Supplemental Information

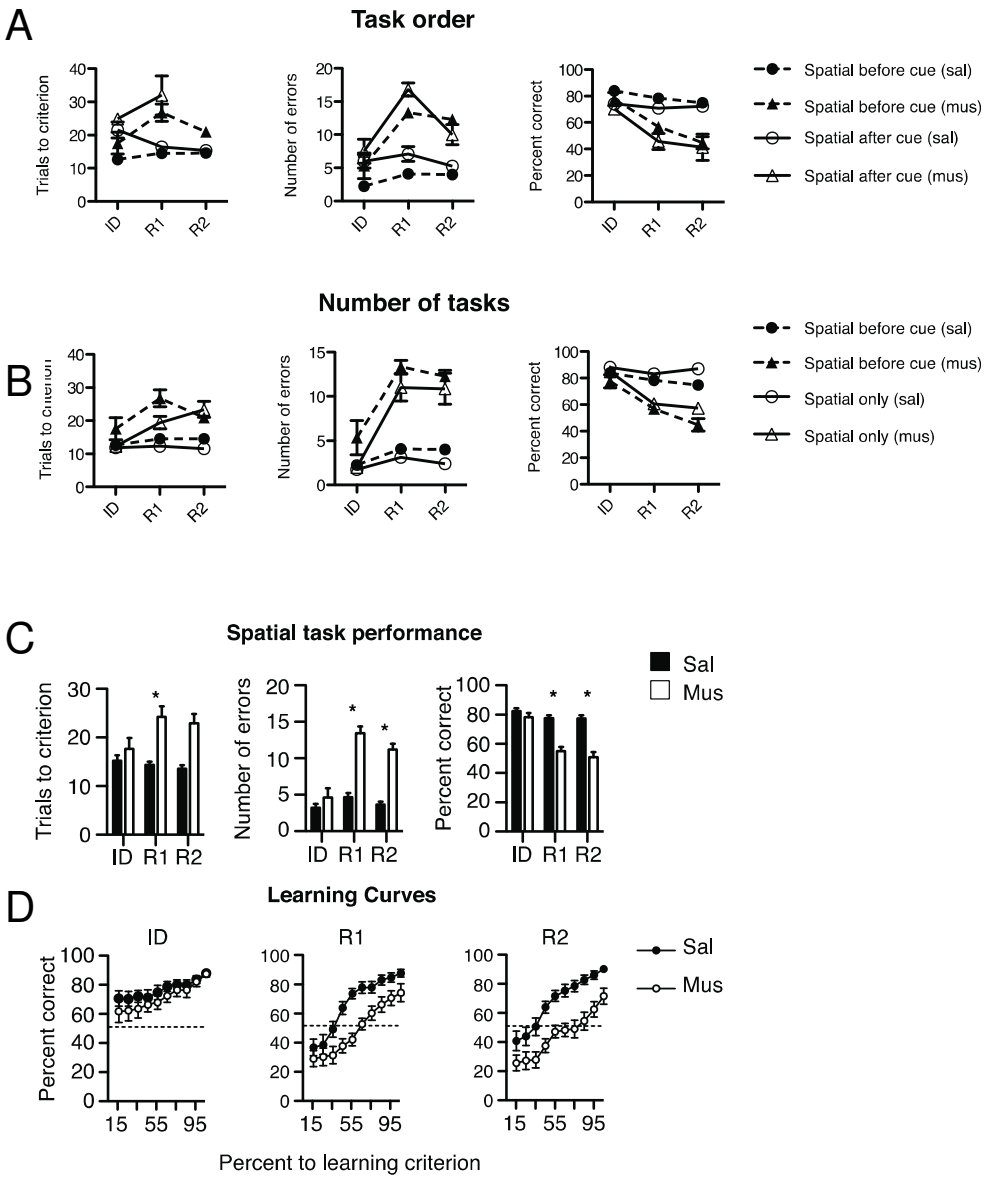


Figure S1 (related to Figure 1): Neither infusion timing nor cue response testing altered the effect of mPFC inactivation on learning measured by trials to criterion (TTC), number of errors (NE), or percent correct (PC). TTC analyzed only reversals in which animals reached learning criterion; NE and PC included all reversal trials. ANOVAs included ID and R1 completed by all animals. **(A)** Infusion time (drug × infusion time repeated measures ANOVA, F(1,5): TTC = 0.09, NE: = 0.95, PC: F(1,5) = 1.37, all $p > 0.05$). Spatial learning preceded by the cue task was slower than when it followed a spatial reversal (SR) (F(1,5): infusion time = 24.44, NE= 9.80, PC = 9.87, all $p < 0.05$; Figure S1A). Task order (TO) did not affect mPFC inactivation effects (TTC F(1,3) TO × SR = 3.51, TO × drug = 1.47, TO × SR × drug = 1.11, all $p > 0.05$; NE F(1,5) TO × SR = 0.05, TO × drug = 0.170, TO × SR × drug = 1.18; PC F(1,5), TO × SR = 1.14, TO × drug = 0.24, TO × SR × drug = 0.08, all $p > 0.05$). **(B)** Rats trained only the spatial task (N = 4) responded equivalently to those trained in both tasks after mPFC inactivation (N = 6) during the first four days of spatial testing (F(1,8) TTC = 0.91, NE = 0.43, PC= 0.40, all $p > 0.05$; Figure S1B). Rats trained only in the spatial task learn faster than those trained in both tasks,(F(1,8) TTC = 8.38, $p = 0.02$; NE = 6.81, $p = 0.03$) but reached similar performance levels (PC: F(1,8) = 2.69, $p > 0.05$). Analyses reported in the main text included data pooled across all animals, and data from animals trained in both tasks were averaged across task orders to analyze spatial reversal performance.
