HIPPOCAMPAL REMAPPING IS UNAFFECTED BY CHEMOGENETIC INACTIVATION OF THE ANTERIOR THALAMUS OR THE RETROSPLENIAL CORTEX.

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BACKGROUND

- The anterior thalamus (AT), hippocampus (HPC) and retrosplenial cortex (RSC) are interconnected components of a neural circuit that is critical for spatial learning and memory.
- Previous studies found that AT lesions have modest effect on HPC place cell stability (Calton et al., 2003, *J Neurosci*), and RSC inactivation led to spontaneous remapping in HPC (Cooper & Mizumori, 2001, *J Neurosci*).
- However, the specific contributions of the AT and RSC to HPC remapping in response to contextual changes are not known.

METHODS

All rats received either a virus containing the inhibitory DREADD receptor gene (hM4Di) or the same virus without the receptor gene (mCherry) at either AT or RSC at least four weeks before the experiments. Microdrive implants with movable tetrodes targeting at the CA1 region of the HPC were implanted in rats from the context manipulation task. Clozapine-N-oxide (CNO, i.p.) was used as the ligand for the inhibitory DREADD receptors.

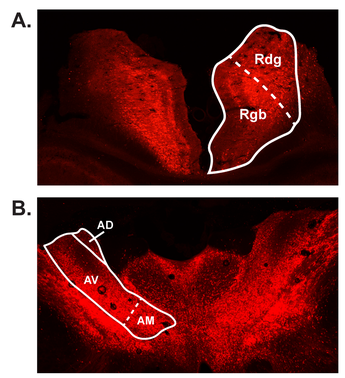

Figure 1: Representative hM4Di-mCherry expression in the RSC and AT. A) Both dysgranular RSC (Rdg) and granular b RSC (Rgb) showed robust hM4Di-mCherry expression. B) Anterior dorsal (AD), anterior ventral (AV), and anterior medial (AM) subnuclei of the anterior thalamus all showed good hM4Di-mCherry expression, although expression was less reliable in AD .

AT inactivation impaired spatial memory.

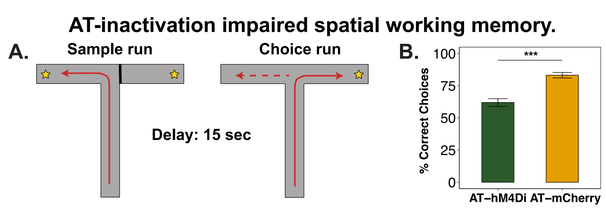

Figure 2: Delayed T-maze alternation task under AT-inactivation. A) Illustration of one trial of alternation. B) Compared to the AT-mCherry group, AT-hM4Di group performed significantly worse under the effect of CNO ($t(10.749) = -5.792$, $p = 0.00013$).

AT-inactivation produced a sex-dependent impairment in spatial learning.

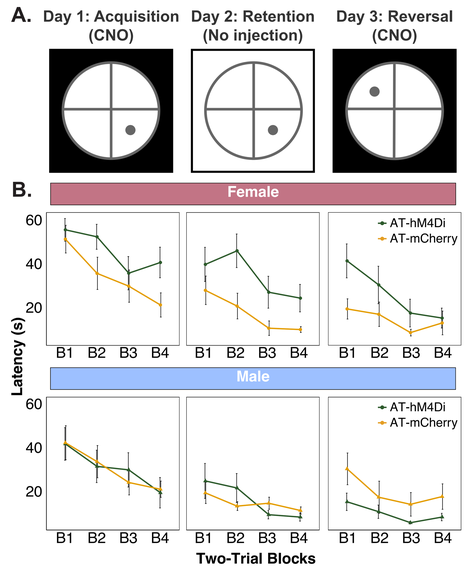

Figure 3: Morris water maze with reversal learning under AT-inactivation. A) Illustration of the design. B) AT-inactivation produced a sex-dependent impairment, as the interaction between group and sex was significant ($F(1, 16) = 4.64$, $p = 0.047$). Tukey posthoc test revealed that the escape latency was significantly different between female groups (p=0.02). No differences were observed between the male groups (p=0.61). **RSC-inactivation also produced similar sex-dependent impairments, with spatial learning performance impaired in females but not in males (data not shown).**

Neither AT nor RSC inactivation blocked remapping in the HPC.

