# Supporting Information

## Forcelli et al. 10.1073/pnas.1320562111

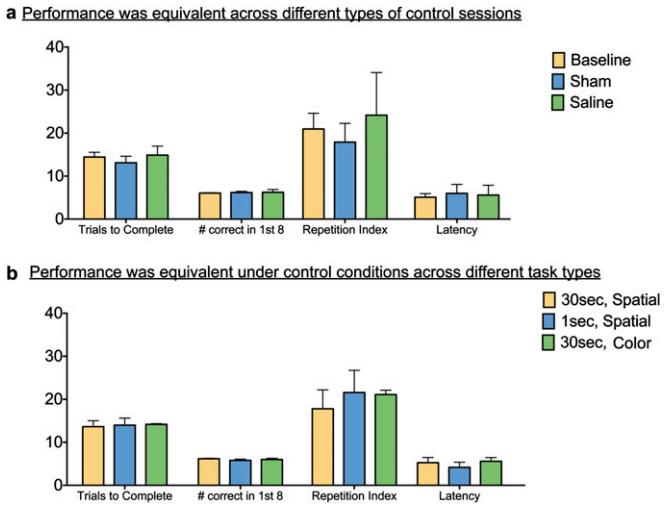


**Fig. S1.** Performance on control sessions. (*A*) Graph presents performance data for the three types of control sessions (i.e., baseline, sham, and saline infusion) for each of the performance measures (i.e., trials to complete a session, number of correct responses in the first eight trials, repetition index, and response latency). For each bar, data were collapsed across the three versions of the task (i.e., spatial with 1-s delay, spatial with 30-s delay, and color-cued); 3 (control session type) × 4 (performance measure) ANOVA yielded no significant main effect of control session type ($F_{2,8} = 0.24$, $P = 0.80$) or interaction between control session type and performance measure ($F_{6,24} = 0.28$, $P = 0.94$). (*B*) Graph presents performance data for the three versions of the task (i.e., spatial with 1-s delay, spatial with 30-s delay, and color-cued) for each of the performance measures. For each bar, data were collapsed across the three types of control session; 3 (version of the task) × 4 (performance measure) ANOVA resulted in no significant effect of the version of the task ($F_{2,8} = 0.11$, $P = 0.94$) or interaction between the version of the task and performance measure ($F_{6,24} = 0.31$, $P = 0.93$). Because the performance data did not differ as a function of either the control session type or the task version, they were collapsed for further analyses and the collapsed data are shown as "control" in Fig. 2. Graphs show means ± SEM.

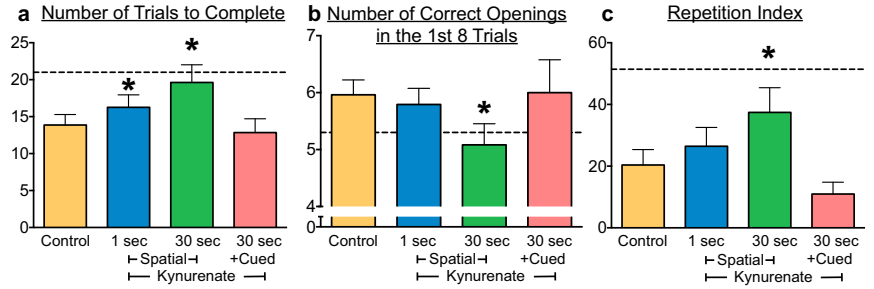


**Fig. S2.** Kynurenate (KYNA) performance compared with saline/sham control sessions. Graphs represent a reanalysis of the data presented in Fig. 2 of the main text. For this analysis the performance in baseline sessions was excluded; instead, only saline-infusion and sham sessions were included in the control. For each monkey, we conducted an approximately equivalent number of sham/saline sessions and KYNA sessions. These sessions were used to derive the average value for each monkey. The analysis revealed a pattern equivalent to that seen when baseline sessions were included in the mean control value for each animal (Fig. 2 of the main text). Skillings–Mack test (with Bonferroni-corrected Conover post hocs) revealed a treatment effect for (*A*) number of trials to complete ($Q = 10.118$, $P < 0.005$), (*B*) number of correct openings in the first eight trials ($Q = 7.16$, $P < 0.05$), and (*C*) repetition index ($Q = 10.827$, $P < 0.001$). *Significantly different from control, $P < 0.05$.

