < 0.025$)—but not KOR group ($p > 0.10$)—learning rates significantly decreased from pre- to posttreatment. When considering individual scores, 16 of the 24 participants (66.7%) randomized to the KOR antagonist (binomial $p(16/24) < 0.044$) but only 9 of the 31 participants (29.0%) randomized to placebo (binomial $p(9/31) < 0.01$) showed an

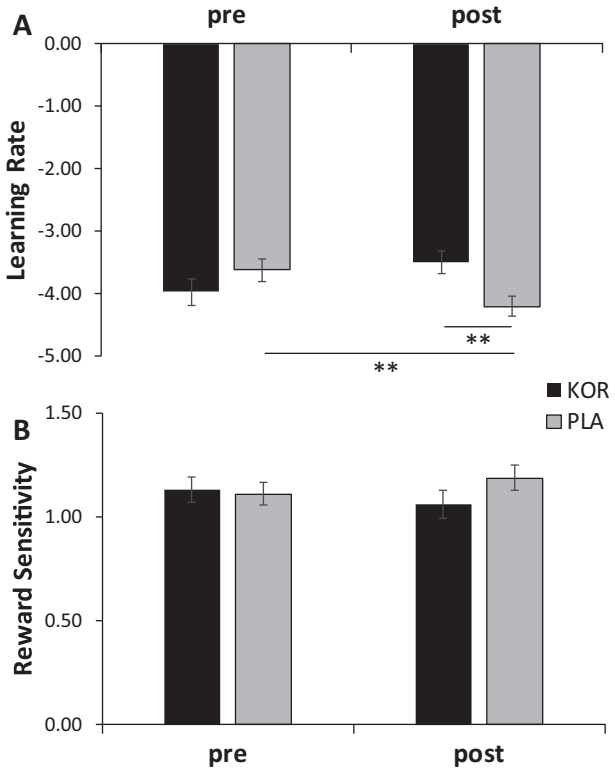

Fig. 2 Pre- to Post-treatment changes in Computational Modeling Parameters as a Function of Treatment. a Learning rate and **b** reward sensitivity in the KOR ($n = 24$) and Placebo ($N = 31$) group pre- and posttreatment. Error bars denote standard errors. Estimated means are plotted (covariate: pretreatment SHAPS scores). Note that the learning rate and reward sensitivity parameters were transformed to prevent issues with nonnormal distribution. ***$p < 0.01$, **$p < 0.05$, *$p < 0.10$.

increase from pre- to posttreatment in learning rates ($\chi 2 = 7.73$, df = 1, $p < 0.005$).

Reward sensitivity

A *Time* (pre-, posttreatment) × *Treatment Arm* (KOR, placebo) ANCOVA on reward sensitivity revealed no significant effects involving *Treatment Arm* (all $Fs < 1.45$, all $ps > 0.23$; Fig. 2b).

Control analyses

Two separate *Time* × *Block* × *Treatment Arm* ANCOVAs revealed no effects involving *Treatment Arm* on rich-to-lean rewards or discriminability (Supplementary Results), indicating that the main findings were not affected by group differences in reinforcement schedule or task difficulty.

DISCUSSION

Anhedonia is a major clinical issue across multiple neuropsychiatric disorders. In MDD, anhedonia is typically poorly addressed by first-line treatments (e.g., SSRI) and predicts worse disease trajectory [10–13]. Moreover, anhedonia has been found to precede fully symptomatic syndromes in MDD [63], Parkinson's disease [64, 65], and substance abuse [66], and has long been identified as a core vulnerability factor for schizophrenia [8]. Accordingly, identifying novel treatment targets for anhedonia is a major priority. Supported by compelling preclinical evidence that KOR antagonism has anti-anhedonic effects, normalizes DA signaling in the nucleus accumbens (one of the core hubs of the brain reward system), and removes the inhibiting effects of dynorphin on DA neurons [35, 48], the FAST-MAS study was specifically designed to test the hypothesis that a KOR antagonist would ameliorate anhedonia across three units of analysis: brain (as operationalized as ventral striatal activation to reward-predicting cues), behavior (i.e., reward learning in the PRT), and self-report (i.e., SHAPS scores). As recently described, this hypothesis was supported [49]. Highlighting the specificity of the effects to anhedonia, posttreatment differences in ventral striatal activation during reward anticipation, reward learning abilities, and self-reported anhedonia between the KOR antagonist and placebo group emerged in the context of no changes in overall depression severity. This indicates that the use of broad syndrome-based clinical scales might cloud identification of treatment targets for anhedonia.

