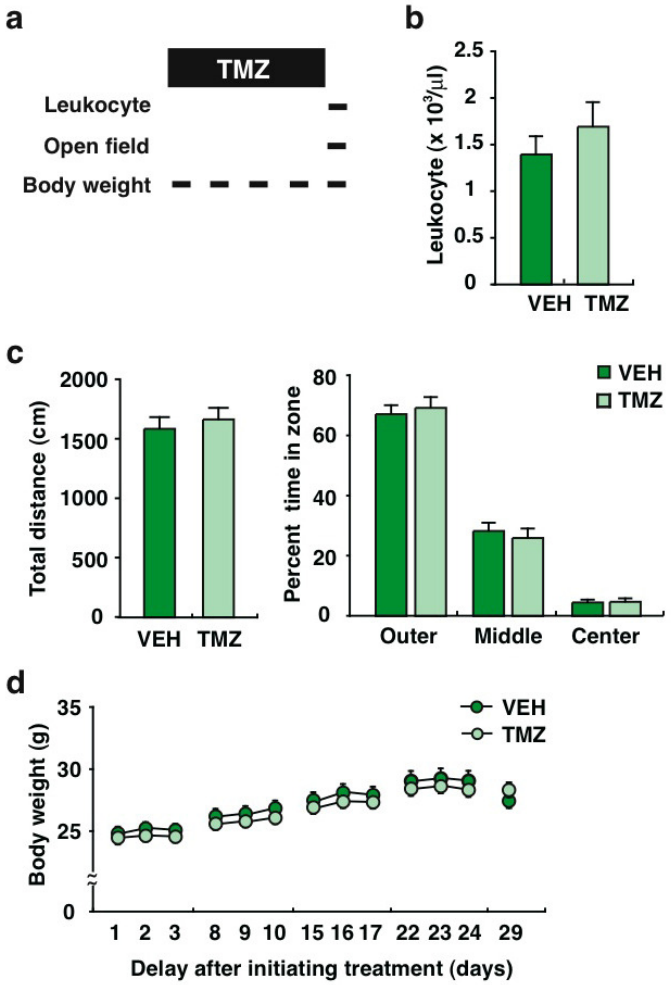
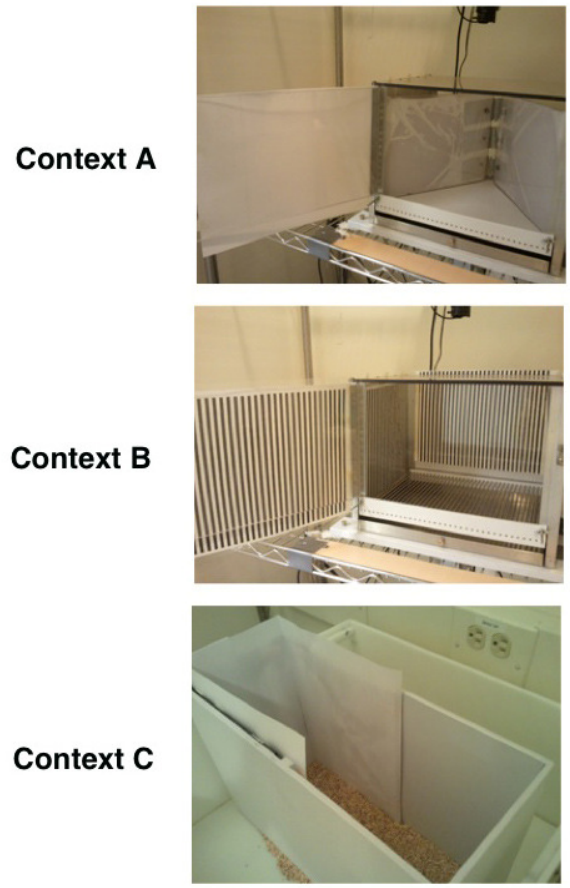
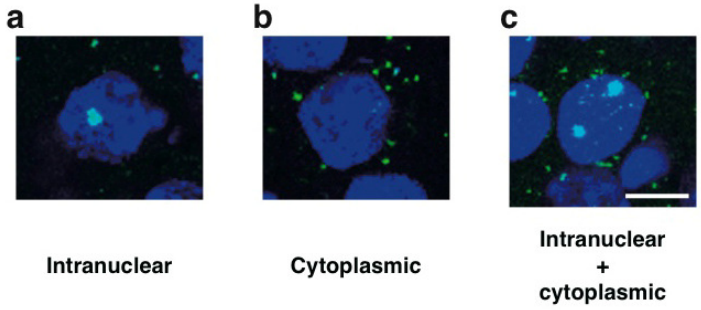