Additional behavioral measures. (C) The main text measured behavior performance as the percent of correct trials. The same pattern of results hold when performance was measured by trials to criterion or number of errors (* $p < 0.05$, Bonferroni corrected). **(D)** mPFC inactivation impaired reversal learning (muscimol versus saline). The curves show the normalized length of each learning epoch (i.e., ID, R1, or R2) divided into consecutive, non-overlapping blocks of 10% of the total trial number and averaged within each block.

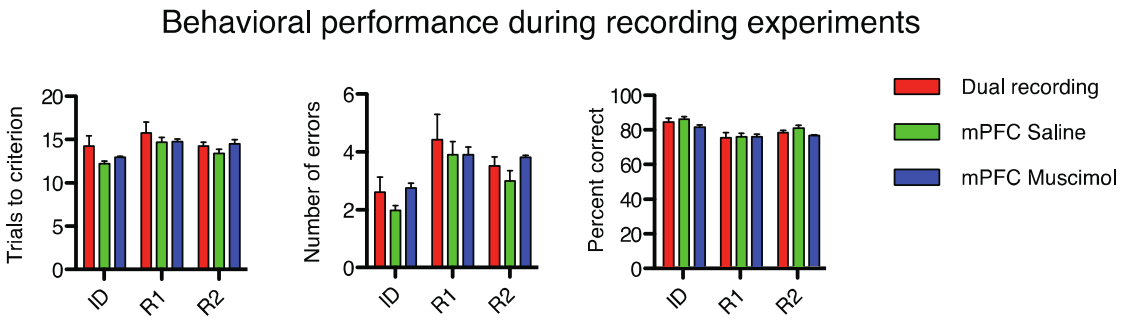


Figure S2.1 (related to Figure 4): Behavior during recording experiments.

Animals with unilateral mPFC infusions of saline and muscimol performed the spatial reversal task similarly, and their overall level of performance resembled that observed during the dual recording experiment. Though muscimol infusions increased errors overall, the slight performance effects on ID and reversal learning were statistically indistinguishable (TTC: drug $F(1,2) = 6.84$, $p > 0.05$; drug x reversal, $F(2,4) = 0.173$, $p > 0.05$; NE: drug, $F(1,2) = 18.23$, $p = 0.049$, drug x reversal: $F(2,4) = 0.369$, $p > 0.05$; PC: drug, $F(1,2) = 14.84$, $p = 0.061$, drug x reversal, $F(2,4) = 0.776$, $p > 0.05$). The trend towards poorer performance after unilateral muscimol infusions due to ~1 additional error per reversal.