The overarching goal of the current secondary analyses was twofold. First, we aimed to confirm that posttreatment group differences in reward learning were not unduly affected by the unexpected observation that, before randomization, patients with usable PRT data who went on to receive the KOR antagonist had significantly higher pretreatment SHAPS scores relative to patients in the placebo group. This control analysis was motivated by prior findings that self-reported anhedonia is inversely related to reward learning in the PRT [16, 23, 24, 26, 29]. Of note, the *Time* × *Treatment Arm* interaction was confirmed, and post-hoc tests clarified that this interaction was driven by significantly higher posttreatment response bias in the KOR relative to the placebo group, with no pretreatment differences. Additional analyses on accuracy scores clarified that response bias findings were driven by posttreatment group differences in rich—but not lean—accuracy, and a significant increase from pre- to posttreatment in rich accuracy for the KOR group, whereas the placebo group showed a significant reduction in rich accuracy from pre- to posttreatment.

Second, using computational modeling and trial-level analyses probing the probabilities of specific behavioral responses as a function of prior trials, we sought to pinpoint the putative sources of group differences in posttreatment response bias. Building on prior work, we implemented a model-based Bayesian modeling approach [51] to disentangle the contribution of two subconstructs on PRT performance: *reward sensitivity* (which captures hedonic response to the reward feedback) and *learning rate* (which captures the ability to learn from reward feedback). In light of vast evidence implicating DA in learning rate [52–54] and prior PRT findings indicating that a DA challenge modulated learning rate [51], we expected that the KOR and placebo groups would differ in their posttreatment learning rate, but not posttreatment reward sensitivity. This hypothesis was confirmed. Higher learning rate reflects better ability to choose by integrating reinforcement history into modulating option values. Finally, and further highlighting that a KOR antagonist boosted patients' ability to sustain a preference toward a more frequently rewarded stimulus, probability analyses clarified that, relative to placebo, KOR antagonism was associated with a higher likelihood of selecting "rich" irrespective of whether the prior trial had been a rewarded or nonrewarded rich or lean stimulus. Thus, the preference for the rich stimulus was boosted regardless of the immediately preceding stimulus and whether it had been rewarded or not. Overall, this points to a better ability to sustain reward-related behavior after KOR antagonism. These findings represent an important contribution as they allow us to increase the precision with which we can define the specific type of reward-related deficit that is ameliorated by KOR antagonism. The evidence suggests that KOR antagonism specifically impacts learning rate but not reward sensitivity and improves a specific element of impaired reward learning: the ability to express a response bias toward a more frequently rewarded stimulus irrespective of the outcome of the immediately preceding trial.

The current findings, particularly the KOR-related effects on response bias and learning rates, are consistent with a large body

of preclinical research indicating that KOR receptors modulate brain reward function [44], influence positive reinforcement [47], and are implicated in the acquisition and consolidation of learned associations. Directly relevant to the task used here, prior rodent studies have shown that KOR modulation shape learning on a variety of tasks [67–69]. These pharmacological findings are consistent with the anatomical distribution of KOR, which are prominently represented in brain regions critically implicated in reinforcement learning and reward prediction coding, including the ventral tegmental area, nucleus accumbens, caudate, and putamen in both the rat [70] and human [71, 72] brain. Critically, these regions show abnormal reward-related activation and functional connectivity (including during reinforcement learning tasks) in MDD [40, 41, 73]. Thus, we speculate that the current behavioral findings might reflect some degree of normalization within this brain circuitry.