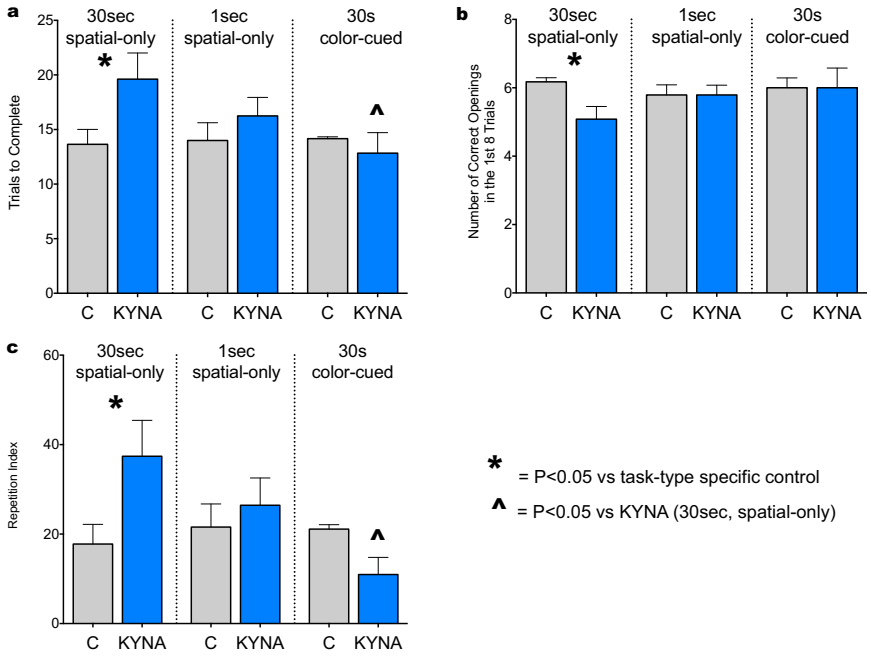


**Fig. S3.** Performance compared with task-specific control sessions. For this analysis we compared performance on each task type under KYNA-infused conditions with its task-type-specific control using a mixed-effects model (with treatment within task type as a repeated measure and monkey as a random effect). This analysis also allowed us to compare differences in task type within each treatment. (*A*) For trials to complete, we found a significant main effect of treatment within task type ($F_{1,5} = 4.45$, $P = 0.015$). Post hoc analysis revealed a significant difference between control and KYNA sessions for the 30-s spatial condition ($P < 0.005$), but no other conditions. Moreover, the performance with KYNA for the 30-s spatial condition was significantly impaired compared with the color-cued condition ($P < 0.01$) but did not differ from the 1-s spatial condition. (*B*) For number of correct openings in the first eight trials, the analysis revealed a trend toward a treatment-within-task-type effect ($F_{1,5} = 2.675$, $P = 0.068$), with the KYNA-infused 30-s spatial condition significantly worse than the respective control ($P < 0.005$), but not different from KYNA-infused sessions for the other task types. (*C*) For repetition index, the analysis revealed a significant effect of treatment within task type ($F_{1,12.58} = 5.337$, $P < 0.01$). For the 30-s, spatial condition, but no other task types, KYNA significantly impaired performance ($P < 0.005$) and was significantly worse than the color-cued KYNA-infused condition ($P < 0.005$).