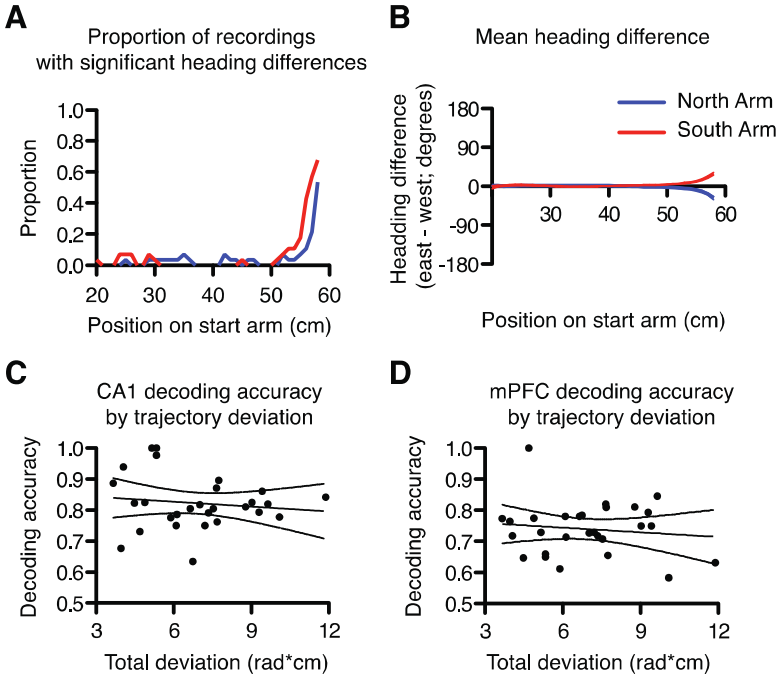


Figure S2.2(related to Figure 3): Trajectory differences between journeys did not account for decoding accuracy.

Systematic differences in heading angles during a given recording session were rare within the 20 to 50 cm segment (**A**), though small systematic differences started to emerge as animals approached the choice point, peaking at ~30 degrees at the 58 cm mark (**B**). Because the 50-58 cm segment was used in the calculation of the average firing rates, we examined if the magnitude of the heading difference bore any relationship to decoding accuracy. The absolute heading angle difference was integrated over the 50 to 58 cm segment and summed across start arms to generate a total deviation score. As shown in **C** and **D**, the total deviation score had no bearing on SVM decoding accuracy (CA1: $r(27) = -0.126$, $p > 0.05$; mPFC: $r(27) = -0.123$, $p > 0.05$). To further test if behavior differences in this segment of the maze informed the ensemble decoding findings, we repeated the SVM decoding analysis using firing rates calculated using only the 20-50 cm segment of the start arm, when heading deviation >1º occurred in <0.05 % of the recordings. The decoding accuracy for the restricted models matched the decoding analysis described in the main text. mPFC activity recorded in the 20-58 cm segment decoded the pending goal accurately in 74.0% of single trials, CA1 ensembles correctly decoded 82.3% of single trials. Excluding data recorded in the last 8 cm, the models restricted to the 20-50 cm segment were similarly accurate mPFC ensembles decoded single trials with 74.5% accuracy, CA1 ensembles correctly decoded 81.8% of the trials. The prediction accuracy of the two models was statistically indistinguishable (all p's > 0.05) demonstrating conclusively that micro behaviors in the start arm did not contribute to ensemble decoding predictions.

