TITLE: A tale of two receptors: simultaneous targeting of NMDARs and 5-HT_4Rs exerts additive effects against stress

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ABSTRACT

BACKGROUND: Serotonin (5-HT) receptors and *N*-methyl-D-aspartate receptors (NMDARs) have both been implicated in the pathophysiology of depression and anxiety disorders. Here, we evaluated whether targeting both receptors through combined dosing of (*R*,*S*)-ketamine, an NMDAR antagonist, and prucalopride, a serotonin type IV receptor (5-HT_4R) agonist, would have additive effects, resulting in reductions in stress-induced fear, behavioral despair, and hyponeophagia.

METHODS: A single injection of saline (Sal), (*R*,*S*)-ketamine (K), prucalopride (P), or a combined dose of (*R*,*S*)-ketamine and prucalopride (K+P) was administered before or after contextual fear conditioning (CFC) stress in both sexes. Drug efficacy was assayed using the forced swim test (FST), elevated plus maze (EPM), open field (OF), marble burying (MB), and novelty-suppressed feeding (NSF). Patch clamp electrophysiology was used to measure the effects of combined drug on neural activity in hippocampal CA3. c-fos and parvalbumin (PV) expression in the hippocampus (HPC) and medial prefrontal cortex (mPFC) was examined using immunohistochemistry and network analysis.

RESULTS: We found that a combination of K+P, given before or after stress, exerted additive effects, compared to either drug alone, in reducing a variety of stress-induced behaviors in both sexes. Combined K+P administration significantly altered c-fos and PV expression and network activity in the HPC and mPFC.

CONCLUSIONS: Our results indicate that combined K+P has additive benefits for combating stress-induced pathophysiology, both at the behavioral and neural level. Our findings provide preliminary evidence that future clinical studies using this combined

treatment strategy may prove advantageous in protecting against a broader range of stress-induced psychiatric disorders.

INTRODUCTION

Affective disorders are among the leading causes of global disease burden and have significantly increased in prevalence since the start of the COVID-19 pandemic (1). It is estimated that in 2020 alone, there was a 27.6% global increase in major depressive disorder (MDD) as well as an additional 25.6% surge in anxiety disorders. These rising numbers underscore the need for more effective prevention and treatment options for stress-related psychiatric disorders.

Current first-line treatments for anxiety and depression, such as selective serotonin reuptake inhibitors (SSRIs), largely modulate serotonergic signaling in the brain. Discovered several decades ago, the efficacy of SSRIs in reducing depressive symptoms significantly contributed to the monoamine hypothesis of mood disorders (2). This hypothesis suggests that antidepressants exert their efficacy by increasing the extracellular availability of monoaminergic neurotransmitters, including serotonin. Although SSRIs broadly increase serotonergic tone, emerging evidence suggests that specifically activating serotonin type IV receptors (5-HT_4Rs) can provide more immediate, efficacious therapeutic benefits (3). In preclinical models, 5-HT_4R agonists rapidly suppress behavioral despair, anhedonia, and anxiety-like behavior (4–6). Moreover, 5-HT_4R agonists have been shown to enhance resilience to stress (7). Despite these promising data, to date, SSRIs such as fluoxetine and sertraline remain the first-line treatment strategy for depression and anxiety. Nonetheless, despite the ubiquity of SSRIs, issues such as nonspecific side effects, and lack of efficacy in patients suffering from treatment-resistant depression (TRD) have led many

researchers to search for alternative theories to the monoamine hypothesis of mood disorders.

Alternatively, the glutamatergic hypothesis of depression has emerged as a leading hypothesis for affective disorders. This theory proposes that depressive and anxiogenic states arise from an imbalance of excitatory and inhibitory neurotransmission, potentially due to the abnormal activity of *N*-methyl-D-aspartate receptors (NMDARs) or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) (8–10). The glutamatergic hypothesis is strongly supported by the discovery that (*R,S*)-ketamine (K), an NMDAR antagonist, exerts rapid-acting antidepressant effects in as little as two hours, relieves symptoms of depression for up to three weeks, and is effective in treating TRD (11–14). Esketamine, a stereospecific enantiomer of K, recently became the first novel antidepressant approved by the FDA in nearly 20 years (15–19). Our lab and others have shown that K can be administered prior to stress to prevent the onset of stress-induced behavioral despair and decrease learned fear (20–25). Moreover, we have also demonstrated that fluoroethylnormemantine (FENM), a novel NMDAR antagonist, can also be effective when administered prior to or after stress (26,27). Together, these data strongly suggest that targeting NDMARs can be an effective treatment strategy for stress-related psychiatric disorders. However, although NMDAR antagonists exert demonstrated antidepressant effects, their utility in reducing anxiety-like behavior is limited (28).

Here, we sought to determine whether simultaneously targeting NMDARs and 5-HT_4Rs could be effective in suppressing a wide variety of stress-induced fear, behavioral despair, and anxiety-like behaviors. A single injection of Sal, K, prucalopride

(P), or combined K+P at different dosage combinations was administered prior to or after CFC stress. A single combinatorial dose of K+P, given before or after stress, exerted additive effects in reducing a variety of stress-induced behaviors in both sexes. Combined K+P administration attenuated bursts of AMPAR-mediated excitatory post-synaptic currents (EPSCs) in hippocampal CA3 and selectively altered correlated c-fos and parvalbumin (PV) network activity in the medial prefrontal cortex (mPFC) and hippocampus (HPC). Together, these results indicate that combined K+P exerts additive behavioral and neural effects compared to administration of either drug alone, suggesting that combinatorial pharmacological treatments to simultaneously target NMDARs and 5-HT_4R may provide additional anxiolytic effects for further preclinical and clinical study.

METHODS AND MATERIALS

For a full description of Methods and Materials, please refer to the **Supplemental Methods** in **Supplement 1**.

Drugs

A single injection of saline (0.9% NaCl), (*R,S*)-ketamine (Ketaset, Zoetis, Parsippany-Troy Hills, NJ), prucalopride (SML1371, Sigma-Aldrich, St. Louis, MO), or combined (*R,S*)-ketamine + prucalopride was administered once during the course of each experiment at approximately eight weeks of age. All drugs were prepared in physiological saline and administered intraperitoneally (i.p.) in volumes of 0.1 cc per 10 mg body weight.

RESULTS

Prophylactic (*R*,*S*)-ketamine + prucalopride exerts additive anxiolytic effects in male and female mice

We previously reported that K, an NMDAR antagonist, and P, a 5-HT_4R agonist, are effective prophylactics against stress (7,23,27). Although both compounds attenuate learned fear and reduce behavioral despair, neither drug has previously been shown to affect perseverative behavior, exploratory behavior, or hyponeophagia. Here, we hypothesized that combined K+P administration may result in additive behavioral effects. Male mice were injected with Sal, K, P, or combined K+P. One week later, mice were administered 3-shock CFC followed by behavioral testing (**Figure 1A**).

All groups had comparable freezing during CFC training (**Figure 1B**). During re-exposure, K (30 mg/kg), P (3 mg/kg), or K+P (10 + 3 mg/kg), but no other doses, were effective at decreasing fear behavior when compared with Sal (**Figure 1C**). On day 2, but not on day 1 of the FST, K (30 mg/kg), P (3 mg/kg), or K+P (10 + 3 mg/kg and 30 + 10 mg/kg) decreased immobility time when compared with Sal (**Figure 1D-1E**).

Behavior was comparable across all groups in the OF and EPM (**Figure 1F-1G**) In the NSF, our prior work indicated that K and P separately were not effective at reducing hyponeophagia (7, 21, 25). However, combined K+P (10 + 3 mg/kg) decreased the latency to feed in the OF when compared with Sal without altering other measures of appetite or motivation (**Figure 1H-1K**). These data indicate that the combined K+P has a synergistic effect of decreasing stress-induced hyponeophagia in male mice with the additional effect of decreasing the dose of K needed to attenuate fear expression (i.e., 30 versus 10 mg/kg when combined with P).

To determine whether combined K+P, could have additive prophylactic effects in females, we administered the same injection and behavioral schedule to female mice as outlined in **Figure 1,** with the exception that the dose of K and P was chosen based on prior studies in female 129S6/SvEv mice (**Figure 2A**) (7,23). All groups had comparable freezing during CFC training and re-exposure (**Figure 2B**-**2C**). On day 1 of the FST, K (10 mg/kg), P (3 mg/kg), or combined K+P (10 + 1.5 mg/kg) reduced immobility time (**Figure 2D**). On day 2 of the FST, K (10 mg/kg), P (1.5 and 3 mg/kg), or combined K+P (10 + 1.5 mg/kg) reduced immobility time (**Figure 2E**). Behavior was comparable across all groups in the OF (**Figure 2F**). In the EPM, P (3 mg/kg) increased time in the open arms (**Figure 2G**). In the NSF, our prior work indicated that the $5HT_4R$ agonist RS-67,333 was effective at reducing hyponeophagia in female 129S6/SvEv mice, but we have not yet previously tested if P was also effective at reducing hyponeophagia in female 129S6/SvEv mice. Here, only combined K+P (10 + 1.5 mg/kg) reduced the latency to feed in the OF without altering body weight loss or behavior in the home cage (**Figure 2H**-**2K**). These data indicate that combined K+P has an additive effect in reducing stress-induced hyponeophagia in female mice.

Prophylactic (*R,S*)-ketamine + prucalopride facilitates contextual fear discrimination in male, but not female mice

We previously demonstrated that prophylactic administration of K facilitates and enhances CFD in in male mice (29). However, it is still unknown whether our combined K+P findings extend to other models of stress. Here, we administered Sal, K, P, or K+P one week prior to a CFD paradigm in male and female 129S6/SvEv mice (**Figure S1A**).

In male mice, combined K+P accelerated CFD (**Figure S1B-S1I**). Specifically, only mice administered combined K+P could discriminate between the contexts on day 4 of the CFD paradigm (**Figure S1G**). In female mice, K and P both accelerated CFD, but not when administered as combined K+P (**Figure S1J-S1Q**). All mice discriminated by day 10 of the CFD paradigm. In summary, these data suggest that combined K+P administration can slightly facilitate fear discrimination in male, but not female mice.

(*R*,*S*)-ketamine + prucalopride reduces perseverative behavior and hyponeophagia in non-stressed female, but not male mice

To determine whether combined K+P alters behavior in non-stressed mice, we administered Sal, K, P, or K+P and then administered the FST 1 hour later (**Figure S2A**). In male mice, immobility time was not attenuated by drug administration (**Figure S2B-S2E**). In female mice, overall, but not average, immobility time on both Days 1 and 2 was increased by K+P administration (**Figure S2F-S2I**).

Next, we tested whether combined K+P alters exploratory, perseverative, or hyponeophagia behaviors in non-stressed mice. Sal, K, P, or K+P was administered one hour prior to the OF. The EPM, MB, and NSF assays were administered on subsequent days (**Figure S3A**). In male mice, behavior in the OF, EPM, MB, and NSF was not significantly altered by drug administration (**Figure S3B-S3I**). In female mice, P significantly increased locomotion in the OF when compared to Sal (**Figure S3J-S3K**). Behavior in the EPM was comparable across all drug groups (**Figure S3L-S3M**). In the MB assay, mice administered K+P buried significantly fewer marbles compared to mice administered Sal (**Figure S3N**). In the NSF assay, combined K+P reduced the latency

to feed in the OF without altering the latency to feed in the home cage (**Figure S3O-S3Q**). These results indicate that combined K+P reduces perseverative behavior and hyponeophagia in non-stressed female, but not male mice.

Prophylactic (*R*,*S*)-ketamine + prucalopride attenuates AMPAR-mediated bursts of excitatory activity in hippocampal CA3

We previously demonstrated that prophylactic drugs, including K and P, diminish large-amplitude AMPAR-mediated excitatory post-synaptic currents (EPSCs) (7,23,27). Here, we hypothesized that combined K+P would also inhibit AMPAR bursting. Sal or combined K+P was administered and one week later, mice were sacrificed, and patch clamp electrophysiology was performed in hippocampal CA3 (**Figure 3A**). While Sal-administered mice exhibited bursts of large-amplitude AMPAR-mediated EPSCs (**Figure 3B-3C**), K+P-administered mice did not exhibit these AMPAR bursts in CA3 (**Figure 3E-3F**). Combined K+P administration led to a decrease in mean EPSC amplitude (**Figure 3D**) as well as a trending, but not significant reduction in the number of EPSCs (**Figure 3G**). Together, these data show that, similarly to administration of K or P alone, combined K+P also inhibits large-amplitude bursts of AMPAR-mediated excitatory activity in hippocampal CA3.

Prophylactic (*R*,*S*)-ketamine + prucalopride selectively reduces excitatory signaling in mPFC and HPC

Our lab has previously reported that prophylactic K administration upregulates c-fos expression in vCA3 during CFC re-exposure (29). Here, we hypothesized that

combinatorial K+P administration could alter neural signaling along the dorsoventral axis of the HPC as well as in the mPFC, a functionally connected downstream brain region that, along with the HPC, regulates memory encoding, memory retrieval, emotional processing, and the stress response (30–32). Male mice were administered Sal, K, P, or K+P and 1 week later, administered CFC and the FST. One hour later, mice were sacrificed, and brains were processed for c-fos immunoreactivity (**Figure 4A-4B**). As previously demonstrated, K, P, and K+P significantly attenuated learned fear and behavioral despair in male mice **(Figure S4A-S4D**).

Heatmap correlations between selected brain regions revealed an increase in negative correlations in P- and combined K+P-administered mice when compared with saline mice (**Figure 4C-4F**). Using volcano and parallel plots, we confirmed this increase in negative correlations (**Figure 4G-4K, S4E-S4J**). Notably, vCA3 to dDG was the only significantly negative correlation in mice given combined K+P **(Figure 4K**).

We then aimed to determine the functional consequences of altered c-fos expression in the mPFC and HPC. First, we generated cluster network maps to visualize functionally connected subregions of the HPC and mPFC during FST Day 2 (**Figure 4L-4M, 4O-4P**). In mice administered combined K+P, vHPC was disconnected from other regions, but there was interconnectivity within mPFC and within dHPC. This isolation of the vHPC was not observed in Sal mice or in K- or P-administered mice. Next, using a bootstrap prediction analysis, we aimed to identify the regions contributing most to immobility during FST Day 2 (**Figure 4N**). In Sal-administered mice, vCA3 and vCA1 contributed most to immobility time. dCA1 and vCA3 contributed most in K-administered mice, while vCA3 and ACA contributed most to immobility in P-

administered mice. In combined K+P-administered mice, vCA1 and vDG gave the greatest contributions to immobility time. These data establish vHPC as a critical modulator of stress-related behavior in the FST.

Next, we modeled the data as a network, with regions acting as nodes and correlations functioning as edges, then used network analysis to assess circuit-level connectivity during day 2 of the FST (**Figure 5A-5D**). Combined K+P resulted in a sparser network when compared to the three other groups (**Figure 5D**), suggesting a refinement in functionally connected excitatory activity in mice administered combined drug. Interestingly, in experimental drug groups, there was an enhancement of interconnectivity within mPFC subregions, particularly between ACA and ILA. K, but not any other drug, significantly increased mean degree, global efficiency, and distance of the network when compared with control saline (**Figure 5E-5F, 5I**). Mean clustering coefficient and betweenness centrality was comparable across all drug groups (**Figure 5G-5H**). Interestingly, combined K+P, but not K or P alone, significantly increased c-fos expression across the mPFC as well as in dCA3, dCA1, and vCA3 (**Figure 5J-5O**). These results suggest that combined K+P significantly increases excitatory activity in mPFC and HPC.

Prophylactic (*R*,*S*)-ketamine + prucalopride selectively enhances inhibitory signaling in mPFC and HPC

To better understand how inhibitory signaling is altered by drug administration, we examined expression of PV, a calcium-binding protein that is expressed in fast-spiking inhibitory interneurons, because it plays a critical role in modulating neural activity, and

because its expression is sensitive to stress and antidepressant administration (33–35). First, we examined heatmap correlations of PV expression in the mPFC, dHPC, and vHPC followed by volcano and parallel plots (**Figure 6A-6D, S5A-S5K**). Combined K+P significantly increased positively correlated PV expression (**Figure 6D**), particularly between vCA1 and vDG as well as vDG and dCA1 (**Figure S5E**). We then used cluster network maps to reveal functionally correlated PV expression across brain regions (**Figure S5L-S5O**). Combined K+P, in comparison to Sal, enhanced functional connectivity between a majority of dHPC and vHPC regions (**Figure S5L, S5O**). Interestingly, ILA and vCA3 were functionally isolated from other areas of the brain.

Subsequently, we modeled correlated PV expression as an inhibitory network, with the regions as nodes, and correlated expression as edges (**Figure 6E-6H**). Mice administered combined K+P showed an increase in correlated inhibitory expression across the HPC when compared with Sal; in particular, mPFC regions were isolated from both dorsal and ventral HPC regions. Computed network measures showed that mean degree was comparable across all groups (**Figure S5P**). Global efficiency, mean betweenness centrality, and distance measures were significantly increased in P-administered mice, and mean clustering coefficient was significantly reduced in K-administered mice (**Figure S5Q-S5T**). Interestingly, when looking at PV expression across the mPFC and the HPC, combined K+P selectively increased the number of PV cells in vCA3, but not in any other subregion (**Figure 6L-6N**). These data suggest that although combined K+P may enhance PV expression in a select subregion of the vHPC, it may still enhance correlated inhibitory tone throughout the mPFC and HPC.

Prophylactic (*R*,*S*)-ketamine + prucalopride increases c-fos and PV co-localization in the mPFC and vCA3

Finally, we examined co-expression of c-fos and PV in the mPFC and HPC (**Figure 6I-6K**). Across all subregions of the mPFC, combined K+P increased the number of PV^+/c-fos^+ cells when compared to Sal (**Figure 6O**). In the dHPC, all groups exhibited comparable levels of PV^+/c-fos^+ cells (**Figure 6P**). In the vHPC, only combined K+P significantly increased the number of PV^+/c-fos^+ cells in vCA3, but not in the vDG or vCA1 (**Figure 6Q**). These data suggest that simultaneous targeting of the NMDAR and 5-HT_4R increases the activity of PV^+ cells in the mPFC and vCA3.

Combined (*R*,*S*)-ketamine + prucalopride is effective when administered after stress

Recently, we demonstrated that administration of an NMDAR antagonist after stress prevents stress-induced behavioral despair in male and female mice (27). To test whether simultaneously targeting NMDARs and $5HT_4$Rs could also be protective when administered following stress, we administered a single dose of Sal, K, P, or K+P five minutes after CFC (**Figure 7A**).

In male mice, combined K+P, but not single drug administration alone, significantly decreased learned fear (**Figure 7B-7C**), behavioral despair on day 2, but not day 1 of the FST (**Figure 7D-7G**), and hyponeophagia (**Figure 7H-7I**). Of note, combined K+P did not affect behavior in the OF, EPM, or other measures during the NSF (**Figure S6A-S6L**).

In female mice, combined K+P did not alter learned fear (**Figure 7J-7K**). On days 1 and 2 of the FST, combined K+P decreased behavioral despair (**Figure 7L-7O**). In the NSF, combined K+P decreased hyponeophagia (**Figure 7P-7Q**). Of note, combined K+P administration did not affect behavior in the OF, EPM, or other measures during the NSF (**Figure S6M-S6X**). Overall, these data indicate that combined K+P is effective in preventing a variety of stress-induced behaviors in male and female mice when administered after stress.

DISCUSSION

Here, we characterized the behavioral and neural effects of combined K+P administration. We discovered that simultaneous targeting of NMDARs and 5-HT_4Rs prior to or after stress exerts additive protective effects against stress-induced behaviors in male and female mice. Combined K+P, but not either drug administered alone, significantly enhanced c-fos and PV expression in the mPFC and select regions of the HPC. Overall, our results suggest that the simultaneous targeting of NMDARs and 5-HT_4Rs using a K+P drug combination exerts additional and distinct neural and behavioral benefits compared to administration of a single drug.

To our knowledge, combinatorial targeting of NMDARs and 5-HT_4Rs has not previously been studied; clinical studies have shown that adjunctive administration of Spravato® in addition to continued SSRI treatment is an effective therapeutic strategy for patients suffering from TRD and suicidal ideation (15–18). Thus, implementing combined drug administration in the clinic is a tractable and applicable method of treatment for patients suffering from psychiatric disorders. Behaviorally, we found that combined K+P was effective in reducing hyponeophagia in both male and female mice. These results are critical, as they indicate that simultaneously targeting NMDARs and 5-HT_4Rs can suppress a larger variety of anxiety-related phenotypes compared to targeting either receptor alone. In particular, the NSF assay is a measure of the degree to which stress (e.g., a novel environment) can affect feeding behavior and is purported to quantify hyponeophagia (36,37). Our data suggest that although K and P are not reported to affect clinical symptoms of anxiety, when combined, they may be an effective treatment option for further study (28,38).

We demonstrated a strong dose specificity of the K+P combination. Although we initially hypothesized that combining the behaviorally-effective doses of (*R,S*)-ketamine (30 mg/kg in male mice or 10 mg/kg in female mice) and prucalopride (3 mg/kg in male mice or 1.5 mg/kg in female mice) would exhibit the strongest behavioral effect, our experiments indicated that the most effective dose was 10 mg/kg of (*R,S*)-ketamine combined with 3 or 1.5 mg/kg of prucalopride in male or female mice, respectively. This unexpected result shows that there is a specific drug concentration sufficient to both block NMDARs and activate 5-HT_4Rs to an optimal degree. Our data suggest that combined K+P may have an inverted U-shaped dose-effect curve that is common in many active compounds (39). Further experimentation may shed light on this phenomenon by testing a greater range of K+P doses and examining potential mechanisms contributing to the drug combination's dose-specific effect.

Previously, we have demonstrated that a variety of prophylactic drugs, including NMDAR antagonists and 5-HT_4R agonists, block bursts of large-amplitude AMPAR-mediated EPSCs in CA3 (7,23,27). Our results indicate that combined K+P administration also attenuates AMPAR-mediated bursts of activity in CA3. The spontaneous firing and large amplitude of these AMPAR-mediated bursts closely resemble the characteristic features of hippocampal sharp wave activity (SPW), which plays an important role in memory formation and sleep (40–43). Sharp wave ripples (SPW-Rs) emerge from the combined synchronous activity of a small subset of excitatory pyramidal cells and inhibitory interneurons, particularly PV^+ basket cells, in CA3 (41,42,44). These hippocampal neural events are critical for memory encoding, consolidation, and retrieval and may function to link emotional salience with contextual

information (45,46). SPW-Rs are reported to trigger long-lasting synaptic depression which may help to refine the specificity of memory engrams (47). K has been previously shown to reduce the occurrence of SPW-Rs in CA1 up to 30 minutes after administration (48,49). Our results suggest that this K-induced suppression of SPW-Rs may also occur in CA3 and may last for up to one week after administration. Furthermore, CA3 SPW-Rs are suppressed by high 5-HT levels (50). As 5-HT_4R agonists may increase the release of 5-HT, P may also suppress hippocampal SPW-Rs by increasing serotonergic tone (51). Our data suggest that targeting both NMDARs and 5-HT_4Rs together, along with targeting either receptor individually, may block hippocampal SPW-Rs in CA3 for up to 1 week. Functionally, this suppression of SPW-Rs may cognitively decouple the contextual experience of a stressor with negative valence, allowing for subsequent memory retrieval of the event without debilitating fear and preventing associated symptoms of affective disorders. However, further study is necessary to test the validity of this hypothesis.