The current study has several important strengths. First, the FAST-FAIL initiative represents a novel conceptualization for clinical trials, whereby the primary outcome variable was not a clinical scale but rather a neural marker of target engagement (with two additional secondary outcome measures, which were also narrowly selected: a self-reported and a behavioral measure of anhedonia). Second, the multi-site FAST-MAS study used a promising target (KOR antagonism), which has received compelling support from the preclinical literature [35, 48] but has not been thoroughly investigated in humans. Third, patients were selected transdiagnostically with the common feature of reporting some degree of anhedonia (baseline SHAPS score ≥ 20). Fourth, Bayesian-based computational modeling was used to disentangle different subconstructs that could contribute to blunted response bias—a reduced hedonic responsiveness to reward vs. preserved hedonic responsiveness but reduced ability to learn from reward.

Despite these significant strengths and high degree of conceptual and methodological innovation, the study had some limitations. First, relative to the original sample ($N = 89$), only a smaller subsample had PRT data at both sessions ($N = 55$). Although the medium-to-large effect sizes we observed speak against low power, it will be important to replicate the current findings in larger samples. Second, the smaller size for the subsample with usable PRT data led to unexpected group differences in baseline SHAPS scores before the randomization not seen in the total study sample, which required that all analyses controlled for pretreatment SHAPS scores. Third, in the original analyses [49], we had hypothesized that the *Time* × *Treatment Arm* × *Block* interaction would be significant, driven by significant posttreatment group differences in the change in response bias from block 1 to block 2. In retrospect, this assumption was ill informed given the implementation of a version of the PRT that included only two blocks instead of the usual three blocks (in order to decrease patients' burden). Based on similar experiences in other large studies using a 2-block version of the PRT [74, 75], we believe that the average response bias across the two blocks (rather than the difference between block 1 and 2) is a better metric for PRT studies unable to implement three blocks. Finally, the lack of a psychiatrically healthy control group prevented us to test whether the KOR antagonist normalized reward learning to the level of healthy controls.

These limitations notwithstanding, the current findings provide novel evidence that, relative to placebo, KOR antagonism was associated with better ability to learn from reward feedback and express a behavioral preference toward a more advantageous stimulus, which overall points to better ability to integrate reinforcement over time. Moreover, we were able to confirm that the recently reported effects on response bias [49] remained when controlling for baseline anhedonia. Thus, the findings of this study build on our prior study [49] and strengthen the evidence that KOR antagonism has a therapeutic effect on a behavioral test reflecting a dimension of anhedonia, reward learning. They also increase the precision of the identification of the reward subdomains that are ameliorated by KOR antagonism. Together with the clinical outcome and fMRI data confirming target engagement, the current findings speak for further investigations of KOR antagonism for addressing the unmet needs associated with anhedonia across neuropsychiatric disorders.

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ADDITIONAL INFORMATION

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Supplementary Material

Selective Kappa Opioid Antagonism Ameliorates Anhedonic Behavior: Evidence From the Fast-Fail Trial in Mood and Anxiety Spectrum Disorders (FAST-MAS)

Supplemental Methods

Participants

Participants were recruited at six centers in the United States (Duke University, Yale University, Icahn School of Medicine at Mount Sinai, Baylor College of Medicine, Indiana University, and Case Western Reserve University) between September 2015 and October 2017. The study was approved by each local IRB board.

Quality Control (QC) cutoff for PRT data

QC used predefined cutoffs and was performed blindly to group assignment. Data were excluded if any of the following criteria was met:

1) <80 valid trials per block (i.e., >20% outlier RT). Outlier RTs were defined in two steps:
    a. RT <150 ms or >2,500 ms; and
    b. log-transformed RT exceeding the participant's mean ± 3SD (after removal of outlier responses identified in step 1a).
2) <20 rich rewards or <6 lean rewards per block;
3) <2.0 rich-to-lean reward ratio per block.