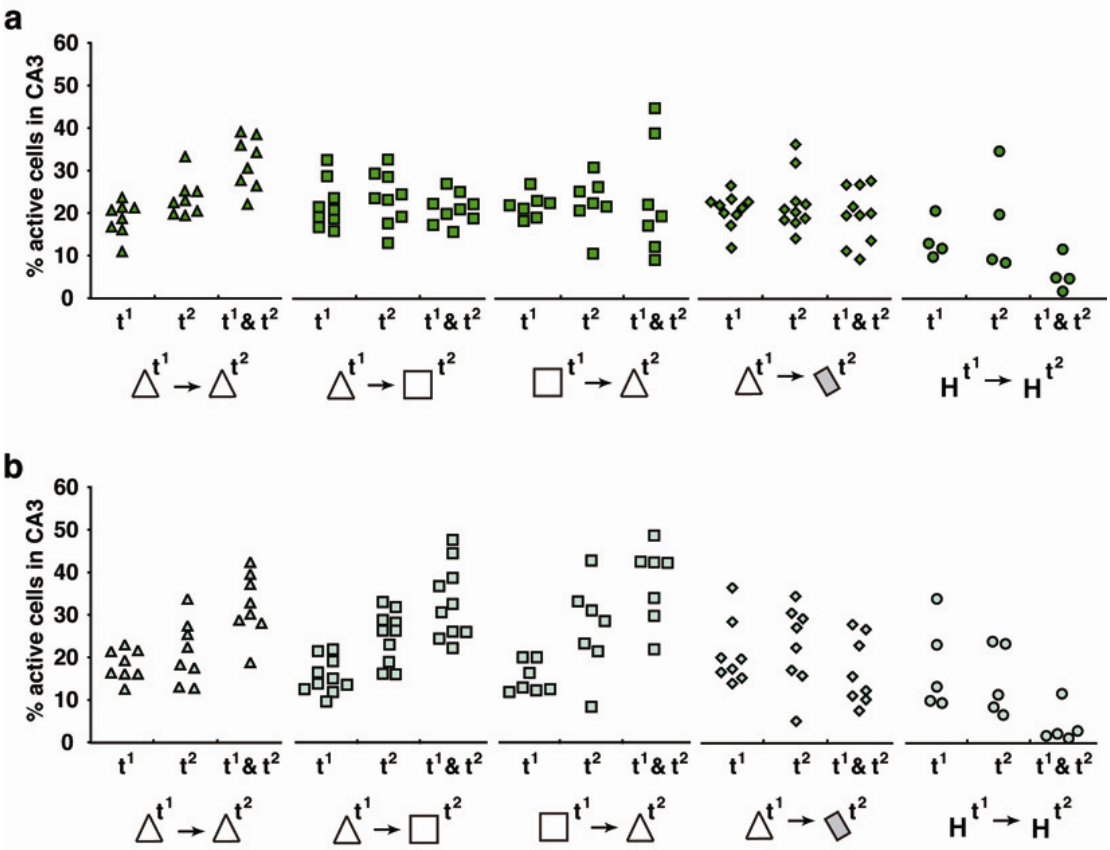

**Supplementary Figure S1. Chemical suppression of adult neurogenesis does not alter general health or behavior.** (**a**) Scheme indicating timing of tests with respect to TMZ treatment; (**b**) Hematology analyses revealed no changes in leukocyte number in TMZ-treated ($n$ = 7; light green bars) vs. VEH-treated ($n$ = 6; dark green bars) mice ($p > .05$); (**c**) Open field activity. TMZ-treated ($n$ = 14; light green bars) and VEH-treated ($n$ = 12; dark green bars) mice showed similar levels of activity (left) ($p > .05$), spending equivalent time in different regions of the open field (right) (main effect of *Zone* only, $F_{2,48} = 206.80$, $p < .001$); (**d**) Over the course of treatment, body weight was similar in TMZ-treated ($n$ = 19; light green circles) and VEH-treated ($n$ = 18; dark green circles) mice (during treatment, main effect of *Delay* only, $F_{3,105} = 192.19$, $p < .001$; at test, $p > .05$).