The behavioral and electrophysiological results of our combined drug strategy are complemented by our network analysis of excitatory and inhibitory signaling in the mPFC and HPC. These findings revealed that although prophylactic K, P, or combined K+P result in similar behavioral consequences, they may exert distinct effects on correlated c-fos and PV expression. Curiously, K+P appears to exert similar but still distinct effects on c-fos and PV network activity as P. Notably, K+P reduces correlated c-fos network activity, but only between vCA3 and DG, while increasing c-fos expression in the mPFC, select regions of the dHPC, and vCA3. Combined K+P also increased correlated PV expression, but to a lesser extent than P alone, and

upregulated PV^+ neurons selectively in vCA3. These results suggest that simultaneous NMDAR and 5-HT_4R targeting can refine excitatory/inhibitory (E/I) balance in vCA3, which may contribute to the suppression of SPW-Rs and subsequently affect neural activity in downstream brain regions, thus improving resilience to stress.

In conclusion, we report that combined K+P exerts synergistic effects in reducing stress-induced fear, behavioral despair, and hyponeophagia behaviors in both male and female mouse models of stress. Simultaneously targeting NMDARs and 5-HT_4Rs is sufficient to modulate both excitatory and inhibitory signaling in the mPFC and HPC, brain regions critically involved in stress processing. Nonetheless, further study is necessary to elucidate the molecular mechanisms and clinical efficacy of simultaneous NMDAR antagonist and 5-HT_4R agonist administration. Overall, the present study demonstrates the potential of utilizing adjunctive pharmacological treatment to advance targeted therapies for stress-related psychiatric disorders.

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BKC and CAD conceived of the study. BKC, HCH, AMG, IM-D, DJD, and CAD contributed to experimental design and intellectual interpretation. BKC wrote the manuscript. BKC, AMG, IM-D, DJD, and CAD edited the manuscript. BKC collected behavioral data. VL collected electrophysiological data. BKC, AS, MES, MP, BLW, and VP ran immunohistochemistry, processed images, and performed cell quantification. MJ performed network and statistical analysis.

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BKC, HCH, VL, AMG, IM-D, DJD, and CAD are named on provisional patent applications for the prophylactic use of (*R*,*S*)-ketamine, 5-HT_4R agonists, and other compounds against stress-related psychiatric disorders and Alzheimer's disease. MJ, AS, MES, MP, BLW, and VP have no conflicts of interest to disclose.

ARTICLE INFORMATION

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FIGURE LEGENDS

Figure 1. Combined prophylactic (*R,S*)-ketamine + prucalopride administration protects against stress in male 129S6/SvEv mice. (A) Experimental design. Sal, K, P, or combined K+P at different dosage combinations was administered one week prior to CFC stress in male 129S6/SvEv mice. **(B)** All groups of mice exhibited comparable freezing during CFC training. **(C)** Upon context re-exposure, mice administered K (30 mg/kg), P (3 mg/kg), or K+P (10 + 3 mg/kg) exhibited reduced freezing compared to Sal mice. **(D)** During day 1 of the FST day 1, all groups of mice exhibited comparable immobility time. **(E)** During day 2 of the FST, mice administered K (30 mg/kg), P (3 mg/kg), and K+P (10 + 3 or 30 + 10 mg/kg) exhibited decreased immobility time when compared to mice administered Sal. **(F)** All groups of mice traveled a comparable distance in the OF. **(G)** All groups of mice spent a comparable amount of time in the open arms of the EPM. **(H-I)** In the NSF, mice administered K+P (10 + 3 mg/kg) exhibited decreased latency to feed in the OF arena. **(J)** All groups of mice exhibited comparable latencies to feed in the HC. **(K)** All groups of mice loss a comparable amount of body weight following the NSF. (n = 5-15 male mice per group). Error bars represent $\pm$ SEM. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$, **** $p < 0.0001$. Sal, saline; K, (*R,S*)-ketamine; P, prucalopride; CFC, contextual fear conditioning; FST, forced swim test; OF, open field; EPM, elevated plus maze; NSF, novelty suppressed feeding; HC; home cage; cm, centimeter; min, minute; sec, second; mg, milligram; kg, kilogram.

Figure 2. Combined prophylactic (*R,S*)-ketamine + prucalopride administration protects against stress in female 129S6/SvEv mice. (A) Experimental design. **(B-C)**

All groups of mice exhibited comparable freezing during CFC training and re-exposure. **(D)** During day 1 of the FST, mice administered K (10 mg/kg), P (3 mg/kg), and K+P (10 + 1.5 mg/kg) exhibited decreased immobility time when compared to mice administered Sal. **(E)** During day 2 of the FST, mice administered K (10 mg/kg), P (3 or 10 mg/kg), and K+P (10 + 1.5 mg/kg) exhibited decreased immobility time when compared to mice administered Sal. **(F)** All groups of mice traveled a comparable distance in the OF. **(G)** P (3 mg/kg), but no other drug tested, significantly increased time spent in the open arms of the EPM when compared to Sal. **(H-I)** In the NSF, mice K+P (10 + 1.5 mg/kg) exhibited decreased latency to feed in the OF arena. **(J)** All groups of mice exhibited comparable latencies to feed in the HC. **(K)** All groups of mice loss a comparable amount of body weight following the NSF. (n = 6-12 female mice per group). Error bars represent ± SEM. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$, **** $p < 0.0001$. Sal, saline; K, (*R,S*)-ketamine; P, prucalopride; CFC, contextual fear conditioning; FST, forced swim test; OF, open field; EPM, elevated plus maze; NSF, novelty suppressed feeding; HC; home cage; cm, centimeter; min, minute; sec, second; mg, milligram; kg, kilogram.

Figure 3. Combined (*R,S*)-ketamine + prucalopride blocks reduces AMPAR-mediated bursting in hippocampal CA3. (A) Experimental design. Male 129S6/SvEv mice were i.p. injected with Sal or K+P (10 + 3 mg/kg) and sacrificed for electrophysiology one week later. Representative EPSCs in **(B)** Sal- and **(E)** K+P-administered mice. **(C)** Sal-administered mice exhibited bursts of large-amplitude AMPAR-mediated activity (circled in blue) which were blocked in **(F)** K+P-administered mice. **(D)** Mean EPSC amplitude was significantly reduced by K+P administration. **(G)**

There was also a trending, but not significant, decrease in number of EPSCs in mice given K+P when compared with Sal. (n = 5-7 cells per group). Error bars represent ± SEM. * $p < 0.05$. Sal, saline; K+P, (*R,S*)-ketamine + prucalopride; CA3, Cornu ammonis 3; sec, second; pA, picoampere; mg, milligram; kg, kilogram; ms, millisecond; EPSC, excitatory post-synaptic current.

Figure 4. Combined (*R,S*)-ketamine + prucalopride alters correlated excitatory signaling in the mPFC and HPC. (A) Behavioral paradigm. Mice were administered a single prophylactic injection of Sal, K, P, or combined K+P one week prior to CFC stress. Five days later, mice were re-exposed to the training context and tested in the FST. Mice were sacrificed one hour after day 2 of the FST, and immunohistochemistry was used to quantify c-fos and PV expression. **(B)** Representative images of c-fos immunostaining in (left) Sal- and (right) combined K+P-administered mice. Insets reveal close-ups of hippocampal c-fos expression. Heat map correlations of c-fos expression in **(C)** Sal-, **(D)** K-, **(E)** P-, and **(F)** combined K+P-administered mice. Green, blue, pink, or purple indicate strong positive correlations, while gray indicates strong negative correlations. **(G)** Volcano plot indicating regional correlation differences greater than 0.5 between Sal- and K-administered mice. **(H-I)** Volcano and parallel plots indicating regional correlation differences greater than 0.5 between Sal- and P-administered mice. **(J-K)** Volcano and parallel plots indicating regional correlation differences greater than 0.5 between Sal- and combined K+P-administered mice. Notably, mice given combined K+P exhibited a decrease in correlated vCA3-dDG activity when compared with Sal. Cluster maps of correlated c-fos expression in **(L)** Sal-, **(M)** K-, **(O)** P-, and **(P)**

combined K+P-administered mice. The cluster map reveals strongly interconnected activity in Sal-, K-, and P-administered mice. In contrast, the combined K+P-administered cluster map is less cohesive, with the most isolation in all ventral hippocampal regions. **(N)** A bootstrap prediction analysis revealed that vCA1 and vDG contribute the most to immobility time during FST Day 2 in K+P-administered mice. (n = 7-8 mice per group). Error bars represent ± SEM. * $p < 0.05$. Sal, saline; K, (*R,S*)-ketamine; P, prucalopride; K + P, (*R,S*)-ketamine + prucalopride; CFC, contextual fear conditioning; FST, forced swim test; μm, micrometers; ACA, anterior cingulate area; ILA, infralimbic area; PL, prelimbic area; dDG, dorsal dentate gyrus; dCA3, dorsal field CA3; dCA1, dorsal field CA1; vDG, ventral dentate gyrus; vCA3, ventral field CA3; vCA1, ventral field CA1.

Figure 5. Combined (*R,S*)-ketamine + prucalopride alters network c-fos activity in the mPFC and HPC. c-fos expression modeled as networks of functional activity in **(A)** Sal-, **(B)** K-, **(C)** P-, and **(D)** combined K+P-administered mice. Green, blue, pink, or purple indicate positive correlations, while gray indicates strong negative correlations. Thicker lines indicate stronger correlations and larger circles represent an increased degree of nodes. Combined K+P administration led to sparser network activity when compared with Sal, K, and P administration. **(E-F)** Mean degree and global efficiency are significantly increased in K-administered, but not P- or combined K+P-administered mice, when compared to Sal-administered mice. **(G-H)** Mean clustering coefficient and betweenness centrality are comparable across all drug groups. **(I)** K significantly increases network distance in comparison to Sal. Representative images of c-fos

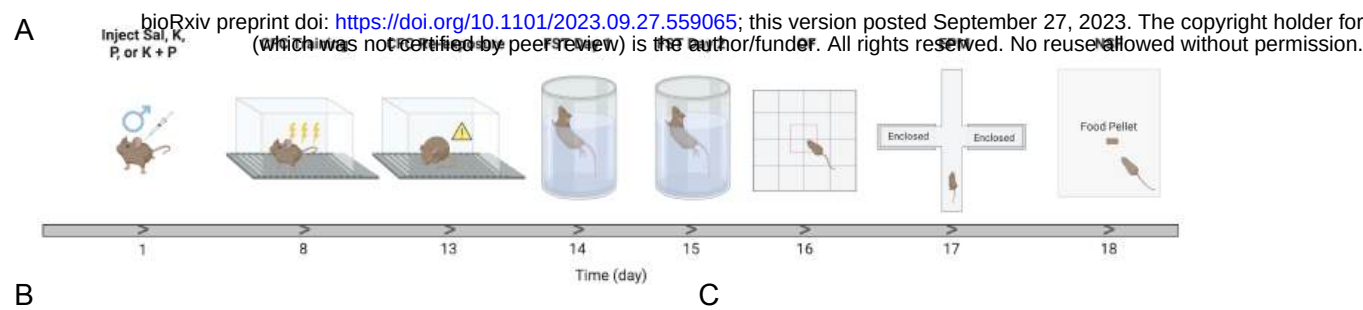
immunostaining in **(J)** ACA, PL, and ILA of the mPFC, **(L)** dDG, dCA3, and dCA1 of the dHPC, and **(N)** vDG, vCA3, and vCA1 of the vHPC. When compared with Sal, (*K+P* significantly increased the number of c-fos$^+$ cells in **(K)** mPFC, **(M)** dCA3, dCA1, and **(O)** vCA3. (n = 7-8 mice per group). Error bars represent ± SEM. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$. ACA, anterior cingulate area; ILA, infralimbic area; PL, prelimbic area; dDG, dorsal dentate gyrus; dCA3, dorsal field CA3; dCA1, dorsal field CA1; vDG, ventral dentate gyrus; vCA3, ventral field CA3; vCA1, ventral field CA1; Sal, saline; K, (*R,S*)-ketamine; P, prucalopride; K + P, (*R,S*)-ketamine + prucalopride; mg, milligram; kg, kilogram; µm, micrometers; no., number; mPFC, medial prefrontal cortex; dHPC, dorsal hippocampus; vHPC, ventral hippocampus.

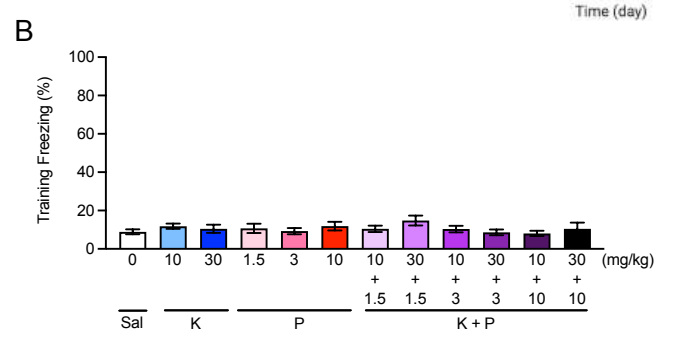
Figure 6. Combined (*R,S*)-ketamine + prucalopride selectively enhances correlated PV expression. Heat map correlations of PV expression in **(A)** Sal-, **(B)** K-, **(C)** P-, and **(D)** combined K+P-administered mice. Green, blue, pink, or purple indicate strong positive correlations, while gray indicates strong negative correlations. PV expression modeled as networks of functional activity in **(E)** Sal-, **(F)** K-, **(G)** P-, and **(H)** combined K+P-administered mice. Green, blue, pink, or purple indicate positive correlations, while gray indicates strong negative correlations. Thicker lines indicate stronger correlations and larger circles represent an increased degree of nodes. Combined K+P administration led to increased inhibitory network connectivity when compared with Sal administration. Representative images of c-fos and PV immunostaining in **(I)** mPFC, **(J)** vHPC, and **(K)** dHPC. The number of PV$^+$ cells is comparable in all subregions of the **(L)** mPFC and **(M)** dHPC. **(N)** Combined K+P

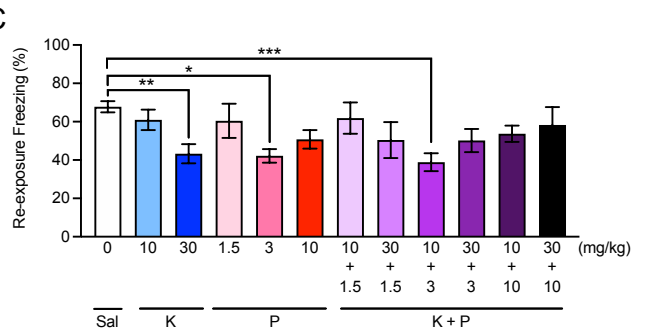
increases PV expression in vCA3, but no other subregion of the vHPC. **(O)** Combined drug administration significantly increased the number of c-fos$^+$/PV$^+$ co-labeled cells across the mPFC. **(P)** The number of c-fos$^+$/PV$^+$ co-labeled cells was comparable across the dHPC in all groups. **(Q)** Combined K+P increased the number of PV$^+$/c-fos$^+$ co-labeled cells in vCA3, but no other subregion of the vHPC. (n = 7-8 mice per group). Error bars represent ± SEM. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. ACA, anterior cingulate area; ILA, infralimbic area; PL, prelimbic area; dDG, dorsal dentate gyrus; dCA3, dorsal field CA3; dCA1, dorsal field CA1; vDG, ventral dentate gyrus; vCA3, ventral field CA3; vCA1, ventral field CA1. μm, micrometers; mPFC, medial prefrontal cortex; dHPC, dorsal hippocampus; vHPC, ventral hippocampus.

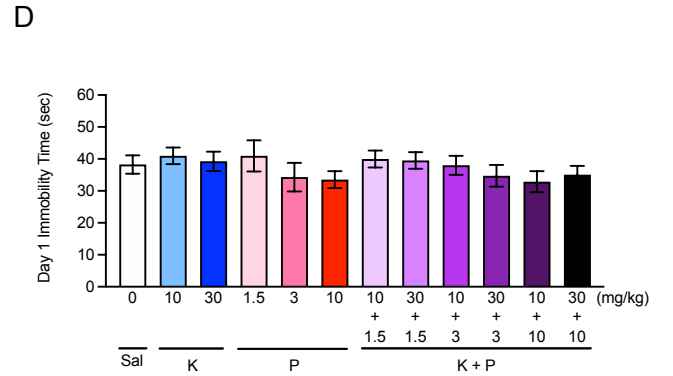
Figure 7. Combined (*R,S*)-ketamine + prucalopride attenuates learned fear in male mice and reduces behavioral despair and hyponeophagia in both sexes when administered after stress. (A) Experimental design. Male and female 129S6/SvEv mice were administered a single administration of Sal, K, P, or a combined K+P five minutes after 3-shock CFC. **(B-C)** In male mice, during context re-exposure, combined K+P, but not K or P alone, significantly reduced freezing when compared to Sal . **(D-E)** During day 1 of the FST, all groups of mice exhibited comparable immobility. **(F-G)** During day 2 of the FST, male mice administered K or combined K+P exhibited decreased immobility time when compared to Sal. **(H-I)** In the NSF, mice administered combined K+P exhibited a reduced latency to feed in the OF when compared with mice administered Sal. **(J-K)** In female mice, during context re-exposure, freezing was comparable across all groups. **(L-M)** During day 1 of the FST, mice administered

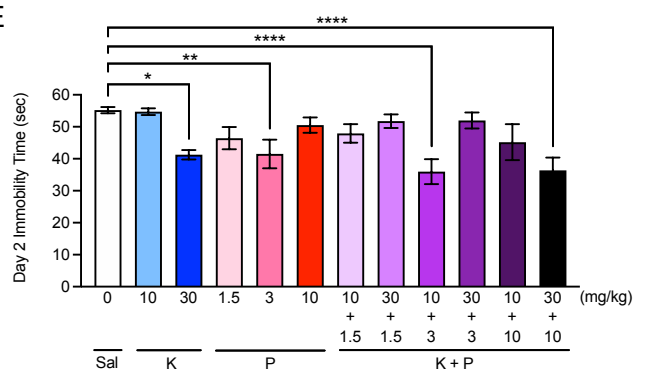
combined K+P exhibited decreased immobility time when compared to Sal. **(N-O)** During day 2 of the FST, female mice administered K or K+P exhibited decreased immobility time when compared to Sal. **(P-Q)** In the NSF, mice administered combined K+P exhibited decreased latency to feed when compared to Sal. (n = 5-7 male or female mice per group). Error bars represent ± SEM. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$, **** $p < 0.0001$. CFC, contextual fear conditioning; FST, forced swim test; OF, open field; EPM, elevated plus maze; NSF, novelty suppressed feeding; mg, milligram; kg, kilogram; Sal, saline; K, (*R,S*)-ketamine; P, prucalopride; K + P, (*R,S*)-ketamine + prucalopride; min, minute; sec, second.