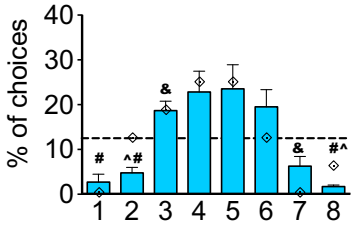


**Fig. S4.** Distribution of box selections on the first trial of a run. Frequency distribution showing the percent of times a given box (out of the eight possibilities) was selected on the first trial. For control runs, the distribution was calculated for each monkey and averaged across all subjects (blue bars, mean ± SEM). For the 30-s KYNA condition (♢), because there were fewer sessions a single distribution was built pooling data from all of the monkeys. The dashed line indicates chance level (12.5%). The data show that the animals avoided boxes at the ends of the array in favor of those in the middle for the first choice in the run. The pattern was similar for the KYNA and control conditions. #Values that are significantly below those expected by random box selection ($t = 5.6$, $P = 0.01$; $t = 6.4$, $P = 0.008$; and $t = 30.6$, $P < 0.001$ for boxes 1, 2, and 8, respectively). &A trend ($P < 0.10$). ^A significant difference from the control distribution when tested with KYNA on the 30-s spatial version of the task.

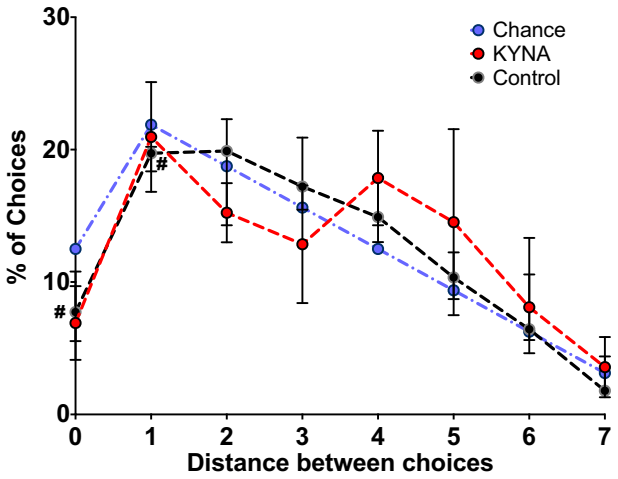


**Fig. S5.** Distance between boxes selected on successive trials. The figure shows the mean percent frequency (± SEM) with which each distance between boxes was selected on successive trials. A 0 represents selecting the same box on two consecutive trials (i.e., an error), 1 represents selecting a box immediately to the left or right of the box selected on the previous trial, and 7 is the maximum distance and reflects selecting a box on one end of the array, followed by the box on the opposite end on the next trial. These data were cumulated across the first eight trials within each session for each monkey. #Significantly lower percent choices than would be expected by chance ($P < 0.05$). Only the 0 and 1 distances under control conditions differed from chance. Two-way ANOVA with treatment and distance as repeated measures revealed a significant main effect of distance ($F_{7,21} = 7.183$, $P = 0.0002$) but no effect of treatment ($F_{1,3} = 0.9997$, $P = 0.3911$) nor a treatment × distance interaction ($F_{7,21} = 0.4962$, $P = 0.8267$). The rate of revisiting a box (0 condition) did not differ from chance in the KYNA condition.