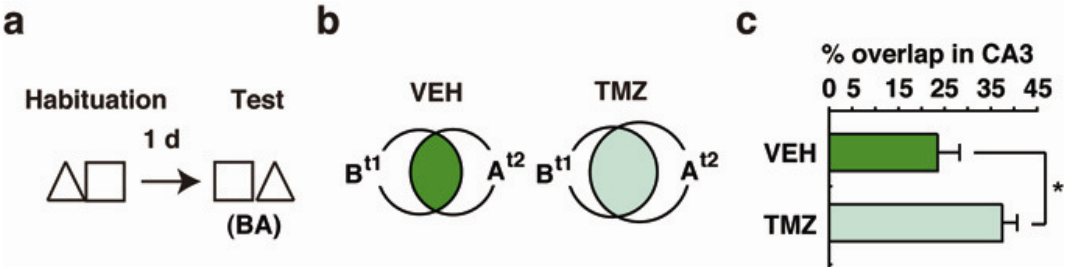

**Supplementary Figure S2. Context configurations**. (**a**) Context A; (**b**) Context B; and (**c**) Context C. Contexts A and B were located in the same room. Context C was located in a different room.



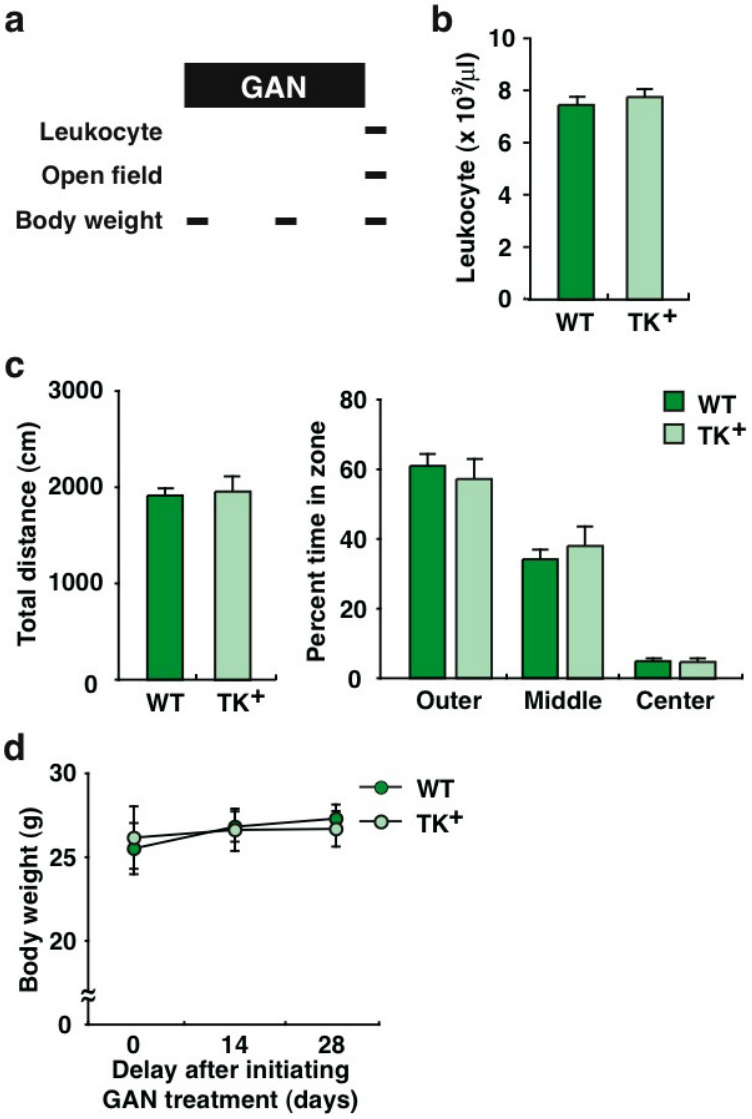

**Supplementary Figure S3. Localization of *arc* mRNA following consecutive context exposures.** Representative image of CA3 region following consecutive context exposures. Exposures were spaced 20 min apart, and brains removed after the second exposure. Examples of cells with *arc* mRNA localized to the nucleus (**a**), cytoplasm (**b**) or both (**c**). *arc* = green, Hoechst = blue. Scale bar = 10 μm.



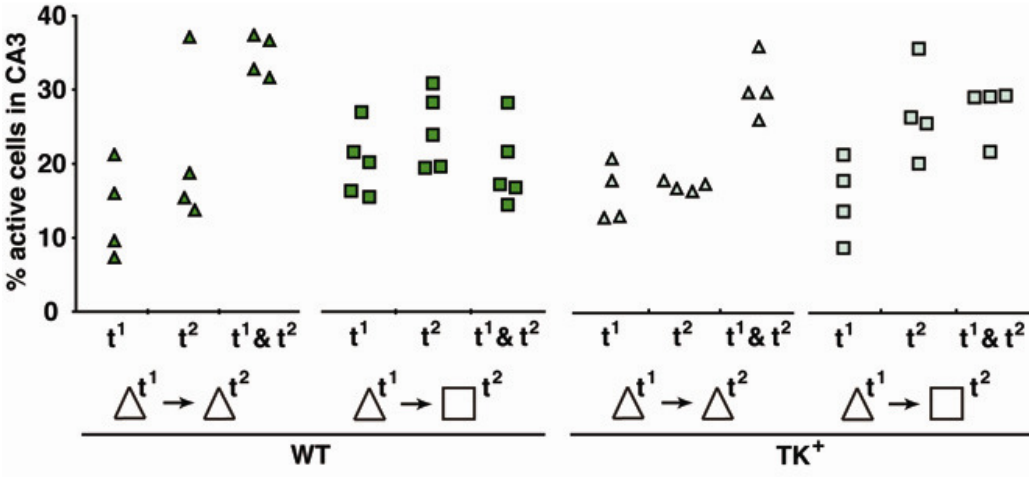

**Supplementary Figure S4. Scatterplots of individual mouse data from cellular imaging experiment.