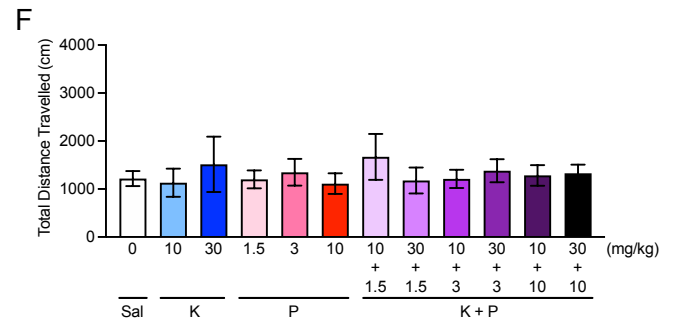


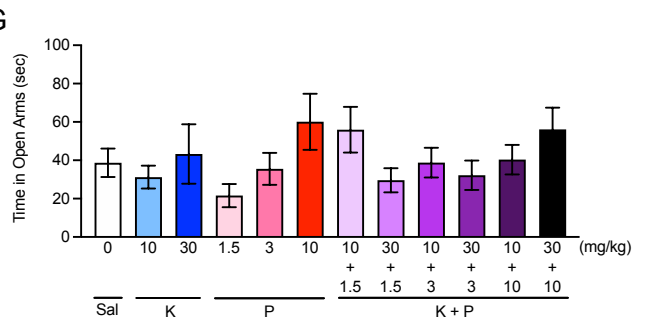


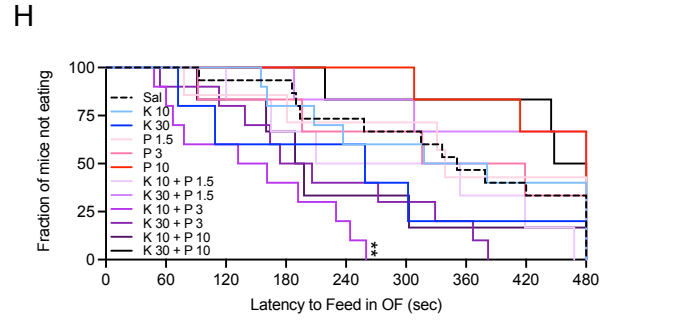


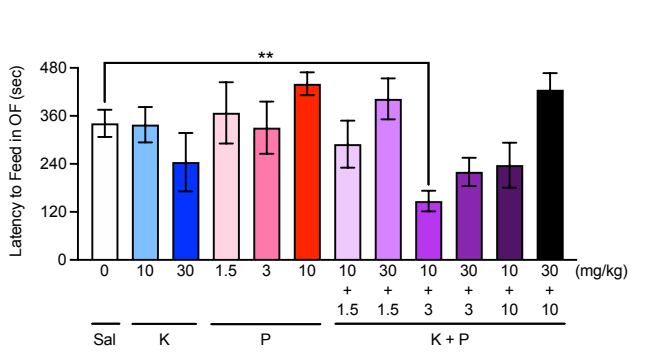


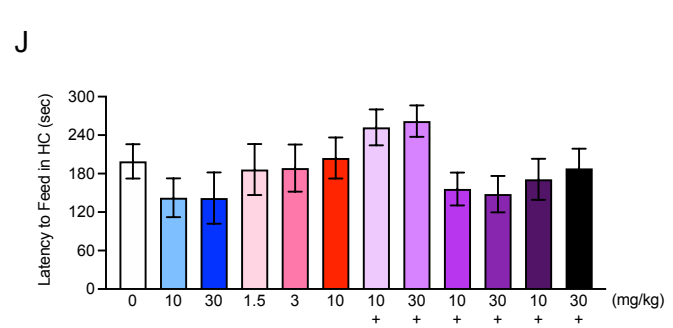


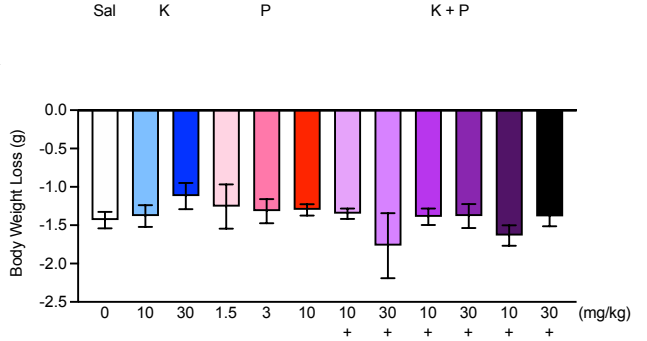


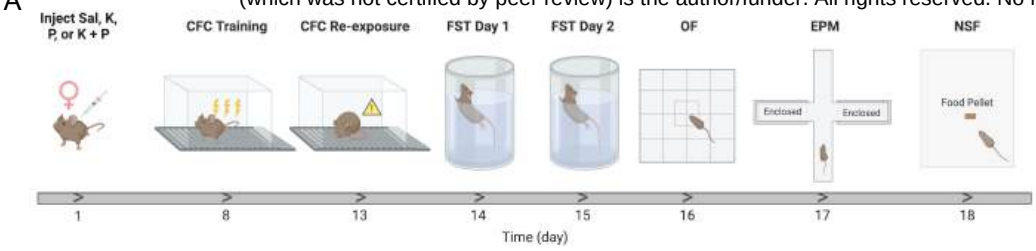


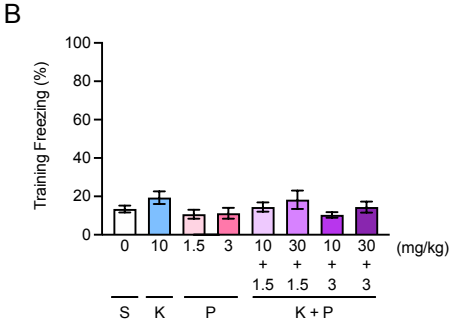


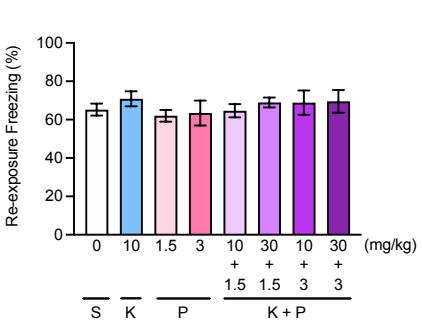


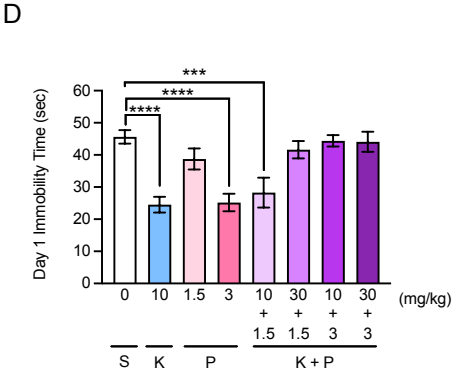


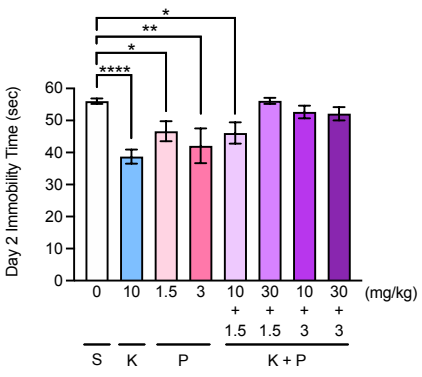


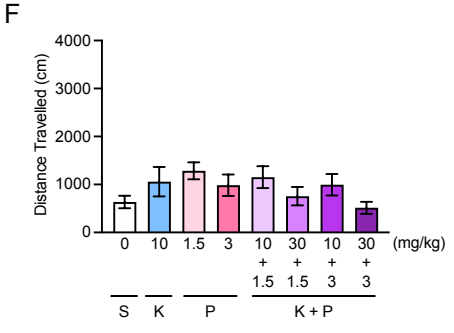


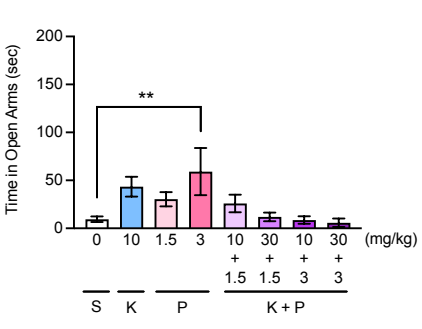


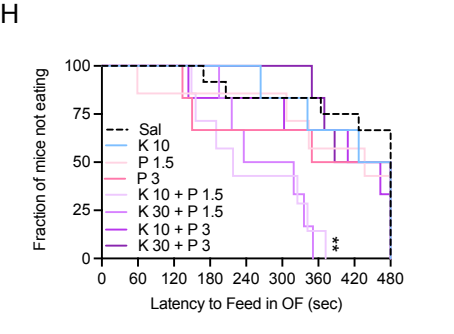


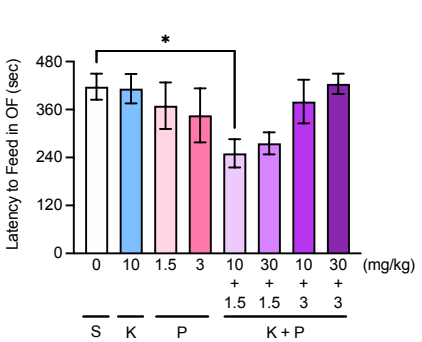


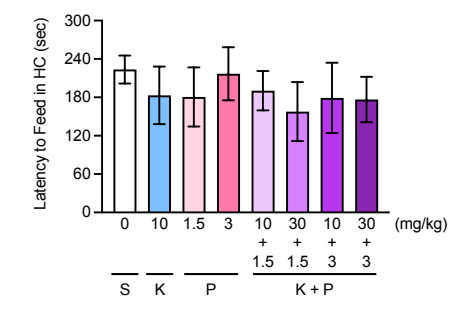


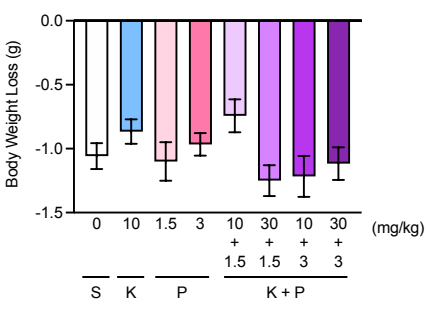


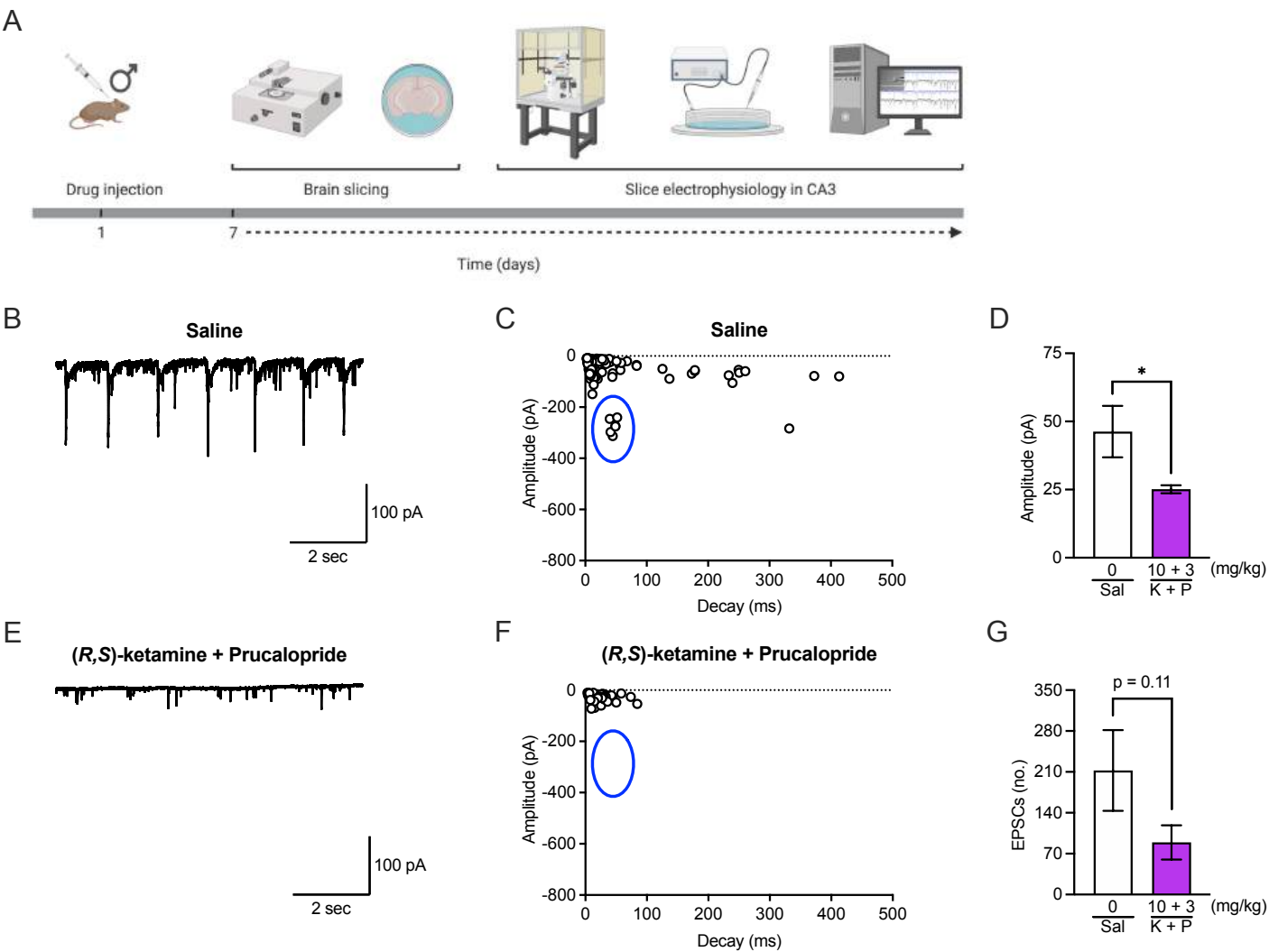


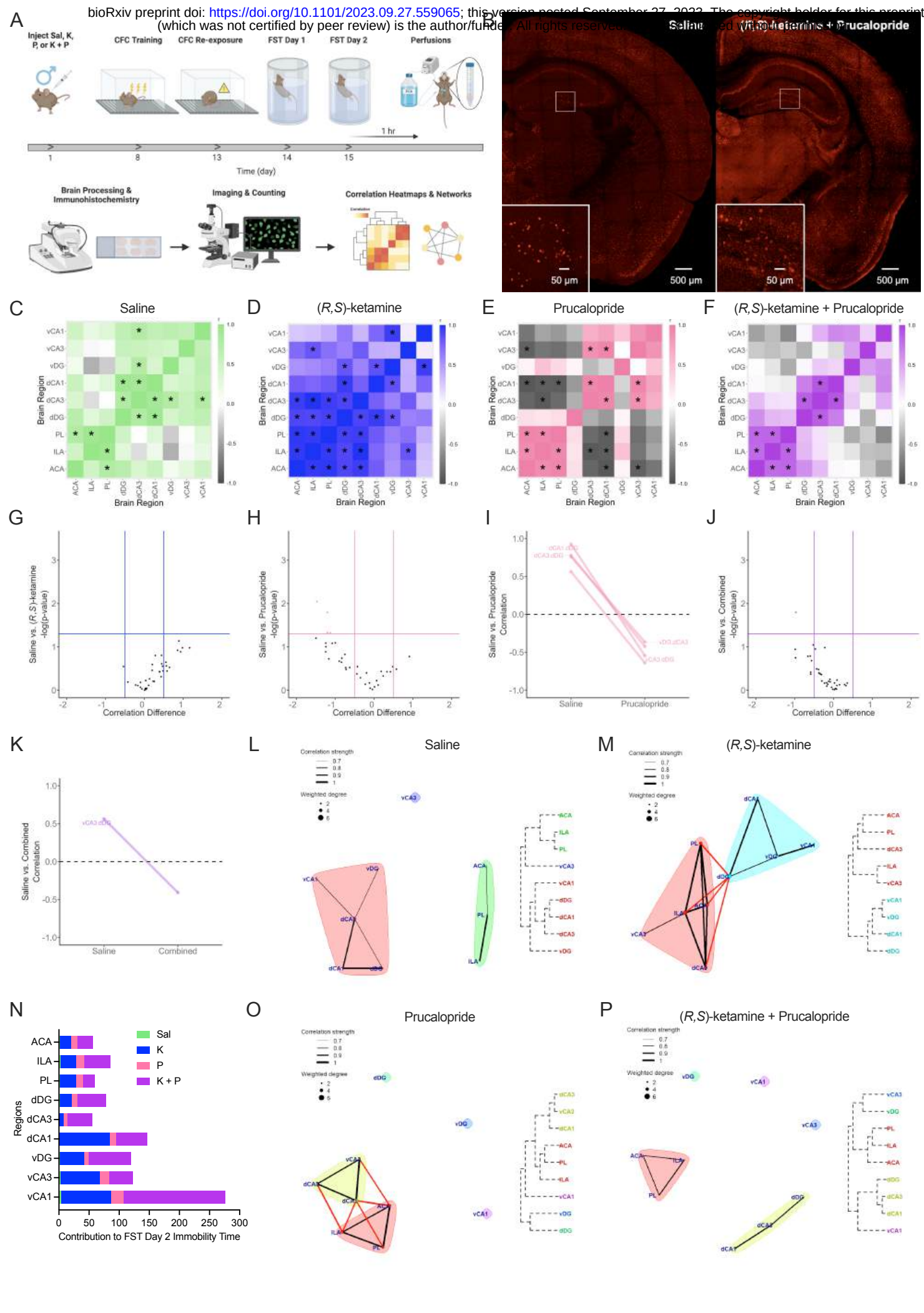


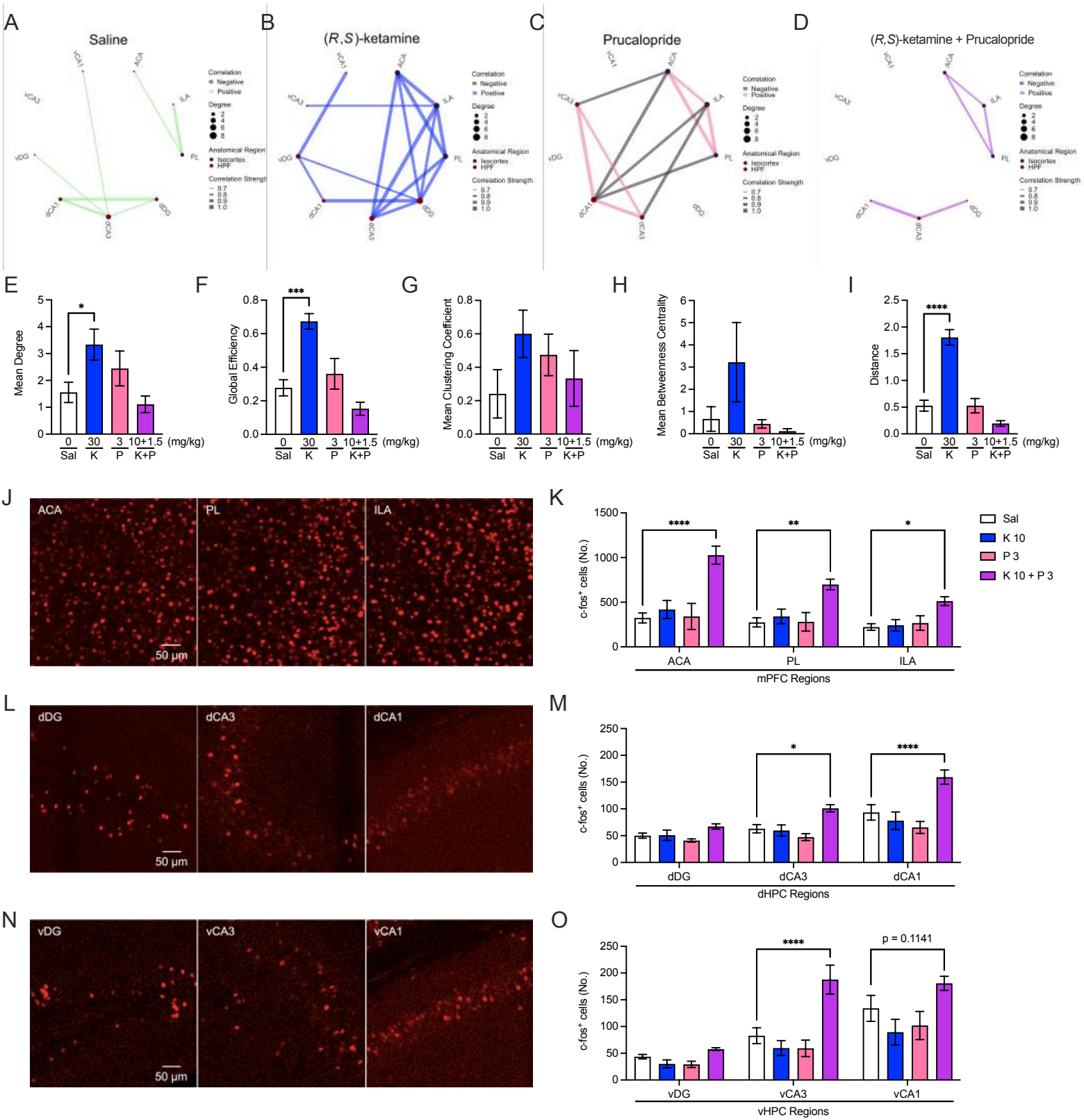


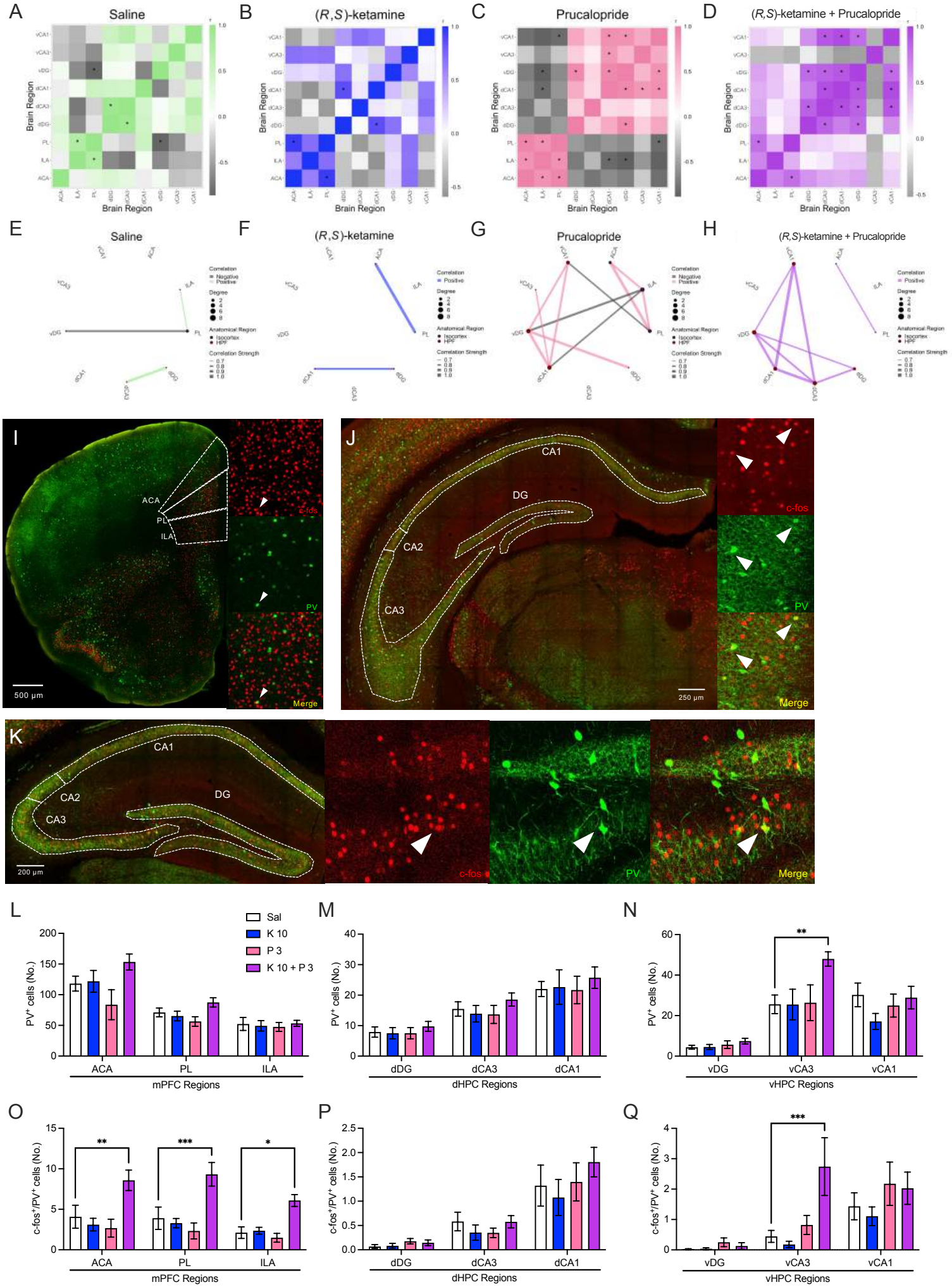


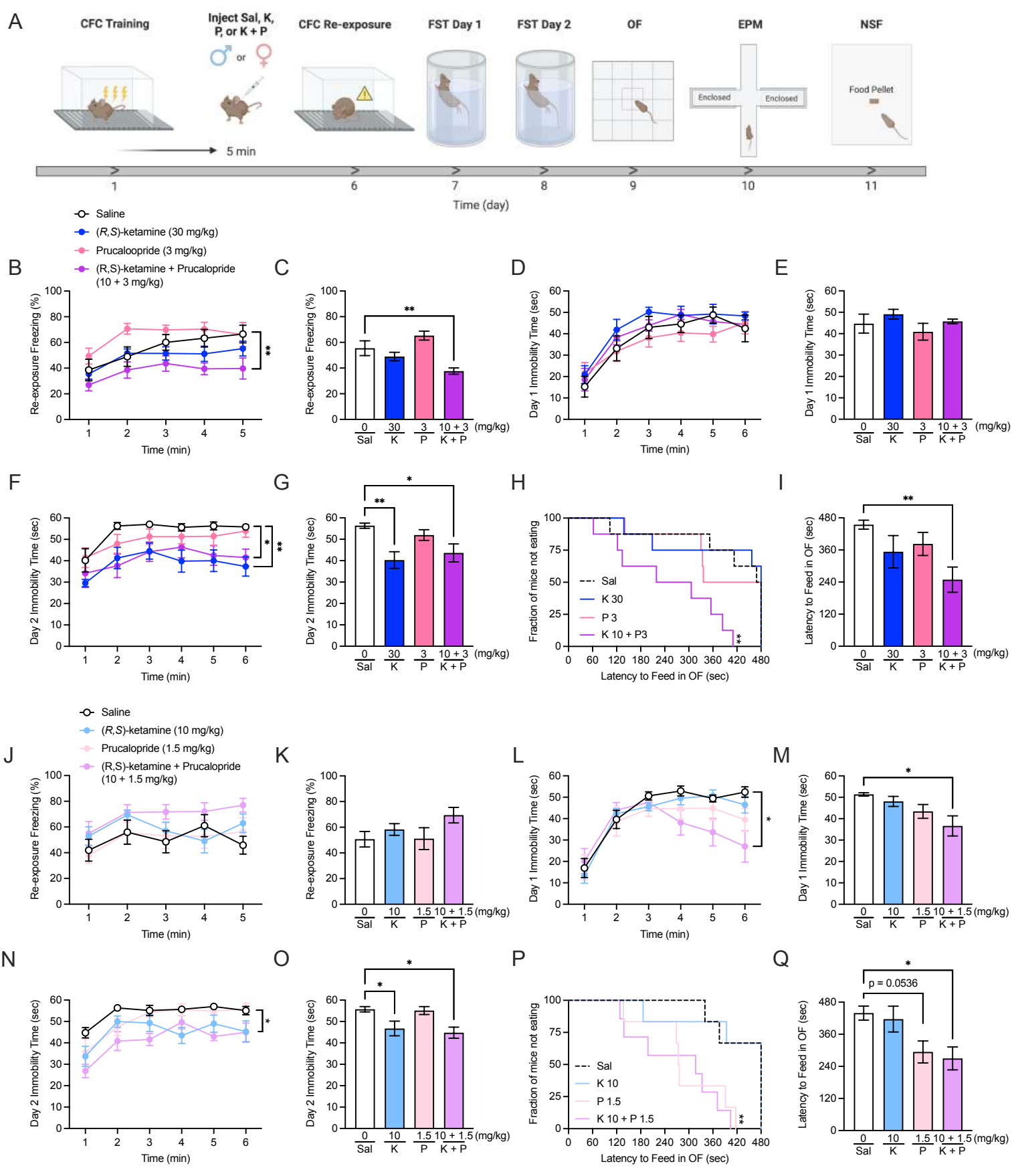



A
Drug injection
Brain slicing
Slice electrophysiology in CA3
1
7
Time (days)
B
Saline
100 pA
2 sec
C
Saline
Amplitude (pA)
Decay (ms)
D
Amplitude (pA)
*
0
Sal
10 + 3
K + P
(mg/kg)
E
(R,S)-ketamine + Prucalopride
100 pA
2 sec
F
(R,S)-ketamine + Prucalopride
Amplitude (pA)
Decay (ms)
G
EPSCs (no.)
p = 0.11
0
Sal
10 + 3
K + P
(mg/kg)




A
Saline
B
(R,S)-ketamine
C
Prucalopride
D
(R,S)-ketamine + Prucalopride
vCA1
ACA
vCA3
ILA
vDG
PL
dCA1
dCA3
dDG
Correlation
Negative
Positive
Degree
Anatomical Region
Isocortex
HPF
Correlation Strength
E
Mean Degree
F
Global Efficiency
G
Mean Clustering Coefficient
H
Mean Betweenness Centrality
I
Distance
0 Sal
30 K
3 P
10+1.5 K+P
(mg/kg)
J
ACA
PL
ILA
50 μm
K
c-fos+ cells (No.)
Sal
K 10
P 3
K 10 + P 3
mPFC Regions
L
dDG
dCA3
dCA1
M
dHPC Regions
N
vDG
vCA3
vCA1
O
p = 0.1141
vHPC Regions




A
CFC Training
Inject Sal, K, P, or K + P
or
CFC Re-exposure
FST Day 1
FST Day 2
OF
EPM
NSF
Enclosed
Enclosed
Food Pellet
5 min
1
6
7
8
9
10
11
Time (day)
Saline
(R,S)-ketamine (30 mg/kg)
Prucaloopride (3 mg/kg)
(R,S)-ketamine + Prucalopride (10 + 3 mg/kg)
B
Re-exposure Freezing (%)
Time (min)
C
Re-exposure Freezing (%)
0 Sal
30 K
3 P
10 + 3 K + P
(mg/kg)
D
Day 1 Immobility Time (sec)
Time (min)
E
Day 1 Immobility Time (sec)
F
Day 2 Immobility Time (sec)
Time (min)
G
Day 2 Immobility Time (sec)
H
Fraction of mice not eating
Sal
K 30
P 3
K 10 + P3
Latency to Feed in OF (sec)
I
Latency to Feed in OF (sec)
Saline
(R,S)-ketamine (10 mg/kg)
Prucalopride (1.5 mg/kg)
(R,S)-ketamine + Prucalopride (10 + 1.5 mg/kg)
J
Re-exposure Freezing (%)
Time (min)
K
Re-exposure Freezing (%)
0 Sal
10 K
1.5 P
10 + 1.5 K + P
(mg/kg)
L
Day 1 Immobility Time (sec)
Time (min)
M
Day 1 Immobility Time (sec)
N
Day 2 Immobility Time (sec)
Time (min)
O
Day 2 Immobility Time (sec)
P
Fraction of mice not eating
Sal
K 10
P 1.5
K 10 + P 1.5
Latency to Feed in OF (sec)
Q
p = 0.0536
Latency to Feed in OF (sec)

SUPPLEMENTAL INFORMATION

A tale of two receptors: simultaneous targeting of NMDARs and 5-HT$_4$Rs exerts additive effects against stress

Authors

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SUPPLEMENTAL METHODS

Mice

Male and female 129S6/SvEvTac mice were purchased from Taconic (Hudson, NY) at 7 weeks of age. Mice were housed 5 per cage in a 12-h (06:00-18:00) light-dark colony room at 22ºC. All experiments were approved by the Institutional Animal Care and Use Committee (IACUC) at the New York Psychiatric Institute (NYSPI).

Behavioral Assays

For all experiments, food and water were provided *ad libitum*, unless otherwise noted. Behavioral testing was performed during the light phase.

Contextual Fear Conditioning (CFC)

A 3-shock CFC paradigm was administered as previously described (1,2). CFC was conducted in chambers obtained from Med Associates (St. Albans, VT), with internal dimensions of approximately 20 cm wide x 16 cm deep x 20.5 cm high. The chambers had metal walls on each side, clear plastic front and back walls and ceilings, and stainless-steel bars on the floor. A house light (CM1820 bulb, 28v, 100mA) mounted directly above the chamber provided illumination. Each chamber was located inside a larger, insulated, plastic cabinet that provided protection from outside light and noise. Each cabinet contained a ventilation fan that was operated during the sessions. A paper towel dabbed with lemon solution was placed underneath the chamber floor. Mice were held outside the experimental room in their home cages prior to testing and transported to the conditioning apparatus individually in standard mouse cages. Chambers were

cleaned with 70% EtOH between each set of mice. Mice were placed into the conditioning chamber and received shocks at 180 s, 240 s, and 300 s (2 s duration, 0.75 mA). Fifteen seconds after the last shock, mice were removed from the chamber. Overall, the training session lasted 317 s. During re-exposure, mice were placed in the conditioning chamber for 5 minutes and did not receive any shocks. All sessions were scored for freezing using FreezeFrame4.

Forced Swim Test (FST)

The FST was administered as previously described (3–5). Briefly, mice were placed into clear plastic buckets 20 cm in diameter and 23 cm deep filled 2/3 of the way with 22°C water. Mice were videotaped from the side for 6 min and were exposed to the swim test on 2 consecutive days. Immobility time was scored by an experimenter blind to the experimental groups.

Open Field (OF)

The OF assay was administered as previously described (3–5). Briefly, motor activity was quantified in 4 open field boxes 43 x 43 cm^2 (MED Associates, Georgia, VT). An overhead camera was used to track locomotor activity. Activity chambers were computer interfaced for data sampling at 100-ms resolution. The computer defined grid lines that dividing center and surround regions, with the center square consisting of four lines 11 cm from the wall.

Elevated Plus Maze (EPM)

Testing was performed as previously described (3–5). Briefly, the maze is a plus-cross-shaped apparatus consisting of four arms, two open and two enclosed by walls, linked by a central platform at a height of 50 cm from the floor. Mice were individually placed in the center of the maze facing an open arm and were allowed to explore the maze for 5 min. The time spent in and the number of entries into the open arms was used as an anxiety index. Videos were scored using ANY-maze behavior tracking software (Stoelting, Wood Dale, IL).

Marble Burying (MB)

The MB assay was conducted in a clean cage (10.5 in x 5.5 in) containing soft pliable Beta Chip bedding (Northeastern Products Corp, Warrensburg, NY). The cage contained 16 marbles set up in 4 rows of 4 across. Mice were given 30 minutes to explore and bury. At the end of the assay, the percentage of marbles buried was calculated.

Novelty Suppressed Feeding (NSF)

Testing was performed as previously described (4,5). Briefly, the NSF testing apparatus consisted of a plastic box (50 x 50 x 20 cm). The floor of which was covered with approximately 2 cm of wooden bedding and the arena was brightly lit (approximately 1000 lux). Mice were food restricted for 12 h prior to testing. At the time of testing, a single pellet of food (regular chow) was placed on a white paper platform positioned in the center of the box. Each animal was placed in a corner of the box, and a stopwatch was immediately started. The latency of the mice to begin eating in the arena was

recorded. Immediately after the latency was recorded, the food pellet was removed from the arena. The mice were then placed back into their home cage. The latency to eat and the amount of food consumed in 5 min were measured (home cage consumption), followed by an assessment of post-restriction weight. A Kaplan-Meier survival analysis was used due to the lack of normal distribution of data. The Mantel-Cox log-rank test was used to evaluate differences between the experimental groups.

Electrophysiology