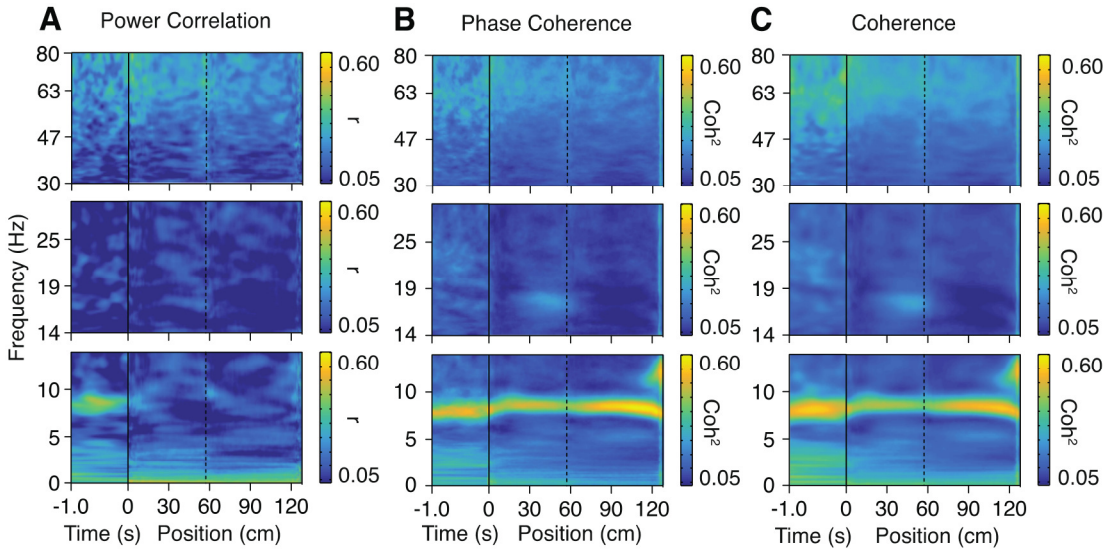
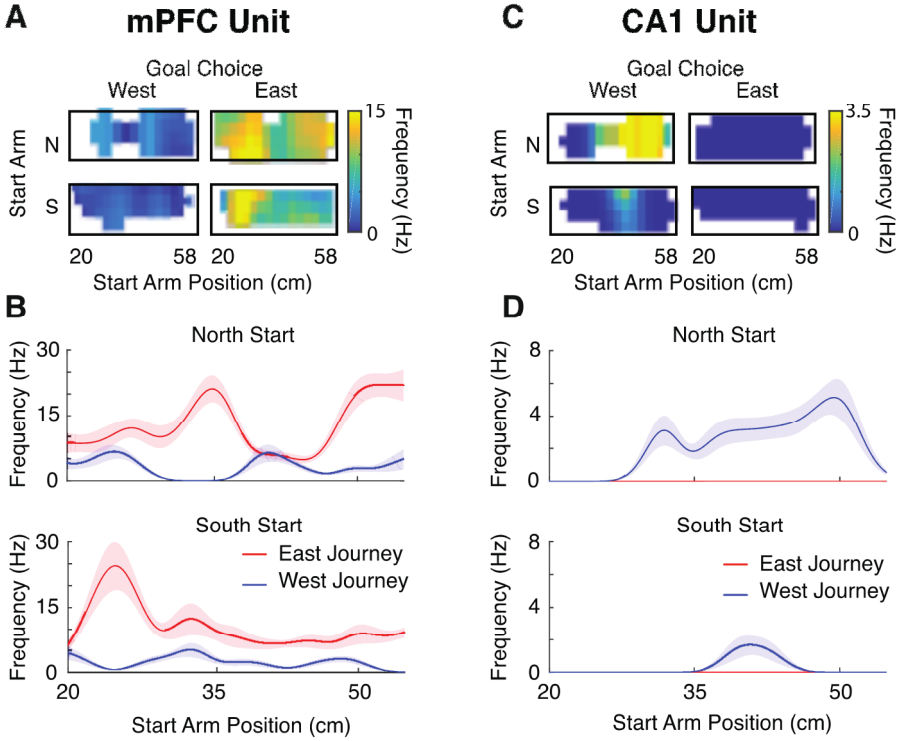