Patients included vs. excluded from the PRT analyses due to QC evaluations did not differ in their pre-treatment SHAPS scores (34.89±7.44 vs. 35.03±7.58, $t(85)=0.08$, $p>0.93$).

Computational modeling

Based on prior work [1,2], we fitted a series of reinforcement-learning models to the PRT choice data (for the complete mathematical formulas of each model, the interested reader is referred to ref. [2]). The first model, 'Belief', evaluated whether patients associated rewards with a mixture of two stimulus-action associations weighted by an uncertainty factor. Another model, 'Stimulus-Action', assumed that participants treated both stimuli as entirely separate and associated rewards with

stimulus-action pairs. The third model, 'Action', proposed that patients neglected the stimuli and learned only the values of actions when forming expectations. Finally, the 'Punishment' model tested whether participants treated zero reward as aversive losses. Following previously established procedures [2], the models were fitted using an empirical Bayesian random-effects approach and contrasted using integrated group-level BIC factors. All data were fitted at once, implying that individual patient's parameter inference was constrained by an empirical prior distribution. The 'Action' model gave the most parsimonious account of the data (group-level log Bayes factor compared to the second-best model = 84, which represents very strong evidence in favor of the better fitting model). Using this approach, we estimated two main parameters, *reward sensitivity* (which measured the immediate behavioral impact of rewards) and learning rate (which captured the ability to accumulate rewards over time and thus to learn from the rewards).

These parameters can be parsed using a mathematical formulation of reward learning based on prediction errors that have been linked to dopaminergic activity [3–5]. Specifically, let us consider an experiment in which a reward is given stochastically on some trials, with rt = 1 when a subject received a reward in trial t, and rt = 0 if no reward was given. The value the subject assigns to the reward is ρ. In this conceptualization, a subject maintains an expectation (Q_t) of the average reward it might gain on a given trial, by means of a prediction error, which represents the difference $\delta t = \rho rt - Q_t$ (i.e., the difference between the obtained ρrt and expected Qt reward). This prediction error is used to adjust expectations [6] according to the formula $Q_{t+1} = Qt + \varepsilon\delta_t$, where $0 \leq \varepsilon \leq 1$ is a learning rate. Thus, two parameters - ρ and ε - could contribute to anhedonic behavior. The larger is ρ, the more sensitive a subject is to the reward (i.e., the greater the internal worth of an external reward or the greater the reward sensitivity). In contrast, ε determines the extent to which reward prediction errors affect learning, specifically the speed at which reward affects behavior [7]. Accordingly, a low learning rate reflects a relatively small impact of the prior reward feedback on the current decision, whereas a higher ε points to a larger impact of reward feedback.

Supplementary Results

<u>Relations among changes in computational modeling parameters, response bias and SHAPS scores</u>

Across both groups, changes from pre- to post-treatment learning rates were significantly correlated with pre- to post-treatment changes in response bias, $r(55)=0.55$, $p<0.00001$ (**Supplemental**

Figure 2) but not SHAPS scores, r(55)=-0.15, p>0.14. Pre- to post-treatment changes in reward sensitivity did not correlate with changes in response bias or SHAPS scores (*Supplementary Table 1*).