Electrophysiology was conducted as previously described (5). One week after a saline or a (*R,S*)-ketamine (10 mg/kg) + prucalopride (3 mg/kg) injection, mice were anesthetized by isoflurane inhalation, decapitated, and brains rapidly removed. CA3 slices (350 μm) were cut on a vibratome (Leica VT1000S) in ice cold partial sucrose artificial cerebrospinal fluid (ACSF) solution (in mM): 80 NaCl, 3.5 KCl, 4.5 $MgSO_4$, 0.5 $CaCl_2$, 1.25 H_2PO4, 25 $NaHCO_3$, 10 $C_6H_{12}O_6$, and 90 $C_{12}H_{22}O_{11}$ equilibrated with 95% O_2 / 5% CO_2 and stored in the same solution at 37°C for 30 minutes, then at room temperature until use. Recordings were made at 30-32°C (TC324-B; Warner Instrument Corp) in ACSF (in mM: 124 NaCl, 8.5 KCl, 1 NaH_2PO_4, 25 $NaHCO_3$, 20 glucose, 1 $MgCl_2$, 2 $CaCl_2$). Whole-cell voltage clamp recordings (-70 mV) were obtained using a patch pipette (4-6 M MΩ) containing (in mM): 135 K Gluconate, 5 KCl, 0.1 EGTA-Na, 10 HEPES, 2 NaCl, 5 ATP, 0.4 GTP, 10 phosphocreatine (pH 7.2; 280–290 mOsm). Bicuculline (5 μM) was also included in the bath solution to inhibit $GABA_A$ receptors. Three-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline (NBQX) (20 mM) was added later in recordings to inhibit AMPAR synaptic currents and unmask NMDAR-mediated

signals. Patch pipettes were made from borosilicate glass (A-M Systems, Sequium, WA) using a micropipette puller (Model P-1000; Sutter Instruments, Novato, CA). Recordings were made without correction for junction potentials. Pyramidal cells were visualized and targeted via infrared-differential interference contrast (IR-DIC; 40x objective) optics on an Axioskop-2 FS (Zeiss, Oberkochen, Germany).

Immunohistochemistry

Immunohistochemistry was performed as previously described (2,5). Mice were deeply anesthetized, and brains were fixed and extracted using transcardial perfusion. For c-fos immunohistochemistry, floating sections were used. Sections were first rinsed 3 times in 1 x phosphate buffered saline (PBS) and then blocked in 1 x PBS with 0.5% Triton X-100 (PBST) and 10% normal donkey serum (NDS) for 2 hours at room temperature (RT). Incubation with primary antibodies was performed at 4ºC overnight (rat anti-c-fos, 226 017, 1:5000, SySy, Göettingen, Germany; rabbit anti-parvalbumin, PV27, 1:3000, Swant, Burgdorf, Switzerland) in 1 x PBST. Sections were then washed 3 times in 1 x PBS and incubated with secondary antibody (Alexa 647 anti-rat, Ab150155, 1:500, Abcam, Cambridge, UK; Alexa 488 anti-rabbit, A-21206, 1:500, Thermo Fisher Scientific, Waltham, MA) for 2 hours at RT. Sections were then washed three times in 1 x PBS, mounted on slides, and coverslipped with Fluoromount G (Electron Microscopy Sciences, Hatfield, PA).

Confocal Microscopy

Fluorescent confocal micrographs were captured with a Leica TCS SPE-II confocal microscope with LAS X software as previously described (4,5). Bilateral hippocampal sections were imaged throughout the rostro-caudal axis of the HPC using a 20X objective. Identification of hippocampal regions involved acquiring 6 dorsal and ventral sections per mouse brain slice at 20X. All individual panels were acquired at a thickness of 3 µm. Z-stack analysis was performed using the LAS X image browser to determine expression of c-fos and PV. Expression levels of c-fos and PV were compared across all sections using identical exposure conditions.

Cell Quantification

An investigator blind to treatment groups used Fiji software to count c-fos$^+$, PV$^+$, and c-fos$^+$/PV$^+$ immunoreactive cells in the ACA, ILA, and PL of the mPFC or in the DG, CA3, and CA1 throughout the entire rostrocaudal axis of the HPC. Cells were counted bilaterally. Number of c-fos$^+$, PV$^+$, and c-fos$^+$/PV$^+$ cells is presented throughout the text.

Correlation and Network Analyses

Regions were mapped across all experimental groups and included a minimum n of 5 mice per group. Pearson correlations between regions were calculated using the Hmisc package in R, with pairwise removal of missing cases. Significance of pairwise regional correlation differences between experimental groups was calculated using permutation analysis. Group labels were randomly shuffled, and correlations were recomputed 1000 times to generate a null distribution of the pairwise regional correlation differences between groups. Correlation differences were compared to these null distributions to

determine the p-value. For the cluster network maps, relevant functional connections were retained by thresholding connections at $p < 0.05$. To ensure that both relevant positive and negative functional connections were used for community detection, the absolute Pearson values were used as edge weights. Using the igraph and tidygraph packages, the cluster fast greedy algorithm was used for community detection and visualized as a color-coded force-directed network (Fruchterman and Reingold layout) and as a dendrogram. Communities and nodes were color-coded, and scales were changed for edge connections (correlation strength).

To compare global network properties of c-Fos$^+$ and PV$^+$ expression across experimental groups, networks were again constructed based on Pearson correlations and edges were thresholded at a $p < 0.05$. For each region, the clustering coefficient and measures of centrality, such as degree, betweenness centrality, and efficiency were calculated using the tidygraph and igraph packages. These measures were averaged across all regions to calculate global network statistics. Networks were visualized using ggraph and summary statistics were plotted in Prism 10 (Graphpad Software, La Jolla, CA).

Statistical Analysis

Data were analyzed using Prism 9.0 (Graphpad Software, La Jolla, CA). Jmp 16 was used for bootstrap prediction analysis. Alpha was set to 0.05 for all analyses. Generally, the effect of Drug or Group was analyzed using an analysis of variance (ANOVA), using repeated measures where appropriate. Post-hoc Dunnett, Sidak, or Tukey tests were

used where appropriate. All statistical tests and *p* values are listed in **Tables S01 and S02**.

SUPPLEMENTAL REFERENCES

1. Drew MR, Denny CA, Hen R (2010): Arrest of adult hippocampal neurogenesis in mice impairs single- but not multiple-trial contextual fear conditioning. *Behav Neurosci* 124: 446–454.
2. Denny CA, Kheirbek MA, Alba EL, Tanaka KF, Brachman RA, Laughman KB, *et al.* (2014): Hippocampal memory traces are differentially modulated by experience, time, and adult neurogenesis. *Neuron* 83: 189–201.
3. Chen BK, Luna VM, LaGamma CT, Xu X, Deng S-X, Suckow RF, *et al.* (2020): Sex-specific neurobiological actions of prophylactic (*R*,*S*)-ketamine, (2*R*,6*R*)-hydroxynorketamine, and (2*S*,6*S*)-hydroxynorketamine. *Neuropsychopharmacol* 45: 1545–1556.
4. Chen BK, Mendez-David I, Luna VM, Faye C, Gardier AM, David DJ, Denny CA (2020): Prophylactic efficacy of 5-HT_4R agonists against stress. *Neuropsychopharmacol* 45: 542–552.
5. Chen BK, Luna VM, Shannon ME, Hunsberger HC, Mastrodonato A, Stackmann M, *et al.* (2021): Fluoroethylnormemantine, a Novel NMDA Receptor Antagonist, for the Prevention and Treatment of Stress-Induced Maladaptive Behavior. *Biol Psychiatry* 90: 458–472.

SUPPLEMENTAL FIGURES AND FIGURE LEGENDS

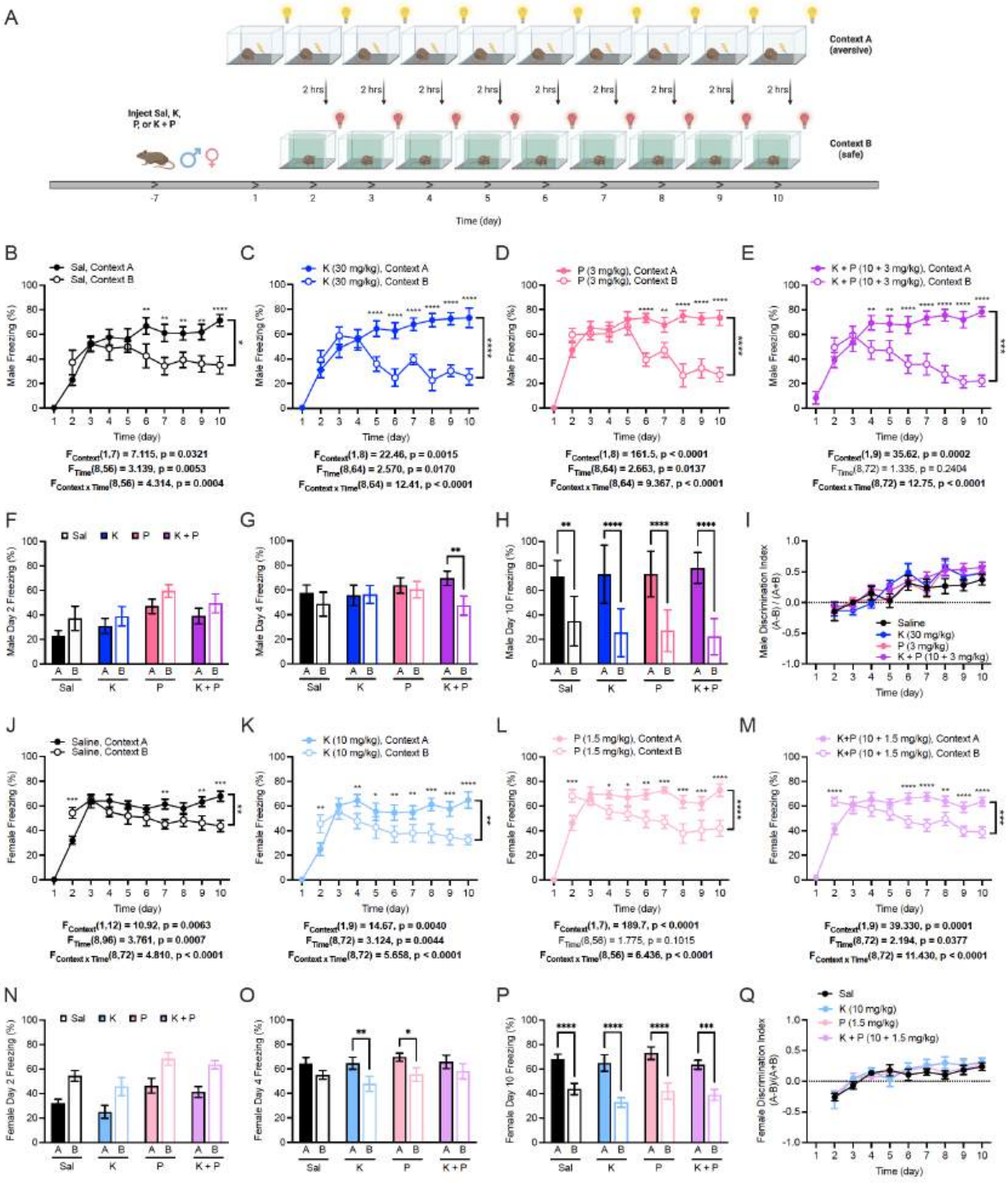

Figure S1. Combined prophylactic (*R,S*)-ketamine + prucalopride administration allows for faster contextual fear discrimination in male mice. (A) Experimental

design. Female and male mice were administered Sal, K (30 mg/kg in male mice, 10 mg/kg in female mice), P (3 mg/kg in male mice, 1.5 mg/kg in female mice), or K+P (10 + 3 mg/kg in male mice, 10 + 1.5 mg/kg in female mice) one week prior to the start of CFD. **(B)** Sal-administered male mice started discriminating on day 6. **(C)** K-administered male mice started discriminating on day 5. **(D)** P-administered male mice started discriminating on day 6. **(E)** K+P-administered male mice started discriminating on day 4. Average freezing on days **(F)** 2, **(G)** 4, and **(H)** 10 for male mice. **(I)** All groups of male mice showed comparable discrimination ratios during CFD. **(J)** Sal-administered female mice started discriminating on day 7. **(K)** K-administered female mice started discriminating on day 4. **(L)** P-administered female mice started discriminating on day 4. **(M)** K+P-administered female mice started discriminating on day 6. Average freezing on days **(N)** 2, **(O)** 6, and **(P)** 10 for female mice. **(Q)** All groups of female mice showed comparable discrimination ratios during CFD. (n = 6-10 female mice per group). Error bars represent $\pm$ SEM. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$, **** $p < 0.0001$. Sal, saline; K, (*R,S*)-ketamine; P, prucalopride; K + P, (*R,S*)-ketamine + prucalopride; hrs, hours; mg, milligram; kg, kilogram.