Figure S3.1 (related to Figure 2): Coherence is driven by phase coupling and not by power correlations.
Because LFP oscillations can vary in amplitude and frequency with running speed (e.g., hippocampal theta, ~7-12 Hz (McFarland et al., 1975), we analyzed the effects of running speed on spectral coherence. A GLM quantified the relationship of running speed, acceleration, and time with spectral power at every point on the maze for each frequency band in CA1 and mPFC. The variance in spectral power attributable to these factors was subtracted from the spectra prior to calculating coherence, and the resulting coherence was not attributable to covariation with movement parameters. Figure 2 of the main text shows coherence between mPFC and CA1 theta oscillations as animals perform the spatial reversal task. Coherence measures the degree to which the phase and amplitude of one signal predicts the phase and amplitude of another. Two analyses assess the extent to which the coherence was driven by the correlation in power or the consistency of phase offset across trials. To quantify how power correlated between regions, we calculated the Pearson product-moment correlation coefficient for each time-frequency point across trials. To remove power variations from affecting the coherence analysis, we normalized the power of every time-frequency point to 1, and then evaluated coherence as usual (**A**). There was little correlation in theta power across trials on the start or goal arms of the plus maze, though theta power correlation was high during the 1 second before animals initiated a trial. This correlation may be an artifact of variation in running speed or other overt behaviors that were not well controlled during that epoch. (**B**) The coherence analysis carried out after normalizing power to unity very closely resembled the coherence as calculated on the original data (**C**), demonstrating phase coupling was the key driver of the coherence findings.

Figure S3.2 (related to Figure 3) Single units in mPFC and CA1 differentiate pending goals

MDS analysis of mPFC and CA1 population activity illustrated variation that could signal changing task rules and guide behavior (Figure 3). Prospective coding was apparent in a subset of individual mPFC and CA1 units. (**A**) Heat maps of the firing rate of an example mPFC unit show that the firing rate of this neuron differentiated east and westbound journeys (left vs. right panels), particularly within the first half of the start arm. (**B**) Linearized firing rates confirm the heat maps shown in (A). Each trace shows the mean firing rate across trials (SEM in shaded regions). (**C**) CA1 units showed combined place and rule coding. The multi-peaked rate map reveals strongest selectivity for the north start arm during westbound journeys. (**D**) Linearized firing rates for unit shown in (C).