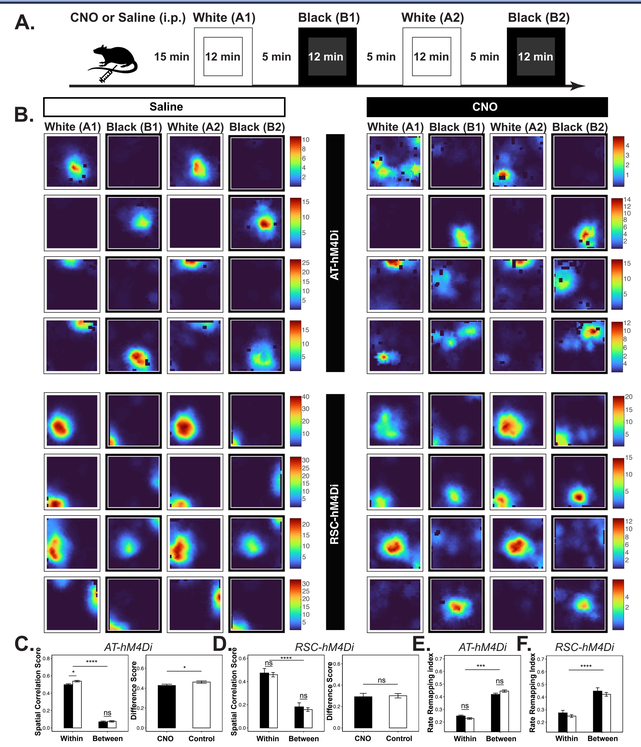

Figure 4: Context manipulation task with CA1 recordings.
A) Illustration of the task. B) Representative CA1 place cells.
C) Left: AT-inactivation failed to abolish HPC global remapping, as within-context spatial correlations were significantly greater than between-context correlations ($F(1, 1205) = 2529.37$, $p < 0.0001$). Interaction of treatment and correlation type was significant ($F(1, 1205) = 3.839$, $p = 0.050$), and Tukey posthoc test showed that AT inactivation produced a small, but significant reduction in the spatial correlation scores for repeated visits to the same context ($p = 0.027$). Right: AT-inactivation slightly reduced difference score between within-context and between-context spatial correlations ($t(1122) = -1.97$, $p = 0.049$).
D) Left: RSC-inactivation did not block HPC global remapping ($F(1, 356) = 198.03$, $p < 0.0001$). Right: difference score was not affected by RSC-inactivation.
E) Rate remapping index was calculated as the difference between firing rates in pairwise trials divided by the sum of the two firing rates. AT-inactivation failed to abolish HPC rate remapping ($F(1, 1205) = 742.4$, $p < 0.001$). Interaction was significant ($F(1, 1205) = 10.52$, $p = 0.001$), but Tukey posthoc tests indicated that AT inactivation did not affect either within-context or between context rate remapping.
F) RSC-inactivation did not block HPC rate remapping ($F(1, 356) = 125.86$, $p < 0.0001$).

CONCLUSIONS

- **Neither AT or RSC inactivation abolished HPC place cell remapping.**
- **AT-inactivation slightly decreased place cell stability for repeated visits to the same context.**
- **Spatial and contextual memory impairments seen after AT or RSC damage are not likely due to disruption of HPC representations.**
- **Our results suggest that the AT and RSC may be more important as output targets for HPC information than as inputs to the HPC.**

This work is supported by NIH grant MH083809 to D.M. Smith.