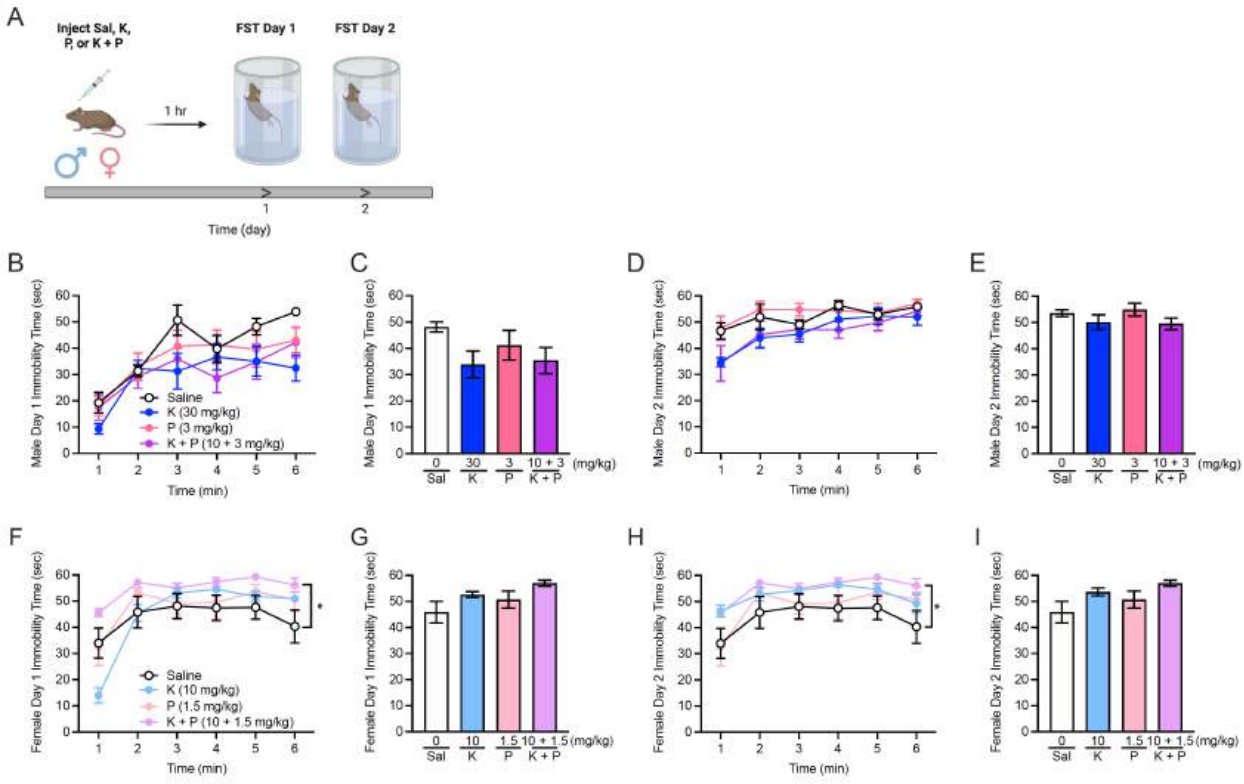

Figure S2. Combined (*R,S*)-ketamine + prucalopride does not attenuate immobility time in the FST in non-stressed 129S6/SvEv mice. (A) Experimental protocol. Sal, K, P, or K+P was administered to male or female mice one hour prior to the FST. In male mice, immobility time was comparable during **(B-C)** day 1 and **(D-E)** day 2 of the FST. **(F-G)** On days 1 and 2 of the FST, K+P-administered female mice exhibited higher overall immobility time when compared to saline controls, but this effect was not significant when comparing average immobility. (n = 4-7 mice per group). Error bars represent ± SEM. * $p < 0.05$. Sal, saline; K, (*R,S*)-ketamine; P, prucalopride; FST, forced swim test; hr, hour; sec, seconds; min, minutes; mg, milligrams; kg, kilograms.

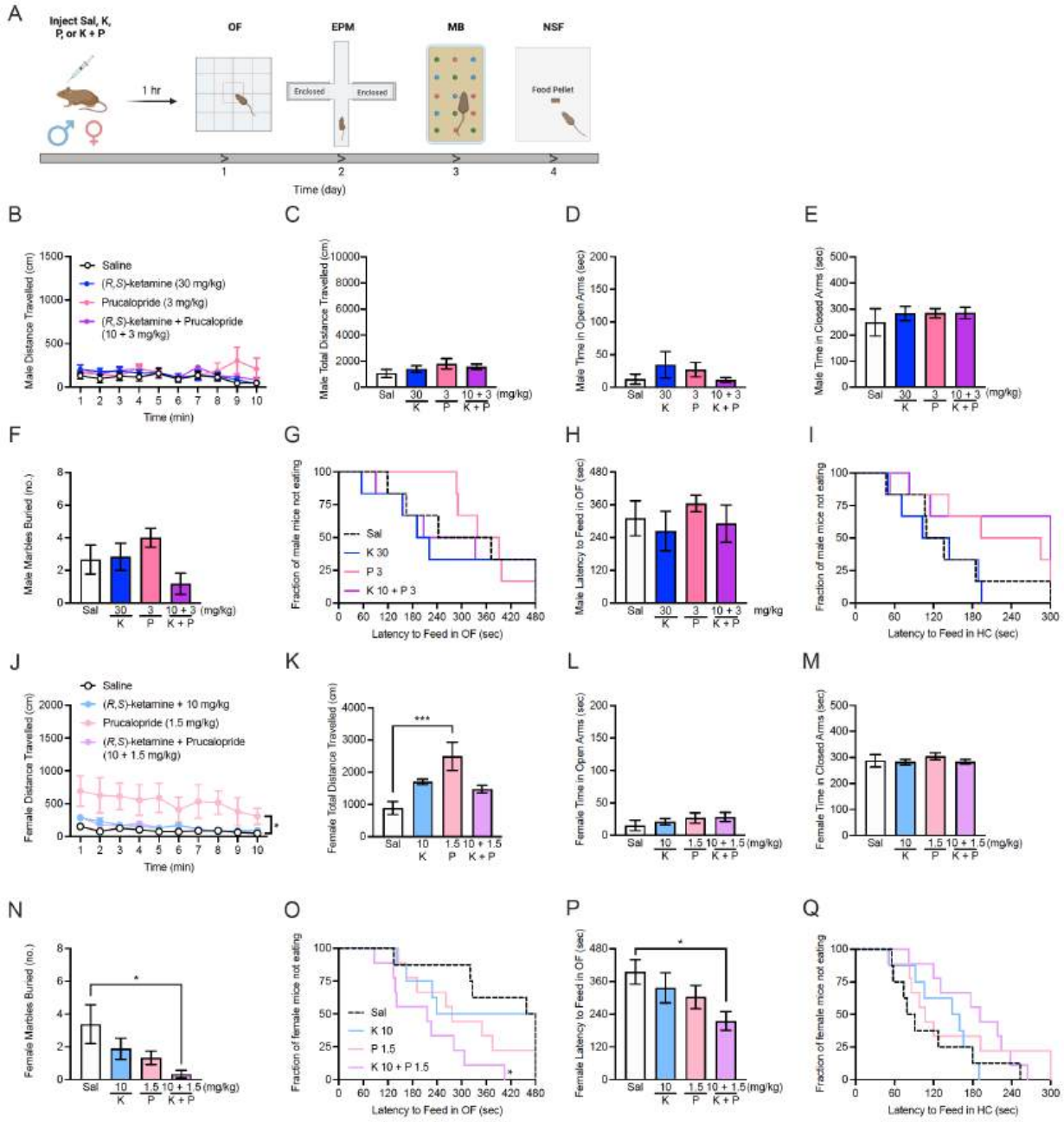

Figure S3. Combined (*R,S*)-ketamine + prucalopride reduces perseverative behavior in non-stressed female mice. (A) Experimental protocol. Male or female 129S6/SvEv mice were given a single injection of Sal, K, P, or K+P one hour prior to the OF test. On subsequent days, mice were administered the EPM, MB, and NSF assays. **(B-I)** Behavior in the OF, EPM, MB, and NSF assays was comparable across all groups

of male mice. **(J-K)** Distance traveled in the OF was significantly higher in prucalopride-administered female mice. **(L-M)** Time spent in the open and closed arms of the EPM was comparable in all groups of female mice. **(N)** Female mice given P or K+P buried a lower number of marbles when compared to Sal-administered mice. **(O-Q)** Behavior in the NSF in female mice was comparable across all groups. Error bars represent ± SEM. * $p < 0.05$. Sal, saline; K, (*R,S*)-ketamine; P, prucalopride; OF, open field; h, hour; EPM, elevated plus maze; MB, marble burying; NSF, novelty-suppressed feeding; cm, centimeters; min, minutes; mg, milligrams; kg, kilograms; sec, seconds; no., number.

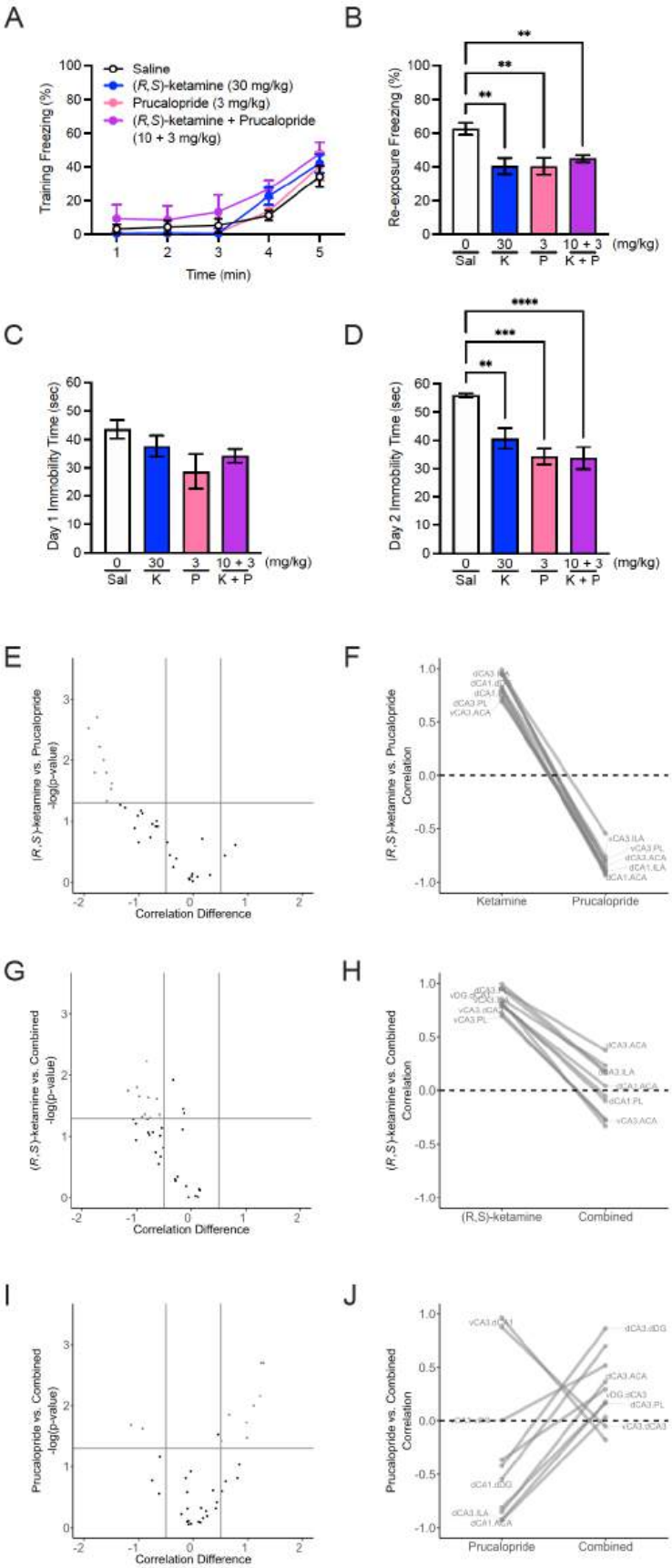

Figure S4. Combined (*R,S*)-ketamine + prucalopride alters correlated excitatory signaling in mPFC and HPC. (A-B) K, P, and K+P reduced freezing during CFC re-exposure but did not alter freezing during CFC training. **(C-D)** K, P, and K+P reduced immobility time during day 2, but not day 1 of the FST. Volcano and parallel plots indicating regional c-fos correlation differences greater than 0.5 between **(E-F)** K and P, **(G-H)** K and K+P, and **(I-J)** P and K+P. (n = 7-8 mice per group). Error bars represent ± SEM. ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$. Sal, saline; K, (*R,S*)-ketamine; P, prucalopride; K + P, (*R,S*)-ketamine + prucalopride; ACA, anterior cingulate area; ILA, infralimbic area; PL, prelimbic area; dDG, dorsal dentate gyrus; dCA3, dorsal field CA3; dCA1, dorsal field CA1; vDG, ventral dentate gyrus; vCA3, ventral field CA3; vCA1, ventral field CA1.

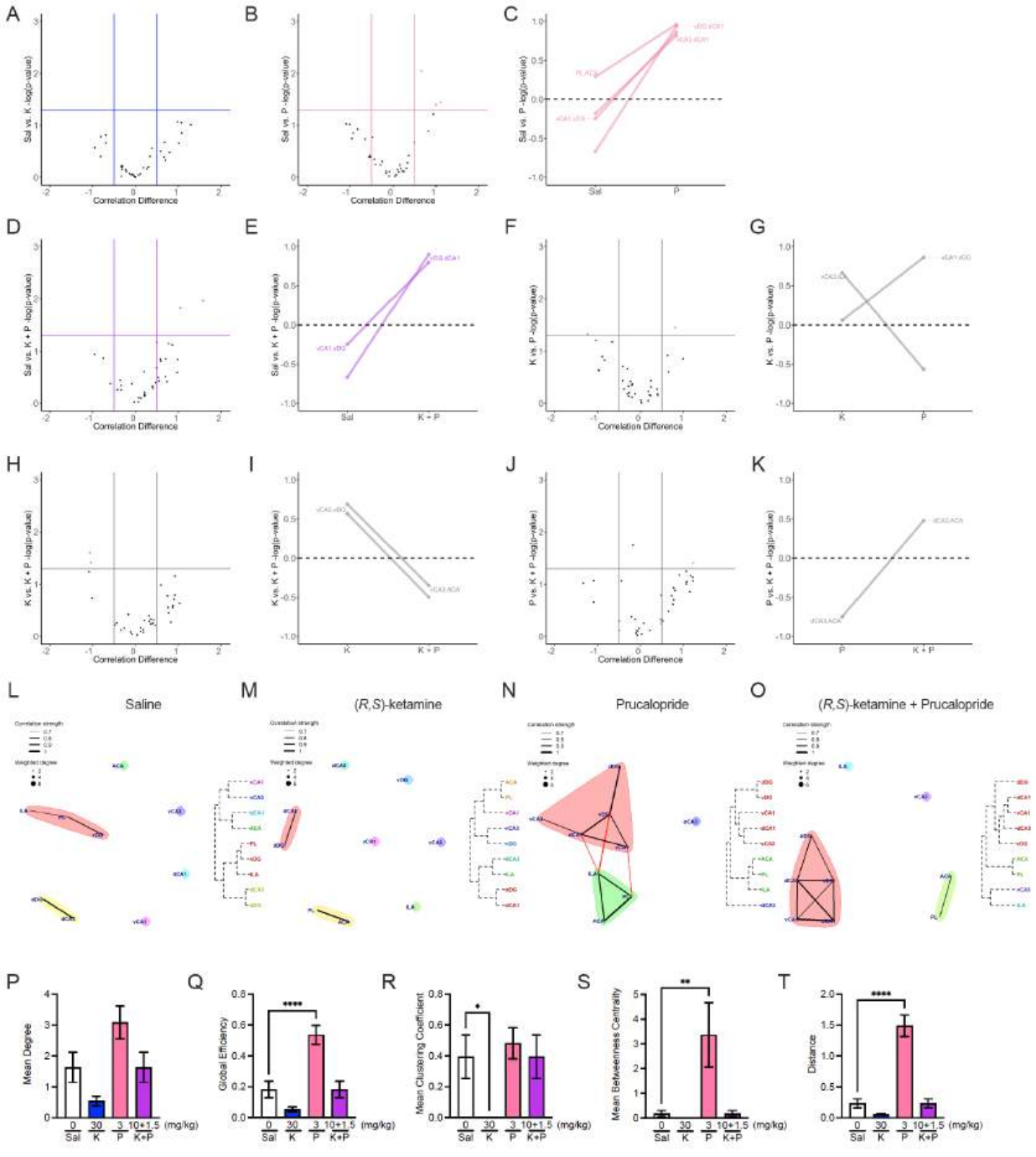

Figure S5. Combined (*R,S*)-ketamine + prucalopride alters correlated PV expression and inhibitory network activity. Volcano and parallel plots indicating regional PV correlation differences greater than 0.5 between **(A)** Sal and K, **(B-C)** Sal and P, **(D-E)** Sal and K+P, **(F-G)** K and P, **(H-I)** K and K+P, and **(J-K)** P and K+P.

Notably, mice given K+P exhibited an increase in correlated vCA1-vDG and vDG-dCA1 activity when compared with Sal controls. Cluster maps of correlated PV expression in **(L)** Sal-, **(M)** K-, **(O)** P, and **(P)** K+P-administered mice reveal sparsely connected activity in Sal- and K-administered mice, while cluster maps for prucalopride and combined drug-administered cluster maps are more cohesive. In particular, vCA3 is an isolated region in the combined drug cluster map, in contrast to all other dorsal and ventral hippocampal regions. **(P)** Mean degree is comparable across all drug groups. **(Q)** P administration increases mean global efficiency when compared with saline administration. **(R)** K administration reduces the mean clustering coefficient compared to saline. **(S-T)** Mean betweenness centrality and network distance are increased in prucalopride-administered mice when compared with saline controls. (n = 7-8 mice per group). Error bars represent ± SEM. ACA, anterior cingulate area; ILA, infralimbic area; PL, prelimbic area; dDG, dorsal dentate gyrus; dCA3, dorsal field CA3; dCA1, dorsal field CA1; vDG, ventral dentate gyrus; vCA3, ventral field CA3; vCA1, ventral field CA1. Sal, saline; K, (*R,S*)-ketamine; P, prucalopride; K + P, (*R,S*)-ketamine + prucalopride; mg, milligram; kg, kilogram.

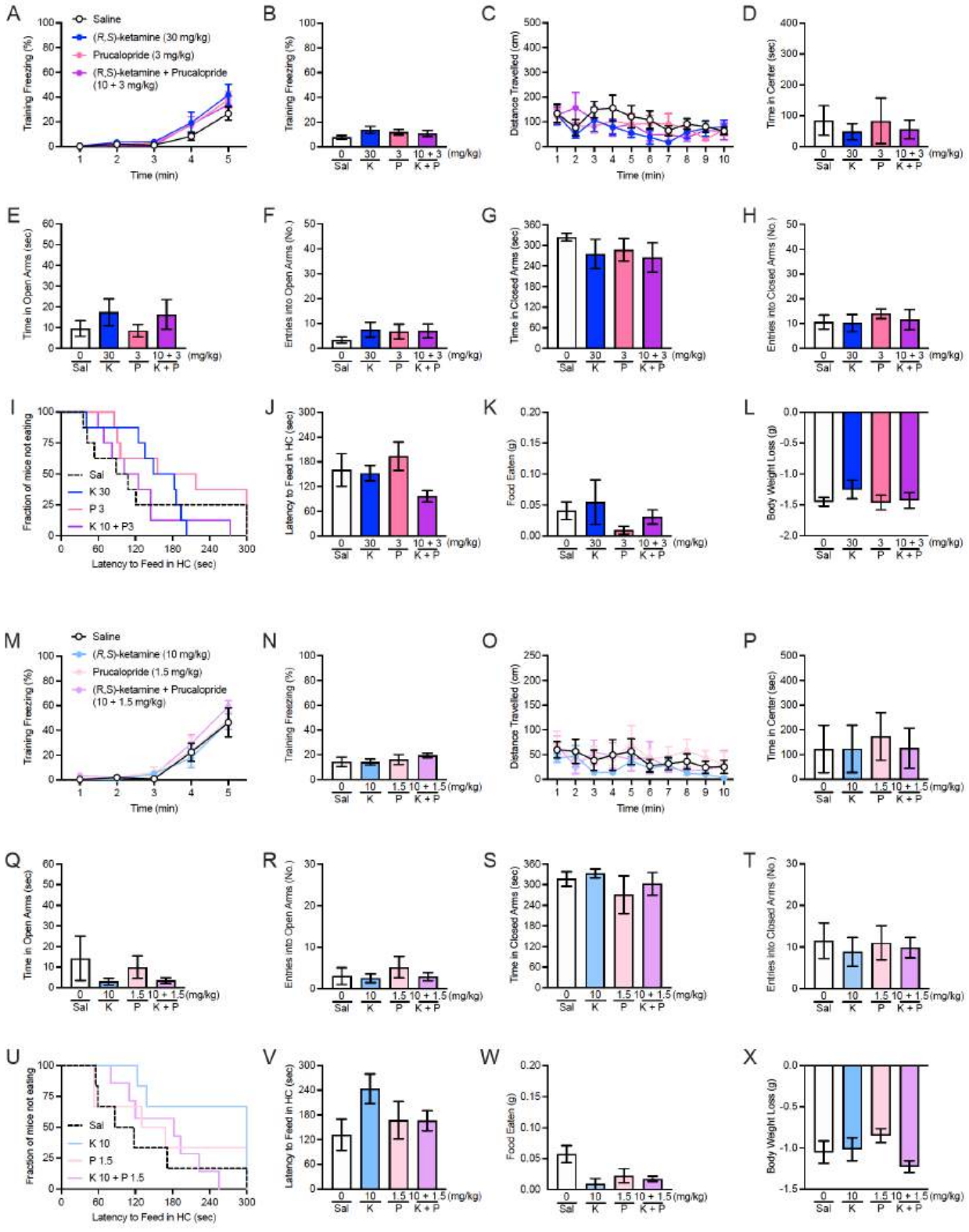

Figure S6. Combined (*R,S*)-ketamine + prucalopride attenuates learned fear in male mice and reduces behavioral despair and hyponeophagia in both sexes

when administered after stress. (A) Freezing was comparable across all groups of male mice during CFC training. Behavior was comparable across all groups of male mice in **(C-D)** the OF and **(E-H)** the EPM. **(I-J)** Latency to feed in the home cage, **(K)** food eaten, and **(L)** body weight loss in the NSF were comparable across all groups of male mice. **(M-N)** Freezing during CFC training was comparable across all drug groups in female mice. In female mice, behavior in **(O-P)** the OF and **(Q-T)** the EPM was not altered by prophylactic drug administration. **(U-V)** Latency to feed in the home cage, **(W)** food eaten, and **(X)** body weight loss in the NSF were comparable across all groups of female mice. (n = 5-7 male or female mice per group). Error bars represent ± SEM. Sal, saline; K, (*R,S*)-ketamine; P, prucalopride; K + P, (*R,S*)-ketamine + prucalopride; mg, milligram; kg, kilogram; cm, centimeter; min, minute; sec, second; no., number; HC, home cage; g, gram.