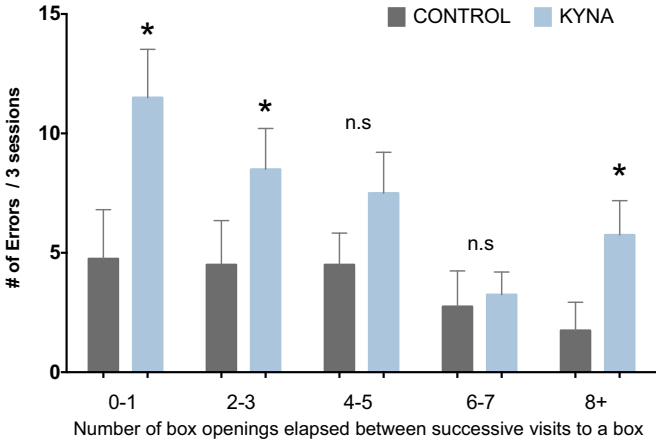


**Fig. S6.** Error distribution as a function of number of openings elapsed between box visits. For each monkey we calculated the number of openings that occurred between two successive visits to a given box (i.e., an error). For example, for the sequence 7–3–7, the number of openings that occurred would be one, for the sequence 7–5–4–7, the number of openings that occurred would be two. In the histogram above, for example, the 0–1 bin reflects opening a box on two consecutive trials and opening a box with one intervening trial, whereas the 8+ reflects openings occurring with eight or more intervening openings. Errors were cumulated for each monkey across their first three control and three KYNA (30-s, spatial) sessions, respectively. The first three sessions were selected because it was the minimum number of KYNA sessions that all monkeys received. Two-way ANOVA (treatment and bin as repeated measures) revealed significant main effects of treatment ($F_{1,3} = 12.38$, $P = 0.0389$) and bin ($F_{4,12} = 7.051$, $P = 0.037$), and a trend toward a treatment × bin interaction ($F_{4,12} = 2.717$, $P = 0.08$). Post hoc tests (Holm–Sidak-corrected) revealed a significant difference between treatment groups in the 0–1, 2–3, and 8+ bins. This indicates increased errors with both short and long delays. *$P < 0.05$.

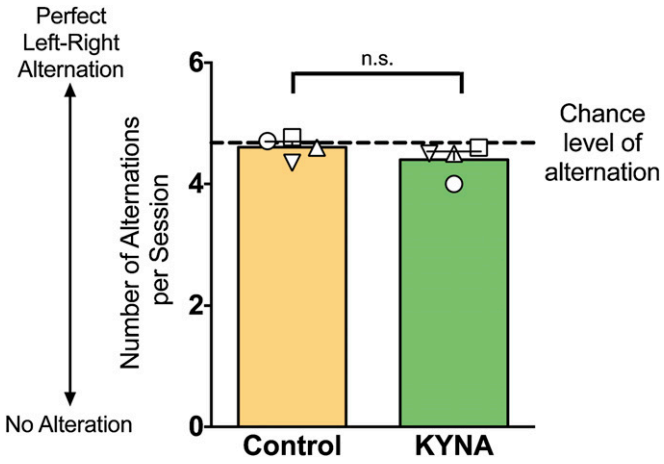


**Fig. S7.** Left–right alternation score. Alternation score, as described in *Methods*, was unaffected by KYNA treatment. This measure assessed the degree to which animals adopted a strategy of alternating between left and then right (or vice versa) on successive box openings over the first eight trials of a session. A score of 6 represents perfect alternation and a score of 0 represents no alternation (i.e., solving the task by moving only from left to right or only right to left). Dashed line represents the level of alternation expected by chance. Control data are an average of all control sessions. KYNA data were restricted to the spatial version of the task with a 30-s delay. KYNA infusions did not affect the animals' strategy with respect to alternation, compared with control (Wilcoxon test: W = 6, $P = 0.38$). The level of alternation the animals displayed was not significantly different from chance, either for control condition (one-sample $t$ test: $t = 1.0$, $P = 0.39$) or for KYNA infusions ($t = 2.2$, $P = 0.39$). Bars show means + SEM.

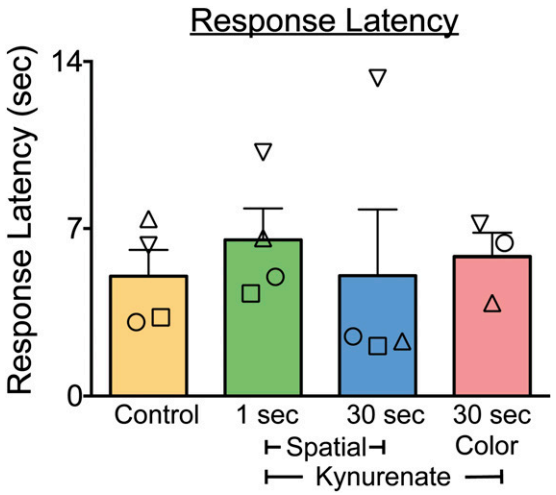


**Fig. S8.** Response latency. Bars show mean + SEM latency to open a box in seconds. Symbols indicate individual subjects as in Fig. 2 of the main text. Response latency did not vary as a function of treatment.