Accuracy and reaction time analyses

Accuracy: The *Time* x *Block* x *Treatment Arm* x *Stimulus* (rich, lean) ANCOVA (covariate: pre-treatment SHAPS scores] revealed a significant main effect of *Stimulus* [F(1,52)=9.43, p=0.003, ηp^2=0.154], driven by significantly higher accuracy for the rich vs. lean stimulus (0.739±0.076 vs. 0.629±0.104). Critically, this effect was qualified by a significant *Time* x *Stimulus* x *Treatment Arm* interaction [F(1,52)=4.97, p=0.030, ηp^2=0.087]. This 3-way interaction was followed up by examining the *Time* x *Treatment Arm* interaction separately for rich and lean accuracy (entering the mean accuracy across blocks 1 and 2 as the dependent variable). For rich accuracy, the *Time* x *Treatment Arm* interaction was significant [F(1,52)=13.40, p=0.001, ηp^2=0.205]. Bonferroni-corrected post hoc tests of simple effects indicated that relative to the placebo group, the KOR group had significantly higher rich accuracy at post-treatment (p=0.002; Cohen's d: 0.88) but not at pre-treatment (p=0.50) (**Supplemental Figure 3A**). Critically, the KOR group showed a significantly increase in rich accuracy from pre- to post-treatment (p=0.026), whereas the placebo group showed a significant reduction in rich accuracy from pre- to post-treatment (p=0.003). On an individual level, 17 of the 24% KOR participants (70.8%; binomial p(17/24)=0.021), but only 11 of the 31 placebo participants (35.5%; binomial p(11/31)=0.039; (χ2= 3.32, df=1, p=.068). Highlighting the specificity of these findings, an analogous ANCOVA on lean accuracy revealed no effects involving *Treatment Arm* (all Fs<0.22, all ps>0.64) (**Supplemental Figure 3B**).

Reaction Time: The *Time* x *Block* x *Treatment Arm* x *Stimulus* (rich, lean) ANCOVA revealed a significant main effect of *Stimulus* [F(1,52)=5.19, p=0.027, ηp^2=0.091], which, as expected, was due to significantly faster RT to the rich relative to the lean stimulus (588.078±104.57 vs. 609.735±111.14 ms). Furthermore, a significant *Stimulus* x *Treatment Arm* interaction emerged [F(1,52)=10.89, p<0.001, ηp^2=0.173]. Bonferroni-corrected post hoc tests of simple effects indicated, however, no overall group differences for RT to the rich or lean stimulus (all ps>0.13). In addition, a significant *Time* x *Treatment Arm* interaction emerged [F(1,52)=6.75, p<0.012, ηp^2=0.115]. Bonferroni-corrected post-hoc tests indicated that at post-treatment (p=0.016) – but not pre-treatment (p=0.91) – the placebo group had overall (averaged across the rich and lean stimulus) faster RT (544.45±118.24 vs.626.70±118.88 ms).

Control analyses

Reward ratio: Given that response bias is directly related to the asymmetrical reinforcement schedule, control analyses were performed to confirm that the two groups did not differ in the ratio of rich-to-lean rewards received across blocks. A *Time* x *Block* x *Treatment Arm* ANCOVA on these ratios confirmed that the main effect of *Treatment Arm* was non-significant, $F(1,51)=0.41$, $p>0.52$ and no significant interactions emerged (all $Fs<3.82$, all $ps>0.057$). Groups were exposed to very similar rich-to-lean reward ratios that mirrored the intended 3:1 ratio at both the pre-treatment (KOR: 2.94±0.14 vs. placebo: 2.98±0.14) and post-treatment (KOR: 3.00±0.16 vs. placebo: 2.92±0.16) session.

Discriminability: The *Time* x *Block* x *Treatment Arm* ANCOVA on discriminability scores revealed no effects involving *Treatment Arm* (all $Fs<3.69$, $ps>0.060$), indicating that task difficulty did not differ between the two groups.

Exploratory analyses within MDD subsample

Thirty-four patients (i.e., 60.7% of the sample) had a primary diagnosis of MDD (KOR: n=16; placebo: n=18). Exploratory analyses were performed to evaluate whether the main effects were confirmed within this subsample (we thank an anonymous reviewer for this suggestion). Results showed that, for both response bias [$F(1,31)=0.89$, $p>0.35$] and learning rate [$F(1,31)=2.14$, $p>0.0.15$], the *Time* x *Treatment Arm* interaction was not significant, likely due to loss of statistical power (since 40% of the sample without a primary MDD diagnosis was omitted from these sub-analyses). When considering probability of rich hit rates, the *Time* x *Treatment Arm* interaction was confirmed [$F(1,31)=6.16$, $p<0.020$, $\eta p^2=0.166$]. Owing to the small sample sizes involved in these exploratory analyses, these findings are not further interpreted.