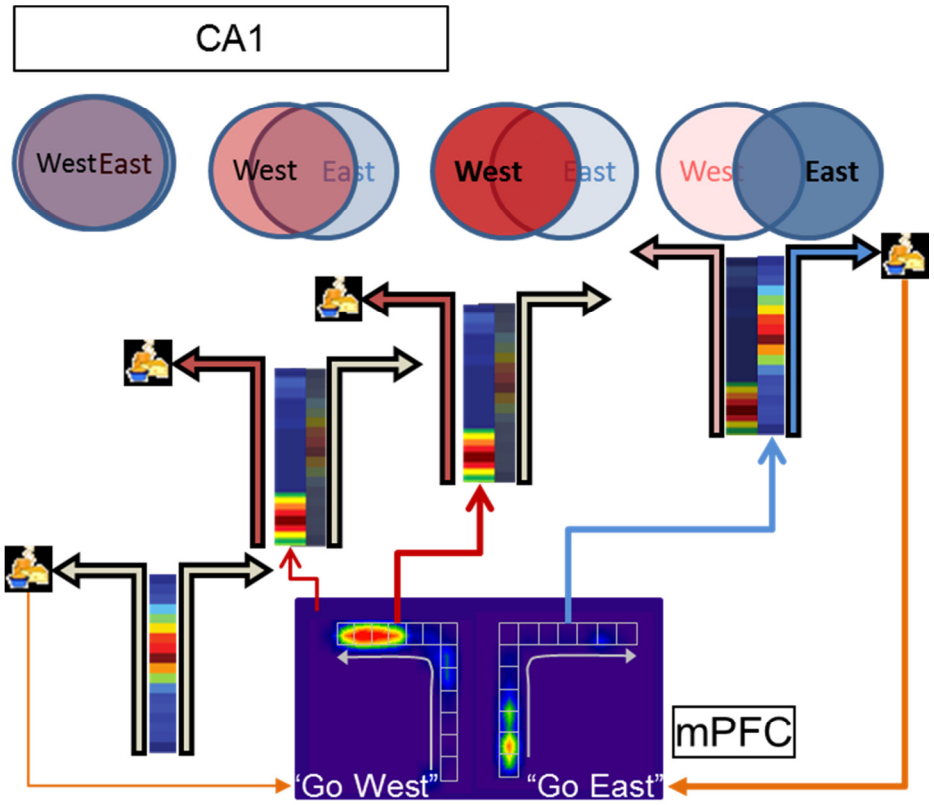


Figure S4.1 (related to Figures 1-5) mPFC rules differentiate CA1 prospective codes

CA1 neurons signal the rat's location in the plus maze via place fields (lower left). During learning in the plus maze, goal-related mPFC activity (lower middle) provides internal context, "rule" signals conveyed to CA1 (red arrows) that are encoded along with other task features in content addressable memory representations (middle start arm plots). When contingencies change, mPFC signals modulate CA1 ensembles so that different firing rates in the start arm predict imminent choices (rightmost start arm plot). mPFC inputs thereby increase the separation between CA1 prospective codes as learning proceeds (Venn diagrams, top row), so that "internal context" associated with a new rule (blue arrow) helps guide selective memory retrieval. By separating prospective codes, mPFC circuits teach the hippocampus to retrieve context associated memories, thereby reducing proactive interference. The orange arrows indicate place reward associations encoded by CA1, spatial goals conveyed to mPFC that are required for accurate memory retrieval (Spellman et al., 2015).

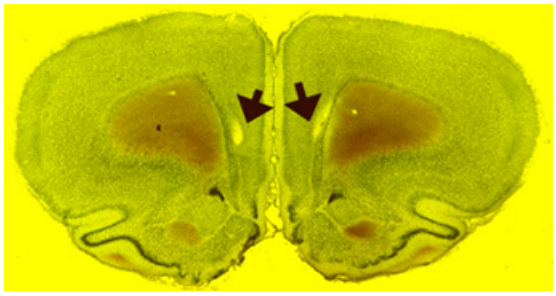


Figure S4.2 (related to Figure 1): Example histological section.
Arrows indicate track marks remaining from tips of infusion cannula for behavioral experiments.

	Initial discrimination	First reversal	Second reversal
Trials to criterion	$t(9) = 1.32$, $p > 0.05$	$t(9) = 5.06$, $p < 0.05$	$t(4) = 3.77$, $p = 0.06$
Number of errors	$t(9) = 1.40$, $p > 0.05$	$t(9) = 12.57$, $p < 0.05$	$t(8) = 8.90$, $p < 0.05$
Percent correct	$t(9) = 2.33$, $p > 0.05$	$t(9) = 8.79$, $p < 0.05$	$t(8) = 11.39$, $p < 0.05$

Note: all p-values are Bonferroni corrected. One animal completed the first reversal within 12 trials of the 64 allotted and did not attempt the second reversal. An additional two animals did not complete the second reversal.

Table S1A (related to Figure 1): Additional behavioral measures.

The spatial reversal task was analyzed using a repeated measures ANOVA of each DV with within subject factors of drug treatment and reversal number, which revealed significant drug × reversal interactions. The main body of the manuscript reported only results related to PC because the findings were similar in all three measures (TTC: $F(2,3) = 13.38$, $p = 0.032$; NE: $F(2,7) = 37.56$, $p < 0.001$; PC: $F(2,7) = 38.84$, $p < 0.001$). The main text reported analyses of drug (saline, muscimol) and reversal (ID, R1) that excluded R2? because only five of the ten rats completed the third discrimination. Analyses of all three learning epochs are described below in Table S1B and included all animals with data for a given reversal.