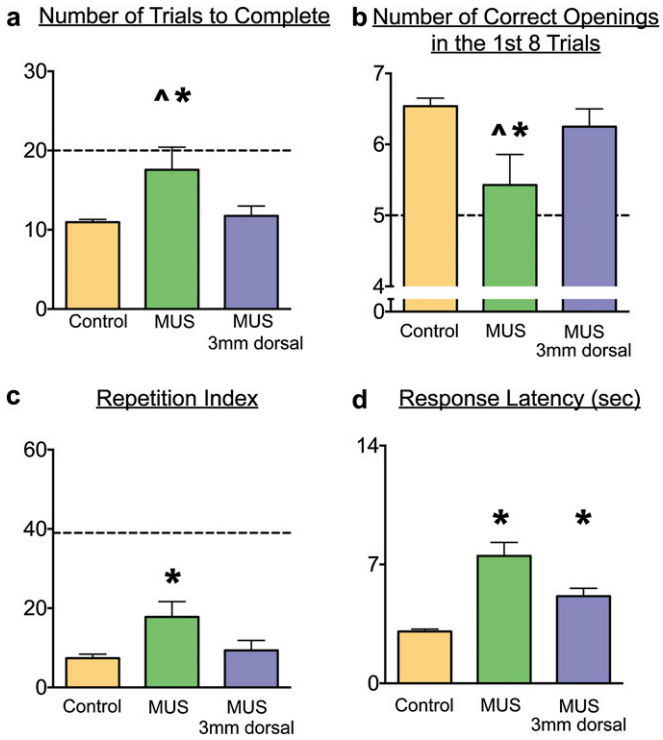


**Fig. S9.** Effects of muscimol (9 nmol) infusions in animal TX. The graphs present data from one animal (TX, represented by ○ in Fig. 2 of the main text) for the 30-s spatial version of the task after muscimol (MUS) infusions into hippocampus, and after MUS infusions placed 3 mm dorsal to the hippocampus. MUS infusions bilaterally into hippocampus reduced performance to a chance level on two measures: (*A*) the number of trials to complete a run (one-sample *t* test: $t = 0.85$, df = 6, $P = 0.21$, compared with chance; ^no difference from chance) and (*B*) the number of correct openings in the first eight trials ($t = 1.0$, df = 6, $P = 0.18$). Further, MUS infusions into hippocampus significantly impaired performance on all measures compared with control. ANOVAs applied to each performance measure yielded the following significant results: (*A*) trials to complete a run; $F_{2,34} = 9.37$, $P = 0.0006$, post hoc analysis for control versus MUS in the hippocampus $P = 0.003$; (*B*) number of correct responses in the first eight trials; $F_{2,34} = 6.83$, $P = 0.0032$; post hoc $P = 0.0015$; and (*C*) repetition index; $F_{2,34} = 7.44$, $P = 0.0021$; post hoc $P = 0.001$. Placement of MUS 3 mm dorsal to the hippocampus did not alter task performance on any measure ($P > 0.05$). (*D*) MUS infusions either into the hippocampus or dorsal to it significantly increased response latency ($F_{2,34} = 47.07$, $P < 0.0001$; post hoc comparisons yielded $P = 0.001$ and $P = 0.0025$, for MUS in the hippocampus or dorsal to it compared with control). Because the increase in response latency and performance decrements were dissociated, motor confounds are not sufficient to account for the effect on memory. Bars show mean + SEM.

**Table S1. Results of chance performance simulations**

| Chance (Monte Carlo simulations) | Mean | Median | No. of valid simulations | SD |
|---|---|---|---|---|
| Trials to complete | 21.0 | 20.00 | 1,971 | 7.5 |
| No. correct in the first eight trials | 5.3 | 5.0 | 2,000 | 0.90 |
| Repetition index | 51.4 | 47.17 | 2,000 | 30.3 |
| Alternation score | 1.3 | 1 | 15,000 | 0.97 |