Supplemental References

1. Webb CA, Dillon DG, Pechtel P, Goer FK, Murray L, Huys QJQJM, et al. Neural correlates of three promising endophenotypes of depression: Evidence from the EMBARC study. Neuropsychopharmacology. 2016;41:454–463.
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5. Montague PR, Dayan P, Sejnowski TJ. A framework for mesencephalic dopamine systems based on predictive Hebbian learning. J Neurosci. 1996;16:1936–1947.

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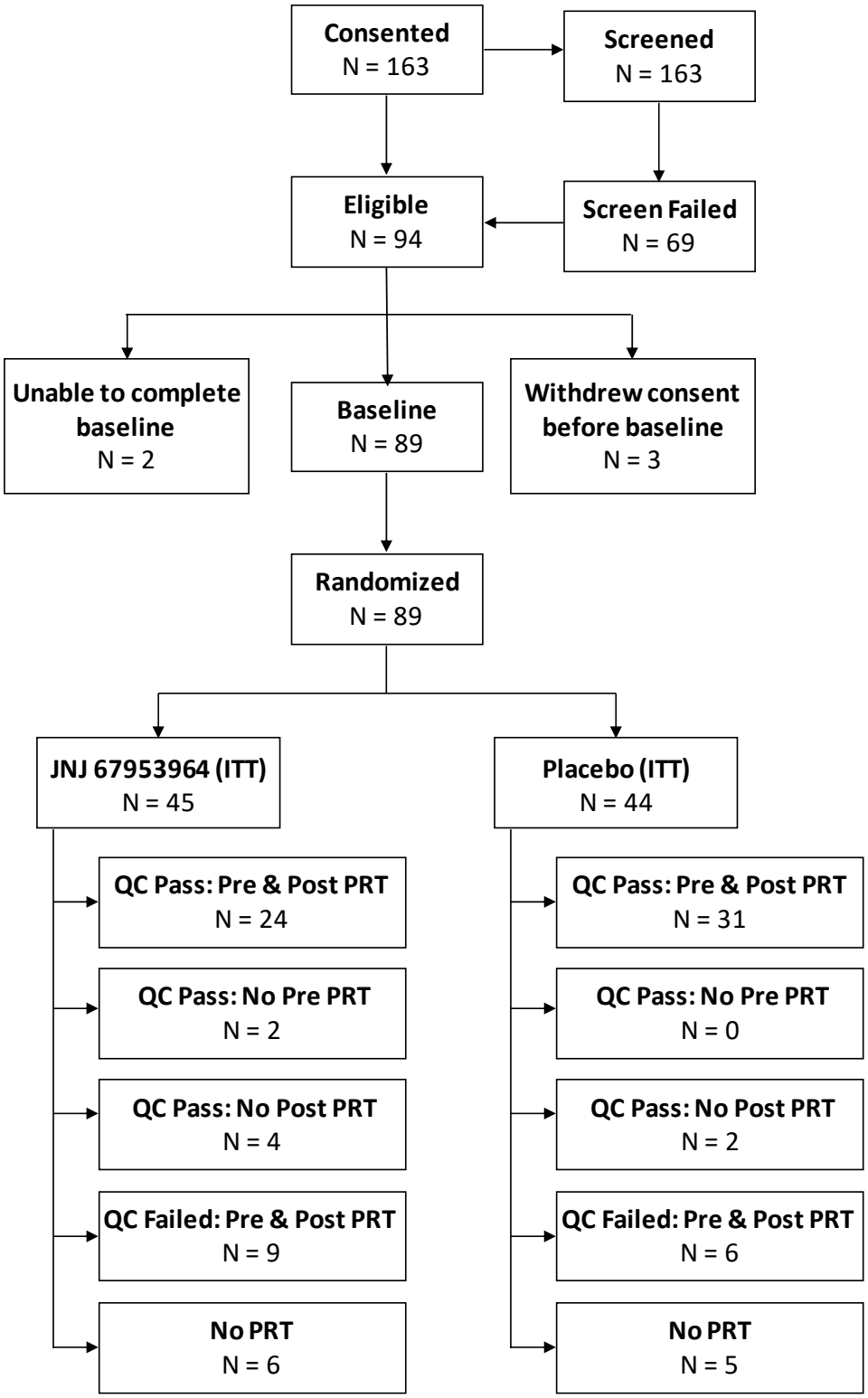
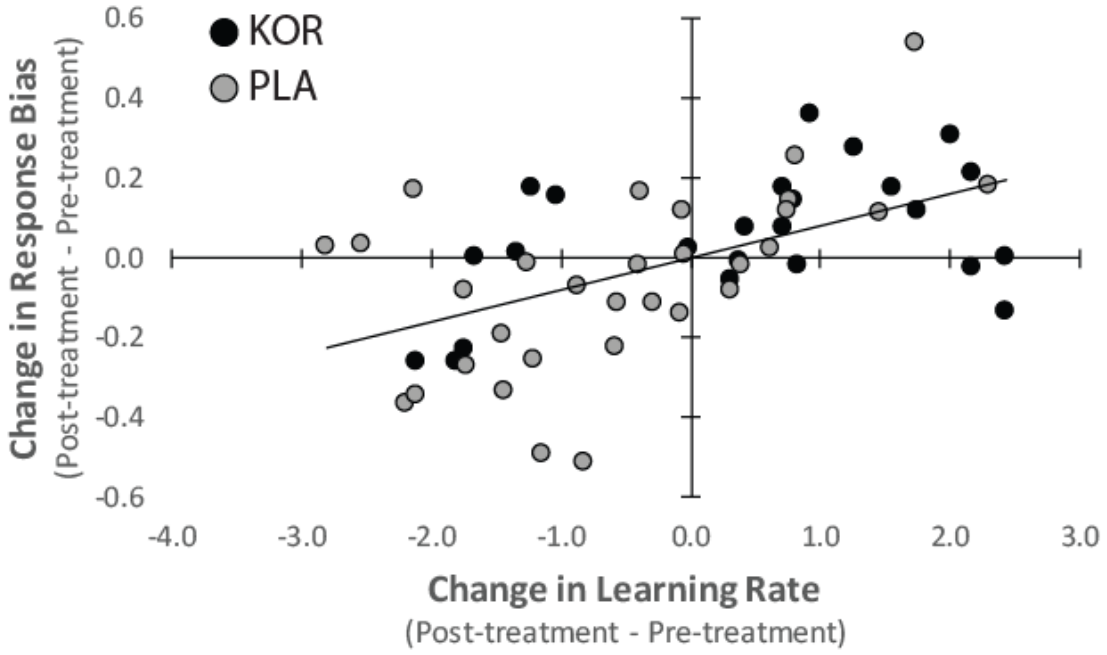
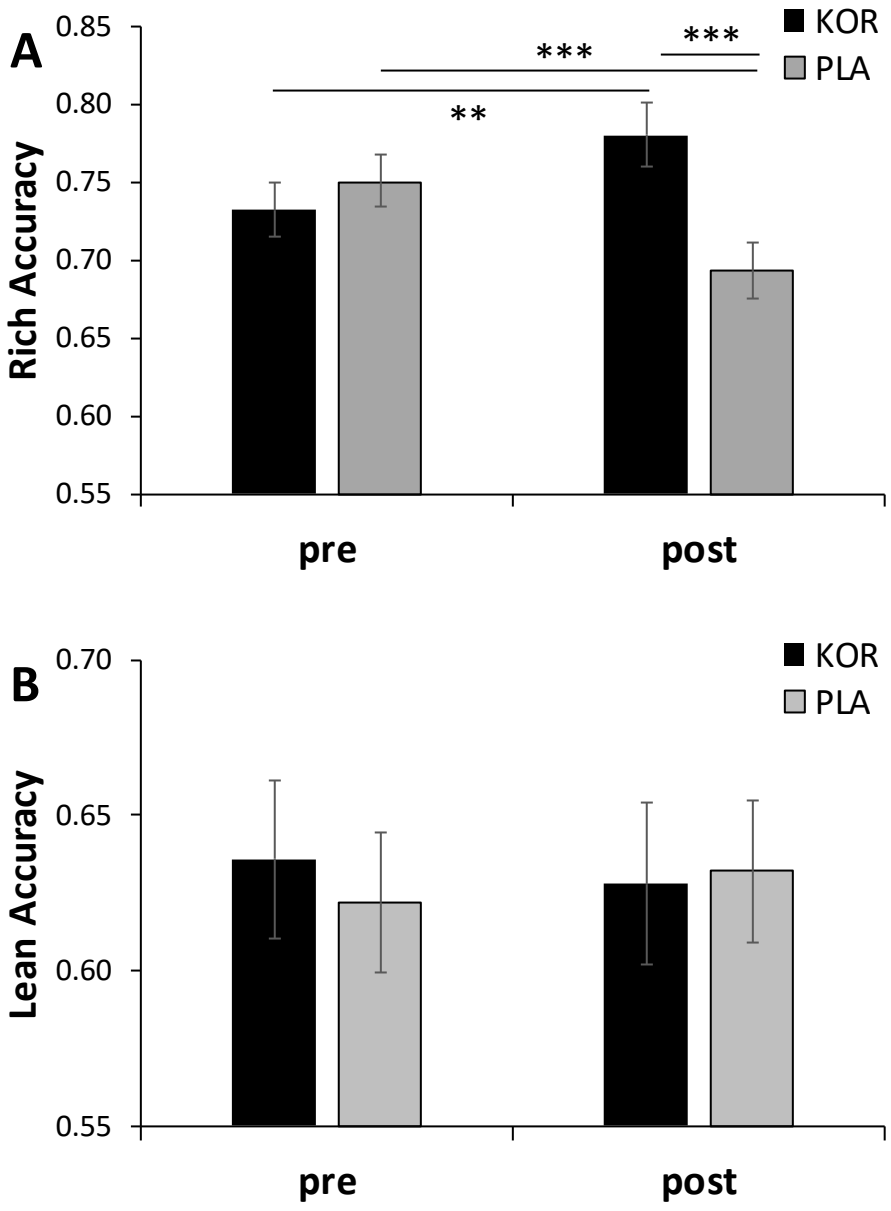
Supplemental Figure 1