Table S01. Behavioral and electrophysiological statistical analysis.

Table S02. Network and immunohistochemical analysis.

Table S03. Key resources.

Table S01: Behavioral and electrophysiological statistical analysis

Cohort	Behavioral Paradigm	Abbrev	Measurement	Statistical Test	Comparison	F / R2	° of freedom	p	*	Fig.
	Contextual Fear Conditioning Training	CFC Training	Freezing (%)	RMANOVA	Time x Drug	1.022	44,344	0.4381	ns	data not shown
					Time	271.7	4,344	<0.0001	****	
					Drug	0.796	11,86	0.6435	ns	
			Average Freezing (min 1-5) (%)	One-way ANOVA	Drug	0.796	11,86	0.6435	ns	1B
	Contextual Fear Conditioning Re-exposure	CFC Re-exposure	Freezing (%)	RMANOVA	Time x Drug	1.38	44,344	0.0619	ns	data not shown
					Time	17.42	4,344	<0.0001	****	
					Drug	2.818	11,86	0.0035	**	
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9663	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.0057	**	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.9761	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0211	*	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.2911	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9960	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.2657	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0006	***	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.1034	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.5278	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9112	ns	
			Average Freezing (min 1-5) (%)	One-way ANOVA	Drug	2.818	11,86	0.0035	**	1C
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9663	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.0057	**	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.9761	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0211	*	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.2911	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9960	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.2657	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0006	***	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.1034	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.5278	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9112	ns	
	Forced Swim Test Day 1	FST Day 1	Immobility Time (sec)	RMANOVA	Time x Drug	1.283	55,405	0.0946	ns	data not shown
					Time	41.3	5,405	<0.0001	****	
					Drug	0.8374	11,81	0.6036	ns	
			Average Immobility Time (min 3-6) (sec)	One-way ANOVA	Drug	0.7144	11,81	0.7215	ns	1D
			Immobility Time (sec)	RMANOVA	Time x Drug	1.473	55,405	0.0202	*	
					Time	12.56	5,405	<0.0001	****	
					Drug	4.568	11,81	<0.0001	****	
			Minute 1: Immobility Time (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9999	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.5332	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.9292	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.8691	ns	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.7500	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0611	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	>0.9999	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9446	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9996	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.8052	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.4336	ns	
			Minute 2: Immobility Time (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9996	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.9885	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.9744	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.2439	ns	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.9994	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.4019	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9998	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0429	*	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9992	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9230	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.0227	*	
			Minute 3: Immobility Time	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9958	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.5967	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.4063	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.1136	ns	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.9997	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.2981	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9918	ns	

	Forced Swim Test Day 2	FST Day 2	(sec)		Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	<0.0001	****	data not shown
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9959	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9225	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.0006	***	
			Minute 4: Immobility Time (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9996	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.6692	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.2322	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.2552	ns	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.9996	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.6904	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9998	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	<0.0001	****	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9994	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.2842	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.0741	ns	
			Minute 5: Immobility Time (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9994	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.0527	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.9606	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0448	*	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.9996	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.8371	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9966	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0006	***	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.7753	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.1463	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.0035	**	
			Minute 6: Immobility Time (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9964	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.7890	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.2200	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.007	**	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.0565	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9889	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9580	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0185	*	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9995	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.1729	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	<0.0001	****	
			Average Immobility Time (min 3-6) (sec)	One-way ANOVA	Drug	5.894	11,81	<0.0001	****	1E
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9999	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.0139	*	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.1779	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0083	**	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.9069	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.4536	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9880	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	<0.0001	****	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9737	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.1132	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	<0.0001	****	
	Open Field Test	OF	Distance Traveled (cm)	RMANOVA	Time x Drug	0.8199	99,729	0.8923	ns	data not shown
					Time	8.975	9,729	<0.0001	****	
					Drug	0.3196	11,81	0.9795	ns	
			Time in Center (sec)	One-way ANOVA	Drug	0.845	11,81	0.5963	ns	data not shown
			Total Distance Traveled (cm)	One-way ANOVA	Drug	0.3196	11,81	0.9795	ns	1F
			Distance Traveled (m)	RMANOVA	Time x Drug	1.999	55,410	<0.0001	****	
					Time	52.04	5,410	<0.0001	****	
					Drug	7.164	11,82	<0.0001	****	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9514	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.0554	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.0068	**	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.9996	ns	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.9991	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0081	**	

			Minute 1: Distance Traveled (m)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Procalopride (1.5 mg/kg)	-	-	0.0060	**	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Procalopride (3 mg/kg)	-	-	0.0262	*	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Procalopride (3 mg/kg)	-	-	0.0018	**	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Procalopride (10 mg/kg)	-	-	0.9996	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Procalopride (10 mg/kg)	-	-	0.9998	ns	
			Minute 2: Distance Traveled (m)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.0103	*	
					Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.2452	ns	
					Saline vs. Procalopride (1.5 mg/kg)	-	-	0.0031	**	
					Saline vs. Procalopride (3 mg/kg)	-	-	0.9993	ns	
					Saline vs. Procalopride (10 mg//kg)	-	-	0.9906	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Procalopride (1.5 mg/kg)	-	-	0.0253	*	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Procalopride (1.5 mg/kg)	-	-	0.0177	*	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Procalopride (3 mg/kg)	-	-	0.1823	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Procalopride (3 mg/kg)	-	-	0.0016	**	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Procalopride (10 mg/kg)	-	-	0.9997	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Procalopride (10 mg/kg)	-	-	0.9997	ns	
			Minute 3: Distance Traveled (m)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9460	ns	
					Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.8122	ns	
					Saline vs. Procalopride (1.5 mg/kg)	-	-	0.0093	**	
					Saline vs. Procalopride (3 mg/kg)	-	-	0.4187	ns	
					Saline vs. Procalopride (10 mg//kg)	-	-	0.6674	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Procalopride (1.5 mg/kg)	-	-	0.0326	*	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Procalopride (1.5 mg/kg)	-	-	0.0310	*	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Procalopride (3 mg/kg)	-	-	0.9474	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Procalopride (3 mg/kg)	-	-	0.7974	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Procalopride (10 mg/kg)	-	-	0.8278	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Procalopride (10 mg/kg)	-	-	0.6430	ns	data not shown
			Minute 4: Distance Traveled (m)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9527	ns	
					Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.5808	ns	
					Saline vs. Procalopride (1.5 mg/kg)	-	-	0.3533	ns	
					Saline vs. Procalopride (3 mg/kg)	-	-	>0.9999	ns	
					Saline vs. Procalopride (10 mg//kg)	-	-	0.9997	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Procalopride (1.5 mg/kg)	-	-	0.6033	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Procalopride (1.5 mg/kg)	-	-	0.5532	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Procalopride (3 mg/kg)	-	-	0.2359	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Procalopride (3 mg/kg)	-	-	0.8235	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Procalopride (10 mg/kg)	-	-	>0.9999	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Procalopride (10 mg/kg)	-	-	0.9993	ns	
			Minute 5: Distance Traveled (m)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9958	ns	
					Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.7852	ns	
					Saline vs. Procalopride (1.5 mg/kg)	-	-	0.0872	ns	
					Saline vs. Procalopride (3 mg/kg)	-	-	0.4370	ns	
					Saline vs. Procalopride (10 mg//kg)	-	-	0.9567	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Procalopride (1.5 mg/kg)	-	-	0.1910	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Procalopride (1.5 mg/kg)	-	-	0.2566	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Procalopride (3 mg/kg)	-	-	0.9996	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Procalopride (3 mg/kg)	-	-	0.9799	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Procalopride (10 mg/kg)	-	-	0.9919	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Procalopride (10 mg/kg)	-	-	0.8251	ns	
			Minute 6: Distance Traveled (m)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9995	ns	
					Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.9994	ns	
					Saline vs. Procalopride (1.5 mg/kg)	-	-	0.5168	ns	
					Saline vs. Procalopride (3 mg/kg)	-	-	0.9600	ns	
					Saline vs. Procalopride (10 mg//kg)	-	-	0.9195	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Procalopride (1.5 mg/kg)	-	-	0.6801	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Procalopride (1.5 mg/kg)	-	-	0.6777	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Procalopride (3 mg/kg)	-	-	0.8552	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Procalopride (3 mg/kg)	-	-	0.4856	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Procalopride (10 mg/kg)	-	-	0.9992	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Procalopride (10 mg/kg)	-	-	0.9748	ns	
Male, 1 week before CFC			Time in Center (sec)	RMANOVA	Time x Drug	1.599	55,405	0.0063	**	
					Time	2.344	1,327	0.0541	ns	
					Drug	1.735	11,81	0.0802	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9999	ns	

	Elevated Plus Maze	EPM	Minute 1: Time in Center (sec)	Dunnett's Test	Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.9025	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.8936	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.9997	ns	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.2468	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9969	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9311	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9998	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9743	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9453	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.2547	ns	
			Minute 2: Time in Center (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9997	ns	
					Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.9994	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.4192	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.9426	ns	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.9994	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	>0.9999	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9994	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.8464	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9932	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.8771	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	>0.9999	ns	
			Minute 3: Time in Center (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	>0.9999	ns	
					Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.9971	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.9997	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.6781	ns	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.9972	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9745	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.8938	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9998	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9923	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9927	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9996	ns	data not shown
			Minute 4: Time in Center (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9761	ns	
					Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.2907	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.9659	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.9972	ns	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.9998	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.8185	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9963	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9410	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9163	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.0819	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9998	ns	
			Minute 5: Time in Center (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9933	ns	
					Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.9896	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.7624	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.6771	ns	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.9995	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.7696	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.8722	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.1963	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9558	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.0080	**	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9998	ns	
			Minute 6: Time in Center (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9482	ns	
					Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.9656	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.9971	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.5808	ns	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.9545	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9993	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9999	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9404	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9887	ns	

					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.4566	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9997	ns	
				Total Time in Center (sec)	One-way ANOVA	Drug	1.735	11,81	0.0801	ns	data not shown
				Entries into Center (no.)	One-way ANOVA	Drug	1.683	11,81	0.0921	ns	data not shown
				Time in Open Arms (sec)	RMANOVA	Time x Drug	1.302	55,405	0.0817	ns	data not shown
						Time	42.77	5,405	<0.0001	****	
						Drug	1.439	11,81	0.1718	ns	
				Total Time in Open Arms (sec)	One-way ANOVA	Drug	1.437	11,81	0.1718	ns	1G
				Entries into Open Arms (no.)	One-way ANOVA	Drug	2.122	11,81	0.0275	*	data not shown
					Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.6072	ns	
						Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.9997	ns	
						Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.7653	ns	
						Saline vs. Prucalopride (3 mg/kg)	-	-	0.9993	ns	
						Saline vs. Prucalopride (10 mg//kg)	-	-	0.9965	ns	
						Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0527	ns	
						Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9682	ns	
						Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9991	ns	
						Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9849	ns	
						Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9996	ns	
						Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9999	ns	
				Time in Closed Arms (sec)	RMANOVA	Time x Drug	1.437	55,405	0.0277	*	
						Time	6.858	5,405	<0.0001	****	
						Drug	1.047	11,81	0.4146	ns	
				Minute 1: Time in Closed Arms (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9991	ns	
						Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.9994	ns	
						Saline vs. Prucalopride (1.5 mg/kg)	-	-	>0.9999	ns	
						Saline vs. Prucalopride (3 mg/kg)	-	-	0.9993	ns	
						Saline vs. Prucalopride (10 mg//kg)	-	-	>0.9999	ns	
						Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.4771	ns	
						Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9996	ns	
						Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9458	ns	
						Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9995	ns	
						Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9992	ns	
						Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9832	ns	
				Minute 2: Time in Closed Arms (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9998	ns	
						Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.9995	ns	
						Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.8030	ns	
						Saline vs. Prucalopride (3 mg/kg)	-	-	0.9211	ns	
						Saline vs. Prucalopride (10 mg//kg)	-	-	0.9924	ns	
						Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9993	ns	
						Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	>0.9999	ns	
						Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9995	ns	
						Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	>0.9999	ns	
						Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9998	ns	
						Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9488	ns	
				Minute 3: Time in Closed Arms (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9995	ns	
						Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.9991	ns	
						Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.9999	ns	
						Saline vs. Prucalopride (3 mg/kg)	-	-	0.8273	ns	
						Saline vs. Prucalopride (10 mg//kg)	-	-	>0.9999	ns	
						Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9994	ns	
						Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9888	ns	
						Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9997	ns	
						Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9993	ns	
						Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9996	ns	
						Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9992	ns	data not shown
				Minute 4: Time in Closed Arms (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9658	ns	
						Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.5725	ns	
						Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.9453	ns	
						Saline vs. Prucalopride (3 mg/kg)	-	-	0.9995	ns	
						Saline vs. Prucalopride (10 mg//kg)	-	-	0.9992	ns	
						Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9962	ns	
						Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9369	ns	
						Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9159	ns	

					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9220	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.3038	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9994	ns	
			Minute 5: Time in Closed Arms (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9103	ns	
					Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	>0.9999	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.8344	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.5166	ns	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.9995	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9594	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.8729	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.3531	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9474	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.2791	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.9963	ns	
			Minute 6: Time in Closed Arms (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9710	ns	
					Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.9665	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.9995	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.1419	ns	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.7082	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9958	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9997	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9756	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9765	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.8625	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	>0.9999	ns	
			Total Time in Closed Arms (sec)	One-way ANOVA	Drug	1.047	11,81	0.4140	ns	data not shown
			Entries into Closed Arms (no.)	One-way ANOVA	Drug	2.547	11,81	0.0081	**	data not shown
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9997	ns	
					Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.9996	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.2088	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.9993	ns	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.9913	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.5950	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.5054	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9999	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9932	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.6072	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.2835	ns	
	Novelty-Suppressed Feeding	NSF	Fraction of mice not eating in OF	Log-rank (Mantel-Cox) Test	Drug	-	-	<0.0001	****	1H
			Latency to Feed in OF	One-way ANOVA	Drug	3.352	11,81	0.0004	***	1I
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	>0.9999	ns	
					Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.7780	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.9995	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.9998	ns	
					Saline vs. Prucalopride (10 mg//kg)	-	-	0.6880	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9915	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9768	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0059	**	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.2231	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.6196	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (10 mg/kg)	-	-	0.8461	ns	
			Fraction of mice not eating in HC	Log-rank (Mantel-Cox) Test	Drug	-	-	0.2521	ns	data not shown
			Latency to Feed in HC	One-way ANOVA	Drug	1.375	11,81	0.2007	ns	1J
			Food Eaten (g)	One-way ANOVA	Drug	0.7015	11,81	0.7336	ns	data not shown
			Body Weight Loss (g)	One-way ANOVA	Drug	0.702	11,81	0.7331	ns	1K
	Contextual Fear Conditioning	CFC Training	Freezing (%)	RMANOVA	Time x Drug	1.235	28,192	0.2042	ns	data not shown
					Time	179.9	4,192	<0.0001	****	
					Drug	1.48	7,48	0.1970	ns	

Training	CFC Training	Average Freezing (min 1-5) (%)	One-way ANOVA	Drug	1.308	7,47	0.2674	ns	2B
Contextual Fear Conditioning Re-exposure	CFC Re-exposure	Freezing (%)	RMANOVA	Time x Drug	1.028	28,192	0.4332	ns	data not shown
				Time	14.57	4,192	<0.0001	****	
				Drug	0.5193	7,48	0.8155	ns	
		Average Freezing (min 1-5) (%)	One-way ANOVA	Drug	0.5193	7,48	0.8155	ns	2C
Forced Swim Test Day 1	FST Day 1	Immobility Time (sec)	RMANOVA	Time x Drug	1.23	35,240	0.1873	ns	data not shown
				Time	46.91	5,240	<0.0001	****	
				Drug	9.038	7,48	<0.0001	****	
			Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	<0.0001	****	
				Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.0955	ns	
				Saline vs. Prucalopride (3 mg/kg)	-	-	<0.0001	****	
				Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0002	***	
				Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.4580	ns	
				Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9975	ns	
				Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9807	ns	
		Average Immobility Time (min 3-6) (sec)	One-way ANOVA	Drug	9.227	7,48	<0.0001	****	2D
			Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	<0.0001	****	
				Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.3418	ns	
				Saline vs. Prucalopride (3 mg/kg)	-	-	<0.0001	****	
				Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0002	***	
				Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.8833	ns	
				Saline vs. (*R*,*S*)-ketamine (10 mg/kg) +	-	-	0.9996	ns	
				Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9994	ns	
Forced Swim Test Day 2	FST Day 2	Immobility Time (sec)	RMANOVA	Time x Drug	1.679	35,240	0.0133	*	data not shown
				Time	17.26	5,240	<0.0001	****	
				Drug	6.494	7,48	<0.0001	****	
		Min 1: Immobility Time (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.2928	ns	
				Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.9887	ns	
				Saline vs. Prucalopride (3 mg/kg)	-	-	0.0207	*	
				Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.3902	ns	
				Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9932	ns	
				Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.1588	ns	
				Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9944	ns	
		Min 2: Immobility Time (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.0060	**	
				Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.0740	ns	
				Saline vs. Prucalopride (3 mg/kg)	-	-	<0.0001	****	
				Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.3559	ns	
				Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	>0.9999	ns	
				Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.7221	ns	
				Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9596	ns	
		Min 3: Immobility Time (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.0018	**	
				Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.0838	ns	
				Saline vs. Prucalopride (3 mg/kg)	-	-	<0.0001	****	
				Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0363	*	
				Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	>0.9999	ns	
				Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.3172	ns	
				Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.8184	ns	
		Min 4: Immobility Time (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	<0.0001	****	
				Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.0271	*	
				Saline vs. Prucalopride (3 mg/kg)	-	-	0.0167	*	
				Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.1575	ns	
				Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9997	ns	
				Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9996	ns	
				Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.1649	ns	
		Min 5: Immobility Time (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.0008	***	
				Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.6272	ns	
				Saline vs. Prucalopride (3 mg/kg)	-	-	0.2876	ns	
				Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.2088	ns	
				Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9997	ns	
				Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9907	ns	
				Saline vs. (*R*,*S*)-ketamine (30 mg/kg) +	-	-	0.9995	ns	
		Min 6: Immobility Time (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.0073	**	
				Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.2151	ns	
				Saline vs. Prucalopride (3 mg/kg)	-	-	0.0225	*	
				Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.1295	ns	
				Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	>0.9999	ns	
				Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9997	ns	

Female, 1 week before CFC					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9997	ns	
			Average Immobility Time (min 3-6) (sec)	One-way ANOVA	Drug	6.164	7,48	<0.0001	****	2E
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	<0.0001	****	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.0382	*	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0013	**	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0246	*	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	>0.9999	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9056	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.8253	ns	
	Open Field Test	OF	Distance Traveled (cm)	RMANOVA	Time x Drug	0.8894	63,432	0.7114	ns	data not shown
					Time	8.17	9,432	<0.0001	****	
					Drug	1.878	7,48	0.0941	ns	
			Time in Center (sec)	One-way ANOVA	Drug	1.01	7,48	0.4360	ns	data not shown
			Total Distance Traveled (cm)	One-way ANOVA	Drug	1.878	7,48	0.0941	ns	2F
	Elevated Plus Maze	EPM	Distance Traveled (m)	RMANOVA	Time x Drug	0.6969	35,240	0.9000	ns	data not shown
					Time	13.08	5,240	<0.0001	****	
					Drug	1.717	7,48	0.1274	ns	
			Time in Center (sec)	RMANOVA	Time x Drug	1.109	35,240	0.3178	ns	data not shown
					Time	2.357	5,240	0.0411	*	
					Drug	0.719	7,48	0.6560	ns	
			Total Time in Center (sec)	One-way ANOVA	Drug	0.7187	7,48	0.6565	ns	data not shown
			Entries into Center (no.)	One-way ANOVA	Drug	2.713	7,48	0.0188	*	data not shown
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.3926	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.0131	*	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.5295	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9934	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9960	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9995	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9858	ns	
			Time in Open Arms (sec)	RMANOVA	Time x Drug	1.164	35,240	0.2524	ns	data not shown
					Time	7.027	5,240	<0.0001	****	
					Drug	3.824	7,48	0.0022	**	
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.0561	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.3975	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0016	**	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.6550	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9997	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	>0.9999	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9996	ns	
			Total Time in Open Arms (sec)	One-way ANOVA	Drug	3.82	7,48	0.0022	**	2G
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.0560	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.3994	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0016	**	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.6562	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9997	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	>0.9999	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9996	ns	
			Entries into Open Arms (no.)	One-way ANOVA	Drug	4.32	7,48	0.0009	***	data not shown
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.1955	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.0728	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0007	***	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9284	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9996	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9977	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9999	ns	
			Time in Closed Arms (sec)	RMANOVA	Time x Drug	1.093	35,240	0.3400	ns	data not shown
					Time	2.508	5,240	0.0309	*	
					Drug	1.057	7,48	0.4056	ns	
			Total Time in Closed Arms (sec)	One-way ANOVA	Drug	1.057	7,48	0.4056	ns	data not shown
			Entries into Closed Arms (no.)	One-way ANOVA	Drug	3.094	7,48	0.0090	**	data not shown
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.4861	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.0054	**	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.9955	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9971	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9849	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9996	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.8860	ns	