	Initial discrimination	First reversal	Second reversal
Trials to criterion	$t(7) = 0.38$, $p > 0.05$	$t(5) = 5.20$, $p < 0.05$	$t(1) = 4.40$, $p > 0.05$
Number of errors	$t(7) = 0.15$, $p > 0.05$	$t(7) = 9.00$, $p < 0.001$	$t(3) = 4.46$, $p = 0.063$
Percent correct	$t(7) = 0.73$, $p > 0.05$	$t(7) = 10.58$, $p < 0.001$	$t(3) = 6.61$, $p < 0.05$

Note: Two animals did not complete the first reversal. Two additional animals completed the first reversal within 12 trials of the 64 allotted, and did not attempt the second reversal.

Table S1B (related to Figure 1): Delayed infusion reversal task; infusion before ID.

Eight of the ten animals that completed testing on both the basic spatial reversal task and delayed infusion experiments. The two remaining animals exhibited signs of rejection of the implant towards the end of the first behavioral experiment and were sacrificed for histology at that point. As in the first experiment, the drug infusion schedule followed an ABBA design (A = saline, B = muscimol), and data were averaged within drug conditions prior to analysis. During the first four days animals received an infusion before ID learning and a sham infusion before R1. During the second four days, animals received a sham infusion before ID learning and the actual infusion before R1.

The statistical approach to analyzing data for the first four days (infusion pre-ID) was similar to that of the basic spatial reversal task, as were the results. Each of the three performance measures declined (TTC: $F(1,5) = 34.875$, $p = 0.002$; NE: $F(1,7) = 73.434$, $p < 0.001$; PC: $F(1,7) = 62.07$, $p < 0.001$ (Figure S2). Table S2 reports post-hoc t-tests between drug conditions for each DV and all three learning epochs. Note that few rats performed the second reversal, reducing the power of the statistical tests.

	Initial discrimination	First reversal	Second reversal
Trials to criterion	$t(7) = 2.02$, $p > 0.05$	$t(7) = 0.74$, $p > 0.05$	$t(5) = 4.11$, $p < 0.05$
Number of errors	$t(7) = 0.88$, $p > 0.05$	$t(7) = 0.87$, $p > 0.05$	$t(7) = 5.91$, $p < 0.001$
Percent correct	$t(7) = 0.16$, $p > 0.05$	$t(7) = 1.06$, $p > 0.05$	$t(7) = 4.91$, $p < 0.01$

Note: Two animals did not complete the second reversal.

Table S2A (related to Figure 1): Delayed infusion reversal task; infusion before R1.

When the order of the sham and actual infusions were switched, R1 performance was unaffected, most rats completed R2, and more reasonable statistical analyses were available for all three trial blocks. In this experiment, the sham infusion was given before ID and the actual infusion was given before R1. All three performance measures were impaired in R2 (TTC: $F(2,10) = 18.14$, $p < 0.001$; NE: $F(2,14) = 18.05$, $p < 0.001$; PC: $F(2,14) = 14.17$, $p < 0.001$. Table S3 lists the post hoc t-test results for ID, R1, and R2.

	Initial discrimination	First reversal	Second reversal
Trials to criterion	$t(7) = 1.47$, $p > 0.05$	$t(5) = 3.68$, $p < 0.05$	$t(1) = 6.00$, $p > 0.05$
Number of errors	$t(7) = 0.61$, $p > 0.05$	$t(7) = 6.21$, $p = 0.001$	$t(3) = 0.22$, $p > 0.05$
Percent correct	$t(7) = 0.67$, $p > 0.05$	$t(7) = 4.37$, $p < 0.01$	$t(3) = 2.16$, $p > 0.05$

Table S2B (Related to Figure 1): Delayed infusion reversal task; comparison of drug effects at different infusion times (pre-ID vs. pre-R1).

As indicated by the main results, mPFC infusions given before the ID impaired learning more than given before R1. A three-way repeated-measures ANOVA compared the effects of drug and infusion sequence, and all three measures of behavior distinguished ID and R1 (TTC: $F(1,5) = 15.17$, $p = 0.011$; NE: $F(1,7) = 49.54$, $p < 0.001$; PC: $F(1,7) = 26.59$, $p < 0.001$). Table S4 lists post-hoc tests showing the difference between drug effects (saline – muscimol) for each block when the infusion was given pre-ID compared to when it was given pre-R1.