** The percent cells (of total DAPI$^+$ cells) expressing only cytoplasmic *arc* (corresponding to t1), only nuclear *arc* (corresponding to t2) or both cytoplasmic and nuclear *arc* (corresponding to t1 & t2) is indicated for (**a**) VEH-treated and (**b**) TMZ-treated mice for different testing conditions.



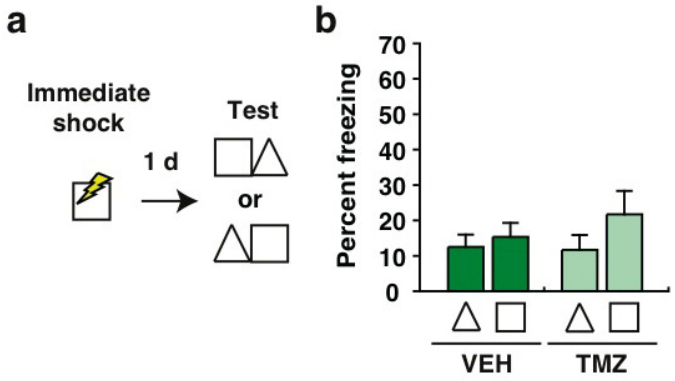

**Supplementary Figure S5. Chemical suppression of adult neurogenesis impairs CA3 population coding of similar contexts. a**. Experimental design. TMZ-treated and VEH-treated mice were habituated to contexts A (triangle) and B (square), and then tested in context B then context A (VEH, $n = 7$, TMZ, $n = 7$). **d**. Venn diagrams indicating populations of CA3 cells activated either by first (t1), second (t2) or both (overlap, shaded) context exposures, as reflected by *arc* expression. **e**. Percent of CA3 cells activated by both context exposures in VEH- vs. TMZ-treated mice (*unpaired t test*, $t_{12} = 2.26$, $p < .05$). These data indicate that impairments in CA3 population coding of similar contexts do not depend on the order of context presentation.