	Novelty-Suppressed Feeding	NSF	Fraction of mice not eating in OF	Log-rank (Mantel-Cox) Test	Drug	-	-	0.0007	**	2H
			Latency to Feed in OF (sec)	One-way ANOVA	Drug	2,242	7,48	0.0467	*	2I
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	>0.9999	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.9467	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.7613	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0250	*	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.1051	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9892	ns	
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9999	ns	
			Fraction of mice not eating in HC	Log-rank (Mantel-Cox) Test	Drug	-	-	0.9371	ns	data not shown
			Latency to Feed in HC (sec)	One-way ANOVA	Drug	0.3653	7,48	0.9179	ns	2J
			Food Eaten (g)	One-way ANOVA	Drug	1.777	7,48	0.1139	ns	data not shown
			Body Weight Loss (g)	One-way ANOVA	Drug	1.774	7,48	0.1145	ns	2K
Male, 1 week before electrophysiology	Electrophysiology	Ephys	Amplitude (pA)	Mann-Whitney test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0101	*	3D
			EPSCs (no.)	Mann-Whitney test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.1136	ns	3G
Male, 5 min after CFC	Contextual Fear Conditioning Re-exposure	CFC Re-exposure	Freezing (%)	RMANOVA	Time x Drug	0.5806	12,112	0.8538	ns	7B
					Time	9.501	4,112	<0.0001	****	
					Drug	8.649	3,28	0.0003	***	
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.5181	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.2104	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0095	**	
			Average Freezing (min 1-5) (%)	One-way ANOVA	Drug	8.649	3,28	0.0003	***	7C
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.5181	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.2104	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0095	**	
	Forced Swim Test Day 1	FST Day 1	Immobility Time (sec)	RMANOVA	Time x Drug	0.6986	15,140	0.7826	ns	7D
					Time	38.38	5,140	<0.0001	****	
					Drug	1.149	3,28	0.3468	ns	
			Average Immobility Time (min 3-6) (sec)	One-way ANOVA	Drug	1.103	3,28	0.3643	ns	7E
	Forced Swim Test Day 2	FST Day 2	Immobility Time (sec)	RMANOVA	Time x Drug	0.715	15,140	0.7662	ns	7F
					Time	10.6	5,140	<0.0001	****	
					Drug	4.93	3,28	0.0071	**	
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.0068	**	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.7016	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0240	*	
			Average Immobility Time (min 3-6) (sec)	One-way ANOVA	Drug	5.399	3,28	0.0046	**	7G
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.0036	**	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.6505	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0234	*	
	Novelty-Suppressed Feeding	NSF	Fraction of mice not eating in OF	Log-rank (Mantel-Cox) Test	Drug	-	-	0.0052	**	7H
			Latency to Feed in OF (sec)	One-way ANOVA	Drug	3.622	3,28	0.0251	*	7I
					Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.2784	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.5402	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0084	**	
	Contextual Fear Conditioning Re-exposure	CFC Re-exposure	Freezing (%)	RMANOVA	Time x Drug	1.29	12,84	0.2395	ns	7J
					Time	6.003	4,84	0.0009	***	
					Drug	1.968	3,21	0.1497	ns	
			Average Freezing (min 1-5) (%)	One-way ANOVA	Drug	1.968	3,21	0.1497	ns	7K
			Immobility Time (sec)	RMANOVA	Time x Drug	3.054	15,105	0.0004	***	7L
					Time	47.08	5,105	<0.0001	****	
					Drug	1.224	3,21	0.3257	ns	
			Min 1: Immobility Time (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9069	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.9999	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9195	ns	
			Min 2: Immobility Time (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9560	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.9975	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.8294	ns	
			Min 3: Immobility Time (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.7827	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.6701	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9313	ns	

Female, 5 min after CFC	Forced Swim Test Day 1	FST Day 1	Min 4: Immobility Time (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9147	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.4570	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0558	ns	
			Min 5: Immobility Time (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9951	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.8278	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0379	*	
			Min 6: Immobility Time (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.6897	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.1284	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0003	***	
			Average Immobility Time (min 3-6) (sec)	One-way ANOVA	Drug	3.935	3,21	0.0225	*	7M
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.8277	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.2497	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0111	*	
	Forced Swim Test Day 2	FST Day 2	Immobility Time (sec)	RMANOVA	Time x Drug	1.435	15,105	0.1447	ns	7N
					Time	22.890	5,105	<0.0001	****	
					Drug	5.851	3,21	0.0045	**	
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	*	0.0456	
					Saline vs. Prucalopride (3 mg/kg)	-	-	ns	0.6424	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	**	0.0025	
			Average Immobility Time (min 3-6) (sec)	One-way ANOVA	Drug	5.38	3,21	0.0066	**	7O
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.0490	*	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.9966	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0113	*	
	Novelty-Suppressed Feeding	NSF	Fraction of mice not eating in OF	Log-rank (Mantel-Cox) Test	Drug	-	-	0.0025	**	7P
			Latency to Feed in OF (sec)	One-way ANOVA	Drug	4.442	3,21	0.0144	*	7Q
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9618	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0562	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0185	*	
	Saline, Contexual Fear Discrimination	Sal, CFD	Freezing (%)	RMANOVA	Time	3.139	8,56	0.0053	**	S1B
					Context	7.115	1,7	0.0321	*	
					Time x Context	4.314	8,56	0.0004	***	
			Day 2: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0698	ns	
			Day 3: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.9547	ns	
			Day 4: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.2475	ns	
			Day 5: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.4174	ns	
			Day 6: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0025	**	
			Day 7: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0010	**	
			Day 8: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0072	**	
			Day 9: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0015	**	
			Day 10: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
	(*R*,*S*)-ketamine (30 mg/kg), Contextual Fear Discrimination	K 30, CFD	Freezing (%)	RMANOVA	Time	2.570	8,64	0.0170	*	S1C
					Context	22.460	1,8	0.0015	**	
					Time x Context	12.410	8,64	<0.0001	****	
			Day 2: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.2499	ns	
			Day 3: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.1427	ns	
			Day 4: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.9085	ns	
			Day 5: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
			Day 6: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
			Day 7: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
			Day 8: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
			Day 9: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
			Day 10: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
	Prucalopride (3 mg/kg), Contextual Fear Discrimination	P3, CFD	Freezing (%)	RMANOVA	Time	2.663	8,64	0.0137	*	S1D
					Context	161.500	1,8	<0.0001	****	
					Time x Context	9.367	8,64	<0.0001	****	
			Day 2: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0877	ns	
			Day 3: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.5018	ns	
			Day 4: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.6430	ns	
			Day 5: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.4394	ns	

	Contextual Fear Discrimination		Day 6: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
			Day 7: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0058	**	
			Day 8: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
			Day 9: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
			Day 10: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
Male, contextual fear discrimination	(*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg), Contextual Fear Discrimination	K 10 + P 3, CFD	Freezing (%)	RMANOVA	Time	1.335	8,72	0.2404	ns	S1E
					Context	35.620	1,9	0.0002	***	
					Time x Context	12.750	8,72	<0.0001	****	
			Day 2: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.1244	ns	
			Day 3: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.3885	ns	
			Day 4: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0033	**	
			Day 5: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0014	**	
			Day 6: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
			Day 7: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
			Day 8: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
			Day 9: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
			Day 10: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
	Contextual Fear Discrimination Day 2 Freezing	CFD Day 2 Freezing	Day 2 Freezing (%)	RMANOVA	Context x Drug	0.164	3,32	0.9198	ns	S1F
					Context	11.200	1,32	0.0021	**	
					Drug	2.817	3,32	0.0548	ns	
				Dunnett's Test	Saline: Context A vs. Context B	-	-	0.1949	ns	
					(*R*,*S*)-ketamine (30 mg/kg): Context A vs. Context B	-	-	0.6834	ns	
					Prucalopride (3 mg/kg): Context A vs. Context B	-	-	0.2579	ns	
					(*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg0: Context A vs. Context B	-	-	0.3800	ns	
	Contextual Fear Discrimination Day 4 Freezing	CFD Day 4 Freezing	Day 4 Freezing (%)	RMANOVA	Context x Drug	2.155	3,32	0.1127	ns	S1G
					Context	5.720	1,32	0.0228	*	
					Drug	0.335	3,32	0.7999	ns	
				Dunnett's Test	Saline: Context A vs. Context B	-	-	0.6581	ns	
					(*R*,*S*)-ketamine (30 mg/kg): Context A vs. Context B	-	-	>0.9999	ns	
					Prucalopride (3 mg/kg): Context A vs. Context B	-	-	0.9827	ns	
					(*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg0: Context A vs. Context B	-	-	0.0090	**	
	Contextual Fear Discrimination Day 10 Freezing	CFD Day 10 Freezing	Day 10 Freezing (%)	RMANOVA	Context x Drug	0.926	3,32	0.4395	ns	S1H
					Context	124.400	1,32	<0.0001	****	
					Drug	0.144	3,32	0.9328	ns	
				Dunnett's Test	Saline: Context A vs. Context B	-	-	0.0010	**	
					(*R*,*S*)-ketamine (30 mg/kg): Context A vs. Context B	-	-	<0.0001	****	
					Prucalopride (3 mg/kg): Context A vs. Context B	-	-	<0.0001	****	
					(*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg0: Context A vs. Context B	-	-	<0.0001	****	
	Context A, Contextual Fear Discrimination	Context A, CFD	Freezing (%)	RMANOVA	Time x Drug	0.811	27,288	0.7366	ns	data not shown
					Time	91.030	9,288	<0.0001	****	
					Drug	1.446	3,32	0.2478	ns	
	Context B, Contextual Fear Discrimination	Context B, CFD	Freezing (%)	RMANOVA	Time x Drug	1.138	24,256	0.3024	ns	data not shown
					Time	12.960	8,256	<0.0001	****	
					Drug	1.223	3,32	0.3173	ns	
	Discrimination Index (A-B) / (A + B)	Discrimination Index	(A-B) / (A + B)	RMANOVA	Time x Drug	0.989	24,256	0.4810	ns	S2I
					Time	26.030	8,256	<0.0001	****	
					Drug	1.532	3,32	0.2251	ns	
				2-way ANOVA	Day x Drug	0.192	6,64	0.9781	ns	data not shown
					Day	48.210	2,64	<0.0001	****	
					Drug	1.504	3,32	0.2322	ns	
	Saline, Contextual Fear Discrimination	Sal, CFD	Freezing (%)	RMANOVA	Time	3.761	8,96	0.0007	***	S1J
					Context	10.920	1,12	0.0063	**	
					Time x Context	4.810	8,96	<0.0001	****	
			Day 2: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0004	***	
			Day 3: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.8551	ns	
			Day 4: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.1377	ns	
			Day 5: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.1484	ns	
			Day 6: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.2460	ns	
			Day 7: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0091	**	
			Day 8: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.1295	ns	
			Day 9: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0058	**	
			Day 10: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0001	***	
			Freezing (%)	RMANOVA	Time	3.124	8,72	0.0044	**	
					Context	14.670	1,9	0.0040	**	

Female, contextual fear discrimination	(R,S)-ketamine (10 mg/kg), Contextual Fear Discrimination	K 10, CFD			Time x Context	5.658	8,72	<0.0001	****	S1K
			Day 2: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0017	**	
			Day 3: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.4270	ns	
			Day 4: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0098	**	
			Day 5: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0467	*	
			Day 6: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0074	**	
			Day 7: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0093	**	
			Day 8: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0004	***	
			Day 9: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0006	***	
			Day 10: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
	Prucalopride (1.5 mg/kg), Contextual Fear Discrimination	P 1.5, CFD	Freezing (%)	RMANOVA	Time	1.775	8,56	0.1015	ns	S1L
					Context	189.700	1,7	<0.0001	****	
					Time x Context	6.436	8,56	<0.0001	****	
			Day 2: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0009	***	
			Day 3: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.3394	ns	
			Day 4: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0281	*	
			Day 5: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0363	*	
			Day 6: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0019	**	
			Day 7: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0001	***	
			Day 8: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0001	***	
			Day 9: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0009	***	
			Day 10: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
	(*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg), Contextual Fear Discrimination	K 10 + P 1.5, CFD	Freezing (%)	RMANOVA	Time	2.194	8,72	0.0377	****	S1M
					Context	39.330	1,9	0.0001	***	
					Time x Context	11.430	8,72	<0.0001	***	
			Day 2: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
			Day 3: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.8211	ns	
			Day 4: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0768	ns	
			Day 5: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0958	ns	
			Day 6: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
			Day 7: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
			Day 8: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	0.0014	**	
			Day 9: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
			Day 10: Freezing (%)	Two-stage step-up Benjamini	Context A vs. Context B	-	-	<0.0001	****	
	Contextual Fear Discrimination Day 2 Freezing	CFD Day 2 Freezing	Day 2 Freezing (%)	RMANOVA	Context x Drug	0.019	3,37	0.9965	ns	S1N
					Context	54.540	1,37	<0.0001	****	
					Drug	5.496	3,37	0.0032	**	
				Dunnett's Test	Saline: Context A vs. Context B	-	-	0.0005	***	
					(*R*,*S*)-ketamine (30 mg/kg): Context A vs. Context B	-	-	0.0049	**	
					Prucalopride (3 mg/kg): Context A vs. Context B	-	-	0.0077	**	
					(*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg0: Context A vs. Context B	-	-	0.0021	**	
	Contextual Fear Discrimination Day 4 Freezing	CFD Day 4 Freezing	Day 4 Freezing (%)	RMANOVA	Context x Drug	0.599	3,37	0.6200	ns	S1O
					Context	18.710	1,37	0.0001	***	
					Drug	0.392	3,37	0.7596	ns	
				Dunnett's Test	Saline: Context A vs. Context B	-	-	0.0680	ns	
					(*R*,*S*)-ketamine (30 mg/kg): Context A vs. Context B	-	-	0.0043	**	
					Prucalopride (3 mg/kg): Context A vs. Context B	-	-	0.0278	*	
					(*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg0: Context A vs. Context B	-	-	0.1650	ns	
	Contextual Fear Discrimination Day 10 Freezing	CFD Day 10 Freezing	Day 10 Freezing (%)	RMANOVA	Context x Drug	0.535	3,37	0.661	ns	S1P
					Context	95.460	1,37	<0.0001	****	
					Drug	0.946	3,37	0.428	ns	
				Dunnett's Test	Saline: Context A vs. Context B	-	-	<0.0001	****	
					(*R*,*S*)-ketamine (30 mg/kg): Context A vs. Context B	-	-	<0.0001	****	
					Prucalopride (3 mg/kg): Context A vs. Context B	-	-	<0.0001	****	
					(*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg0: Context A vs. Context B	-	-	0.0001	***	
	Context A, Contextual Fear Discrimination	Context A, CFD	Freezing (%)	RMANOVA	Time x Drug	1.133	27,333	0.2986	ns	data not shown
					Time	117.000	9,333	<0.0001	****	
					Drug	2.109	3,37	0.1157	ns	
	Context B, Contextual Fear Discrimination	Context B, CFD	Freezing (%)	RMANOVA	Time x Drug	0.521	24,296	0.9707	ns	data not shown
					Time	10.250	8,296	<0.0001	****	

	Discrimination				Drug	1.567	3,37	0.2137	ns	shown
	Discrimination Index (A-B) / (A + B)	Discrimination Index	(A-B) / (A + B)	RMANOVA	Time x Drug	0.531	24,296	0.9672	ns	S1Q
					Time	20.030	8,296	<0.0001	****	
					Drug	1.054	3,37	0.3803	ns	
				2-way ANOVA	Day x Drug	0.419	6,74	0.8643	ns	data not shown
					Day	73.290	2,74	<0.0001	****	
					Drug	0.147	3,37	0.9312	ns	
Male, antidepressant, no stress	Forced Swim Test Day 1	FST Day 1	Immobility Time (sec)	RMANOVA	Time x Drug	1.414	15,90	0.1579	ns	S2B
					Time	29.78	5,90	<0.0001	****	
					Drug	1.337	3,18	0.2935	ns	
			Average Immobility Time (min 3-6) (sec)	One-way ANOVA	Drug	1.434	3,18	0.2657	ns	S2C
	Forced Swim Test Day 2	FST Day 2	Immobility Time (sec)	RMANOVA	Time x Drug	0.866	15,90	0.6032	ns	S2D
					Time	11.370	5,90	<0.0001	****	
					Drug	2.445	3,18	0.0972	ns	
			Average Immobility Time (min 3-6) (sec)	One-way ANOVA	Drug	1.182	3,18	0.3444	ns	S2E
Female, antidepressant, no stress	Forced Swim Test Day 1	FST Day 1	Immobility Time (sec)	RMANOVA	Time x Drug	3.191	15,110	0.0002	***	S2F
					Time	29.230	5,110	<0.0001	****	
					Drug	3.463	3,22	0.0373	*	
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9865	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.5929	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0201	*	
			Minute 1: Immobilty Time	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.0013	**	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.9889	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0811	ns	
			Minute 2: Immobilty Time	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9999	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.4036	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0933	ns	
			Minute 3: Immobilty Time	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.7030	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.9971	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) +	-	-	0.4387	ns	
			Minute 4: Immobilty Time	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.4502	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.9689	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.1614	ns	
			Minute 5: Immobilty Time	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.8028	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.5882	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0791	ns	
			Minute 6: Immobilty Time	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.1452	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.1553	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0104	*	
			Average Immobility Time (min 3-6) (sec)	One-way ANOVA	Drug	2.843	3,22	0.0612	ns	S2G
	Forced Swim Test Day 2	FST Day 2	Immobility Time (sec)	RMANOVA	Time x Drug	0.725	15,110	0.7542	ns	S2H
					Time	11.570	5,110	<0.0001	****	
					Drug	3.356	3,22	0.0373	*	
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.1062	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.5829	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0183	*	
			Average Immobility Time (min 3-6) (sec)	One-way ANOVA	Drug	2.895	3,22	0.0581	ns	S2I
	Open Field Test	OF	Distance Traveled (cm)	RMANOVA	Time x Drug	1.103	27,180	0.3412	ns	S3B
					Time	1.671	9,180	0.0989	ns	
					Drug	1.041	3,20	0.3958	ns	
			Total Distance Traveled (cm)	One-way ANOVA	Drug	1.041	3,20	0.3958	ns	S3C
			Time in Center (sec)	One-way ANOVA	Drug	0.160	3,20	0.9221	ns	data not shown
			Distance Traveled (m)	RMANOVA	Time x Drug	2.062	15,100	0.0179	*	data not shown
					Time	14.610	5,100	<0.0001	****	
					Drug	0.301	3,20	0.8246	ns	
			Minute 1: Distance Traveled	Dunnett's Test	Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.8496	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.2280	ns	
					Saline vs. (R,S)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.1844	ns	
			Minute 2: Distance Traveled	Dunnett's Test	Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.9781	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.2441	ns	
					Saline vs. (R,S)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.2459	ns	
			Minute 3: Distance Traveled	Dunnett's Test	Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.9898	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.8845	ns	
					Saline vs. (R,S)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.6447	ns	

Male, anxiolytic, no stress	Elevated Plus Maze	EPM	Minute 4: Distance Traveled	Dunnett's Test	Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.3783	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.9219	ns	
					Saline vs. (R,S)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.8984	ns	
			Minute 5: Distance Traveled	Dunnett's Test	Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.9710	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.9968	ns	
					Saline vs. (R,S)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.8184	ns	
			Minute 6: Distance Traveled	Dunnett's Test	Saline vs. (R,S)-ketamine (30 mg/kg)	-	-	0.6447	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.9983	ns	
					Saline vs. (R,S)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9219	ns	
			Distance Traveled (m)	One-way ANOVA	Drug	0.301	3,20	0.8246	ns	data not shown
			Time in Center (sec)	RMANOVA	Time x Drug	0.606	15,100	0.8638	ns	data not shown
					Time	1.938	5,100	0.0946	ns	
					Drug	0.414	3,20	0.7449	ns	
			Total Time in Center (sec)	One-way ANOVA	Drug	0.293	3,20	0.8303	ns	data not shown
			Entries into Center (no.)	One-way ANOVA	Drug	0.840	3,20	0.4878	ns	data not shown
			Time in Open Arms (sec)	RMANOVA	Time x Drug	1.125	15,100	0.3443	ns	data not shown
					Time	0.919	5,100	0.4717	ns	
					Drug	0.640	3,20	0.5979	ns	
			Total Time in Open Arms (sec)	One-way ANOVA	Drug	0.828	3,19	0.4950	ns	S3D
			Entries into Open Arms (no.)	One-way ANOVA	Drug	0.702	3,20	0.5617	ns	data not shown
			Time in Closed Arms (sec)	RMANOVA	Time x Drug	0.982	15,100	0.4793	ns	data not shown
					Time	2.351	5,100	0.0461	*	
					Drug	0.269	3,20	0.8345	ns	
			Total Time in Closed Arms (sec)	One-way ANOVA	Drug	0.286	3,20	0.8349	ns	S3E
			Entries into Closed Arms (no.)	One-way ANOVA	Drug	0.627	3,20	0.6059	ns	data not shown
	Marble Burying	MB	Marbles Buried (no.)	One-way ANOVA	Drug	2.421	3,20	0.0960	ns	S3F
	Novelty-Suppressed Feeding	NSF	Fraction of mice not eating in OF	Log-rank (Mantel-Cox) Test	Drug	-	-	0.1906	ns	S3G
			Latency to Feed in OF (sec)	One-way ANOVA	Drug	0.484	3,20	0.6975	ns	S3H
			Fraction of mice not eating in HC	Log-rank (Mantel-Cox) Test	Drug	-	-	0.0953	ns	S3I
			Latency to Feed in HC (sec)	One-way ANOVA	Drug	1.966	3,20	0.1517	ns	data not shown
			Food Eaten (g)	One-way ANOVA	Drug	2.166	3,20	0.1238	ns	data not shown
			Body Weight Loss (g)	One-way ANOVA	Drug	0.455	3,20	0.7169	ns	data not shown
Female, anxiolytic, no stress	Open Field Test	OF	Distance Traveled (cm)	RMANOVA	Time x Drug	0.544	27,180	0.9684	ns	S3J
					Time	1.677	9,180	0.0974	ns	
					Drug	4.231	3,20	0.0181	*	
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9912	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.0168	*	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9924	ns	
			Total Distance Traveled (cm)	One-way ANOVA	Drug	4.231	3,20	0.0181	*	S3K
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.9912	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.0168	*	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.9924	ns	
			Time in Center (sec)	One-way ANOVA	Drug	2.389	3,20	0.0991	ns	data not shown
	Elevated Plus Maze	EPM	Distance Traveled (m)	RMANOVA	Time x Drug	0.765	15,100	0.7127	ns	data not shown
					Time	8.164	5,100	<0.0001	****	
					Drug	0.880	3,20	0.4680	ns	
				One-way ANOVA	Drug	0.880	3,20	0.4681	ns	data not shown
			Time in Center (sec)	RMANOVA	Time x Drug	0.937	15,100	0.5270	ns	data not shown
					Time	1.046	5,100	0.3953	ns	
					Drug	1.066	3,20	0.3858	ns	
			Total Time in Center (sec)	One-way ANOVA	Drug	1.062	3,20	0.3873	ns	data not shown
			Entries into Center (no.)	One-way ANOVA	Drug	0.397	3,20	0.7567	ns	data not shown
			Time in Open		Time x Drug	0.570	15,100	0.8914	ns	data not