Supplemental Figure 2: Scatterplot and Pearson correlation ($r(55)=0.55$, $p<0.00001$) between pre- to post-treatment change in learning rate and response bias across groups.



Supplemental Figure 3: (A) Rich accuracy, and **(B)** Lean accuracy in the KOR (n = 24) and placebo (N = 31) group pre- and post-treatment. Error bars denote standard errors. Estimated means are plotted (covariate: pre-treatment SHAPS scores). KOR = Kappa Opioid Antagonist group; PLA = placebo group; *** $p < 0.01$, ** $p < 0.05$



Supplemental Table 1: Inter-relations (Pearson correlations) among pre- to post-treatment changes (post-treatment minus pre-treatment) in response bias, anhedonic scores (as assessed by SHAPS scores), reward sensitivity and learning rate. [a]Derived from computational modeling

	Response Bias	**SHAPS scores**	**Reward Sensitivity[a]**	**Learning Rate[a]**
Response Bias	1	*r* = -0.09 *p* = .53 *n* = 51	*r* = 0.08 *p* = .56 *n* = 55	*r* = 0.55 *p* < .0001 *n* = 55
SHAPS scores		1	*r* = -0.04 *p* = .77 *n* = 51	*r* = -0.15 *p* = .31 *n* = 51
Reward Sensitivity			1	*r* = -0.04 *p* = .80 *n* = 55
Learning Rate				1