			Time in Open Arms (sec)	RMANOVA	Time	2.341	5,100	0.0469	*	data not shown
					Drug	0.203	3,20	0.8929	ns	
			Total Time in Open Arms (sec)	One-way ANOVA	Drug	0.202	3,20	0.8936	ns	S3L
			Entries into Open Arms (no.)	One-way ANOVA	Drug	0.017	3,20	0.9968	ns	data not shown
			Time in Closed Arms (sec)	RMANOVA	Time x Drug	0.628	15,100	0.8458	ns	data not shown
					Time	1.874	5,100	0.1056	ns	
					Drug	0.406	3,20	0.7500	ns	
			Total Time in Closed Arms (sec)	One-way ANOVA	Drug	0.404	3,20	0.7515	ns	S3M
			Entries into Closed Arms (no.)	One-way ANOVA	Drug	0.784	3,20	0.5167	ns	data not shown
	Marble Burying	MB	Marbles Buried (no.)	One-way ANOVA	Drug	4.099	3,20	0.0203	*	S3N
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.1028	ns	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.0343	*	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0105	*	
	Novelty-Suppressed Feeding	NSF	Fraction of mice not eating in OF	Log-rank (Mantel-Cox) Test	Drug	-	-	0.3095	ns	S3O
			Latency to Feed in OF (sec)	One-way ANOVA	Drug	0.600	3,20	0.6226	ns	S3P
			Fraction of mice not eating in HC	Log-rank (Mantel-Cox) Test	Drug	-	-	0.0852	ns	S3Q
			Latency to Feed in HC (sec)	One-way ANOVA	Drug	2.071	3,20	0.1363	ns	data not shown
			Food Eaten (g)	One-way ANOVA	Drug	10.140	3,20	0.0003	***	data not shown
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.0004	***	
					Saline vs. Prucalopride (1.5 mg/kg)	-	-	0.0006	***	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0014	**	
			Body Weight Loss (g)	One-way ANOVA	Drug	0.635	3,20	0.6009	ns	data not shown
PV/cfos immunolabeling	Contextual Fear Conditioning Training	CFC Training	Freezing (%)	RMANOVA	Time x Drug	0.6061	12,104	0.8328	ns	S4A
					Time	58.58	4,104	<0.0001	****	
					Drug	0.9219	3,26	0.4441	ns	
			Average Freezing (min 1-5) (%)	One-way ANOVA	Drug	0.9219	3,26	0.4441	ns	data not shown
	Contextual Fear Conditioning Re-exposure	CFC Re-exposure	Freezing (%)	RMANOVA	Time x Drug	1.221	12,104	0.2785	ns	data not shown
					Time	7.565	4,104	<0.0001	****	
					Drug	7.624	3,26	0.0008	***	
			Freezing: Min 1 (%)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.5810	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0302	*	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) +	-	-	0.5542	ns	
			Freezing: Min 2 (%)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.0630	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0090	**	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0533	ns	
			Freezing: Min 3 (%)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.0003	***	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0264	*	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0092	**	
			Freezing: Min 4 (%)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.1788	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.9952	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.5740	ns	
			Freezing: Min 5 (%)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.2160	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.1115	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0225	*	
			Average Freezing (min 1-5) (%)	One-way ANOVA	Drug	7.624	3,26	0.0008	***	S4B
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.0011	**	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0010	**	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0051	**	
	Forced Swim Test Day 1	FST Day 1	Immobility Time (sec)	RMANOVA	Time x Drug	0.5431	15,130	0.9116	ns	data not shown
					Time	18.82	5,130	<0.0001	****	
					Drug	2.463	3,26	0.0849	ns	
			Average Immobility Time (min 3-6) (sec)	One-way ANOVA	Drug	1.111	3,26	0.3624	ns	S4C
	Forced Swim Test Day 2	FST Day 2	Immobility Time (sec)	RMANOVA	Time x Drug	1.308	15,130	0.2064	ns	data not shown
					Time	4.037	5,130	0.0019	**	
					Drug	11.92	3,26	<0.0001	****	
			Immobility Time: Min 1 (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.1818	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0068	**	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0421	*	
			Immobility Time: Min 2 (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.1992	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0530	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0009	***	
			Immobility Time: Min 3 (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.1171	ns	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0057	**	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0112	*	
			Immobility Time: Min 4 (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.0232	*	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0400	*	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0091	**	
			Immobility Time:	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.0144	*	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0034	**	

			Min 5 (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0008	***	
			Immobility Time: Min 6 (sec)	Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.0159	*	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0062	**	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0057	**	
			Average Immobility Time (min 3-6) (sec)	One-way ANOVA	Drug	10.18	3,26	0.0001	***	
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.0083	**	S4D
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0003	***	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	<0.0001	****	
Male, 5 min after CFC	Contextual Fear Conditioning Training	CFC Training	Freezing (%)	RMANOVA	Time x Drug	0.5075	12,112	0.9062	ns	S6A
					Time	49.29	4,112	<0.0001	****	
					Drug	1.23	3,28	0.3174	ns	
			Average Freezing (min 1-5) (%)	One-way ANOVA	Drug	1.23	3,28	0.3174	ns	S6B
	Open Field Test	OF	Distance Traveled (cm)	RMANOVA	Time x Drug	0.9938	27,252	0.4779	ns	S6C
					Time	3.419	9,252	0.0005	***	
					Drug	0.442	3,28	0.7248	ns	
			Total Distance Traveled (cm)	One-way ANOVA	Drug	0.442	3,28	0.7248	ns	data not shown
			Time in Center (sec)	One-way ANOVA	Drug	0.1525	3,28	0.9272	ns	S6D
	Elevated Plus Maze	EPM	Distance Traveled (cm)	RMANOVA	Time x Drug	0.6385	15,140	0.8389	ns	data not shown
					Time	14.01	5,140	<0.0001	****	
					Drug	0.4224	3,28	0.7384	ns	
				One-way ANOVA	Drug	0.4233	3,28	0.7378	ns	data not shown
			Time in Center (sec)	RMANOVA	Time x Drug	0.470	15,140	0.9521	ns	data not shown
					Time	1.020	5,140	0.4083	ns	
					Drug	0.481	3,28	0.6983	ns	
			Total Time in Center (sec)	One-way ANOVA	Drug	0.4814	3,28	0.6979	ns	data not shown
			Entries into Center (no.)	One-way ANOVA	Drug	0.2522	3,28	0.8591	ns	data not shown
			Time in Open Arms (sec)	RMANOVA	Time x Drug	0.8179	15,140	0.6564	ns	data not shown
					Time	2.412	5,140	0.0393	*	
					Drug	0.7199	3,28	0.5485	ns	
			Total Time in Open Arms (sec)	One-way ANOVA	Drug	0.7189	3,28	0.5491	ns	S6E
			Entries into Open Arms (no.)	One-way ANOVA	Drug	0.5219	3,28	0.6708	ns	S6F
			Time in Closed Arms (sec)	RMANOVA	Time x Drug	0.582	15,140	0.8849	ns	data not shown
					Time	1.702	5,140	0.1381	ns	
					Drug	0.5498	3,28	0.6524	ns	
			Total Time in Closed Arms (sec)	One-way ANOVA	Drug	0.55	3,28	0.6523	ns	S6G
			Entries into Closed Arms (no.)	One-way ANOVA	Drug	0.279	3,28	0.8401	ns	S6H
	Novelty-Suppressed Feeding	NSF	Fraction of mice not eating in HC	Log-rank (Mantel-Cox) Test	Drug	-	-	0.3194	ns	S6I
			Latency to Feed in HC (sec)	One-way ANOVA	Drug	1.957	3,28	0.1434	ns	S6J
			Food Eaten (g)	One-way ANOVA	Drug	0.8687	3,28	0.4689	ns	S6K
			Body Weight Loss (g)	One-way ANOVA	Drug	0.6852	3,28	0.5686	ns	S6L
Female, 5 min after CFC	Contextual Fear Conditioning Training	CFC Training	Freezing (%)	RMANOVA	Time x Drug	0.4032	12,84	0.9587	ns	S6M
					Time	78.69	4,84	<0.0001	****	
					Drug	0.7362	3,21	0.5421	ns	
			Average Freezing (min 1-5) (%)	One-way ANOVA	Drug	0.7362	3,21	0.5421	ns	S6N
	Open Field Test	OF	Distance Traveled (cm)	RMANOVA	Time x Drug	0.5255	27.189	0.9751	ns	S6O
					Time	2.406	9,189	0.0744	ns	
					Drug	0.6971	3.21	0.5642	ns	
			Total Distance Traveled (cm)	One-way ANOVA	Drug	0.6971	3.21	0.5642	ns	data not shown
			Time in Center (sec)	One-way ANOVA	Drug	0.07038	3,21	0.9751	ns	S6P
	Elevated Plus Maze	EPM	Distance Traveled (m)	RMANOVA	Time x Drug	1.166	15,105	0.3095	ns	data not shown
					Time	6.112	5,105	0.0012	**	
					Drug	0.393	3,21	0.7593	ns	
				One-way ANOVA	Drug	0.3918	3,21	0.7601	ns	data not shown
			Time in Center (sec)	RMANOVA	Time x Drug	0.6831	15,105	0.7958	ns	data not shown
					Time	0.1089	5,105	0.9047	ns	
					Drug	0.545	3,21	0.6569	ns	
			Total Time in Center (sec)	One-way ANOVA	Drug	0.5456	3,21	0.6565	ns	data not shown
			Entries into Center (no.)	One-way ANOVA	Drug	0.148	3,21	0.9299	ns	data not shown
			Time in Open Arms (sec)	RMANOVA	Time x Drug	1.172	15,105	0.3047	ns	data not shown
					Time	1.613	5,105	0.1630	ns	
					Drug	0.8405	3.21	0.4869	ns	
			Total Time in Open Arms (sec)	One-way ANOVA	Drug	0.8401	3,21	0.4871	ns	S6Q

			Entries into Open Arms (no.)	One-way ANOVA	Drug	0.4636	3,21	0.7107	ns	S6R
			Time in Closed Arms (sec)	RMANOVA	Time x Drug	0.6915	15,105	0.7878	ns	data not shown
					Time	0.5166	5,105	0.7632	ns	
					Drug	0.6504	3,21	0.6470	ns	
			Total Time in Closed Arms (sec)	One-way ANOVA	Drug	0.5606	3,21	0.6469	ns	S6S
			Entries into Closed Arms (no.)	One-way ANOVA	Drug	0.1076	3,21	0.9547	ns	S6T
	Novelty-Suppressed Feeding	NSF	Fraction of mice not eating in HC	Log-rank (Mantel-Cox) Test	Drug	-	-	0.1774	ns	S6U
			Latency to Feed in HC (sec)	One-way ANOVA	Drug	1.663	3,21	0.2054	ns	S6V
			Food Eaten (g)	One-way ANOVA	Drug	4.627	3,21	0.0123	*	S6W
				Dunnett's Test	Saline vs. (*R*,*S*)-ketamine (10 mg/kg)	-	-	0.0068	**	
					Saline vs. Prucalopride (3 mg/kg)	-	-	0.0536	ns	
					Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (1.5 mg/kg)	-	-	0.0199	*	
			Body Weight Loss (g)	One-way ANOVA	Drug	2.088	3,21	0.1324	ns	S6X

Table S02: Network and immunohistochemical analysis

Cohort	Network Measure	Statistical Test	Comparison	F	° of freedom	p	*	Fig.
c-fos networks	Mean degree	One-way ANOVA	Drug	3.921	3,32	0.0172	*	5E
		Dunnett's test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.0437	*	
			Saline vs. Prucalopride (3 mg/kg)	-	-	0.4558	ns	
			Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.8633	ns	
	Global efficiency	One-way ANOVA	Drug	13.810	3,32	<0.0001	****	5F
		Dunnett's test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.0001	***	
			Saline vs. Prucalopride (3 mg/kg)	-	-	0.6392	ns	
			Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.3322	ns	
	Mean clustering coefficient	One-way ANOVA	Drug	1.182	3,32	0.3322	ns	5G
	Mean betweenness centrality	One-way ANOVA	Drug	2.296	3,32	0.0965	ns	5H
	Distance	One-way ANOVA	Drug	39.01	3,32	<0.0001	****	5I
		Dunnett's test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	<0.0001	***	
			Saline vs. Prucalopride (3 mg/kg)	-	-	>0.9999	ns	
			Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.1161	ns	
	mPFC	2-way ANOVA	Drug	23.440	3,74	<0.0001	****	5K
			Region	6.849	2,74	0.0019	**	
			Drug x Region	1.663	6,74	0.1421	ns	
		Dunnett's test	ACA: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.7630	ns	
			ACA: Saline vs. Prucalopride (3 mg/kg)	-	-	0.9981	ns	
			ACA: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	<0.0001	****	
			PL: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.8983	ns	
			PL: Saline vs. Prucalopride (3 mg/kg)	-	-	>0.9999	ns	
			PL: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0012	**	
			ILA: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.9970	ns	
			ILA: Saline vs. Prucalopride (3 mg/kg)	-	-	0.9696	ns	
			ILA: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0365	*	
	dHPC	2-way ANOVA	Drug	20.450	3,84	<0.0001	****	5M
			Region	22.950	2,84	<0.0001	****	
			Drug x Region	2.672	6,84	0.0202	*	
		Dunnett's test	DG: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.9999	ns	
			DG: Saline vs. Prucalopride (3 mg/kg)	-	-	0.8584	ns	
			DG: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.4311	ns	
			CA3: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.9911	ns	
			CA3: Saline vs. Prucalopride (3 mg/kg)	-	-	0.5602	ns	
			CA3: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0131	*	
			CA1: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.5647	ns	
			CA1: Saline vs. Prucalopride (3 mg/kg)	-	-	0.1258	ns	
			CA1: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	<0.0001	****	
	vHPC	2-way ANOVA	Drug	15.120	3,83	<0.0001	****	5O
			Region	25.700	2,93	<0.0001	****	
			Drug x Region	2.257	6,83	0.0456	*	
		Dunnett's test	DG: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.9068	ns	
			DG: Saline vs. Prucalopride (3 mg/kg)	-	-	0.8911	ns	
			DG: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.8787	ns	
			CA3: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.6849	ns	
			CA3: Saline vs. Prucalopride (3 mg/kg)	-	-	0.6751	ns	
			CA3: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	<0.0001	****	
			CA1: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.1805	ns	
			CA1: Saline vs. Prucalopride (3 mg/kg)	-	-	0.4289	ns	
			CA1: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.1141	ns	
	mPFC	2-way ANOVA	Drug	4.562	3,74	0.0055	**	6L
			Region	35.190	2,74	<0.0001	****	
			Drug x Region	1.274	6,74	0.2796	ns	
		Dunnett's test	ACA: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.9918	ns	
			ACA: Saline vs. Prucalopride (3 mg/kg)	-	-	0.1178	ns	
			ACA: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0896	ns	
			PL: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.9727	ns	
			PL: Saline vs. Prucalopride (3 mg/kg)	-	-	0.7172	ns	
			PL: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.6265	ns	
			ILA: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.9959	ns	
			ILA: Saline vs. Prucalopride (3 mg/kg)	-	-	0.9866	ns	
			ILA: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9998	ns	
		2-way ANOVA	Drug	1.077	3,84	0.3635	ns	
			Region	25.920	2,84	<0.0001	****	
			Drug x Region	0.064	6,84	0.9989	ns	

PV immunolabeling	dHPC	Dunnett's test	DG: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.9994	ns	6M
			DG: Saline vs. Prucalopride (3 mg/kg)	-	-	0.9994	ns	
			DG: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9360	ns	
			CA3: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.9665	ns	
			CA3: Saline vs. Prucalopride (3 mg/kg)	-	-	0.9517	ns	
			CA3: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.7701	ns	
			CA1: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.9977	ns	
			CA1: Saline vs. Prucalopride (3 mg/kg)	-	-	0.9996	ns	
			CA1: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.6634	ns	
	vHPC	2-way ANOVA	Drug	3.778	3,84	0.0135	*	6N
			Region	31.780	2,84	<0.0001	****	
			Drug x Region	1.820	6,84	0.1049	ns	
		Dunnett's test	DG: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	>0.9999	ns	
			DG: Saline vs. Prucalopride (3 mg/kg)	-	-	0.9954	ns	
			DG: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9368	ns	
			CA3: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	>0.9999	ns	
			CA3: Saline vs. Prucalopride (3 mg/kg)	-	-	0.9990	ns	
			CA3: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0020	**	
			CA1: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.1430	ns	
			CA1: Saline vs. Prucalopride (3 mg/kg)	-	-	0.7873	ns	
			CA1: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9940	ns	
c-fos/PV immunolabeling	mPFC	2-way ANOVA	Drug	21.040	3,74	<0.0001	****	6O
			Region	3.348	2,74	0.0405	*	
			Drug x Region	0.341	6,74	0.9128	ns	
		Dunnett's test	ACA: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.8481	ns	
			ACA: Saline vs. Prucalopride (3 mg/kg)	-	-	0.6589	ns	
			ACA: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0069	**	
			PL: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.9559	ns	
			PL: Saline vs. Prucalopride (3 mg/kg)	-	-	0.6130	ns	
			PL: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0009	***	
			ILA: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.9970	ns	
			ILA: Saline vs. Prucalopride (3 mg/kg)	-	-	0.9559	ns	
			ILA: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0159	*	
	dHPC	2-way ANOVA	Drug	1.025	3,84	0.3858	ns	6P
			Region	30.980	2,84	<0.0001	****	
			Drug x Region	0.495	6,84	0.8103	ns	
	vHPC	2-way ANOVA	Drug	4.411	3,84	0.0062	**	6Q
			Region	12.460	2,84	<0.0001	****	
			Drug x Region	2.026	6,84	0.0711	ns	
		Dunnett's test	DG: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	>0.9999	ns	
			DG: Saline vs. Prucalopride (3 mg/kg)	-	-	0.9701	ns	
			DG: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.9957	ns	
			CA3: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.9560	ns	
			CA3: Saline vs. Prucalopride (3 mg/kg)	-	-	0.8885	ns	
			CA3: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.0007	***	
			CA1: Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.9223	ns	
			CA1: Saline vs. Prucalopride (3 mg/kg)	-	-	0.5203	ns	
			CA1: Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	0.6371	ns	
PV network	Mean degree	One-way ANOVA	Drug	5.535	3,40	0.0028	**	S5P
		Dunnett's test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.2126	ns	
			Saline vs. Prucalopride (3 mg/kg)	-	-	0.0662	ns	
			Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	>0.9999	ns	
	Global efficiency	One-way ANOVA	Drug	17.840	3,40	<0.0001	****	S5Q
		Dunnett's test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.1784	ns	
			Saline vs. Prucalopride (3 mg/kg)	-	-	<0.0001	****	
			Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	>0.9999	ns	
	Mean clustering coefficient	One-way ANOVA	Drug	3.726	3,40	0.0188	*	S5R
		Dunnett's test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.0443	*	
			Saline vs. Prucalopride (3 mg/kg)	-	-	0.9005	ns	
			Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	>0.9999	ns	
	Mean betweenness centrality	One-way ANOVA	Drug	6.127	3,40	0.0016	**	S5S
		Dunnett's test	Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.9947	ns	
			Saline vs. Prucalopride (3 mg/kg)	-	-	0.0040	**	
			Saline vs. (*R*,*S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	>0.9999	ns	
		One-way ANOVA	Drug	42.550	3,40	<0.0001	****	
			Saline vs. (*R*,*S*)-ketamine (30 mg/kg)	-	-	0.4525	ns	

	Distance	Dunnett's test	Saline vs. Prucalopride (3 mg/kg)	-	-	<0.0001	****	S5T
			Saline vs. (*R,S*)-ketamine (10 mg/kg) + Prucalopride (3 mg/kg)	-	-	>0.9999	ns	

Table S03: Key Resources Table

Resource Type	Specific Reagent or Resource	Source or Reference	Identifiers	Additional Information
Add additional rows as needed for each resource type	Include species and sex when applicable.	Include name of manufacturer, company, repository, individual, or research lab. Include PMID or DOI for references; use "this paper" if new.	Include catalog numbers, stock numbers, database IDs or accession numbers, and/or RRIDs. RRIDs are highly encouraged; search for RRIDs at https://scicrunch.org/resources.	Include any additional information or notes if necessary.
Antibody	Rat monoclonal IgG anti-c-fos	Synaptic Systems, Göettingen, Germany	Cat.# 226 017; RRID:AB_2864765	1:5000
Antibody	Rabbit anti-parvalbumin	Swant, Burgdorf, Switzerland	Cat.# PV 27; RRID:AB_2631173	1:3000
Antibody	Donkey Anti-Rat IgG H+L (Alexa Fluor® 647)	Abcam, Cambridge, UK	Cat.# Ab150155; RRID:AB_2813835	1:500
Antibody	Donkey Anti-Rabbit igG H+L (Alexa Fluor® 48	Thermo Fisher Scientific, Waltham, MA	Cat.# A-21206; RRID:AB_2535792	1:500
Mounting Medium	Fluoromount G	Electron Microscopy Sciences, Hatfield, PA	Cat.#17984-25	
Chemical Compound or Drug	Ketaset	Zoetis, Parsippany-Troy Hills, NJ	Cat.# KET-00002R2	10 or 30 mg/kg, i.p
Chemical Compound or Drug	Prucalopride	Sigma Aldrich, St. Louis, MO	SML1371	1.5 or 3 mg/kg
Organism/Strain	Mouse: Male and female 129S6/SvEvTac	Taconic, Hudson, NY	129SVE-M, 129SVE-F	7 weeks of age
Organism/Strain	Mouse: Male and female C57BL/6NTac	Taconic, Hudson, NY	B6-M, B6-F	7 weeks of age
Software; Algorithm	ImageJ v.2.14.0/1.54f	https://fiji.sc/		
Software; Algorithm	R Studio v.1.1.423	https://rstudio.com/		
Software; Algorithm	SMART package + wholebrain	https://mjin1812.github.io/SMART/		Maintainer: Michelle Jin - smart.r.package@gmail.com - @Michelle_Jin1