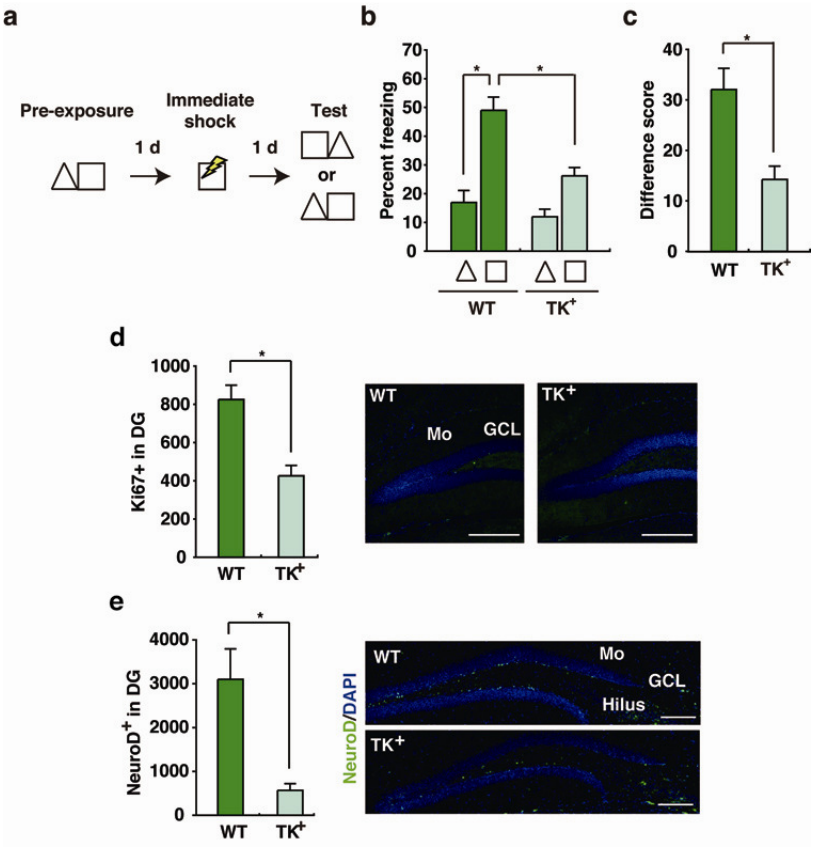

**Supplementary Figure S6. Genetic suppression of adult neurogenesis does not alter general health or behaviour.** (**a**) Scheme indicating timing of tests with respect to GAN treatment; (**b**) Hematology analyses revealed no changes in leukocyte number in $TK^+$ ($n = 3$; light green bars) vs. WT ($n = 3$; dark green bars) mice treated with GAN ($p > .05$); (**c**) Open field activity. $TK^+$ ($n = 7$; light green bars) and WT ($n = 7$; dark green bars) mice treated with GAN showed similar levels of activity (left) ($p > .05$), spending equivalent time in different regions of the open field (right) (main effect of *Zone* only, $F_{2,24} = 69.60$, $p < .001$); (**d**) Over the course of treatment, body weight was similar in $TK^+$ ($n = 6$; light green circles) and WT ($n = 10$; dark green circles) mice treated with GAN (*Genotype* main effect, $p > .05$).




**Supplementary Figure S7. Scatterplots of individual mouse data from cellular imaging experiment.** The percent cells (of total DAPI$^+$ cells) expressing only cytoplasmic *arc* (corresponding to t1), only nuclear *arc* (corresponding to t2) or both cytoplasmic and nuclear *arc* (corresponding to t1 & t2) is indicated for (**a**) GAN-treated WT and (**b**) GAN-treated TK$^+$ mice for different testing conditions.




**Supplementary Figure S8. Discrimination depends upon context pre-exposure.**
**a**. Experimental design. VEH-treated ($n$ = 10) and TMZ-treated ($n$ = 10) mice were placed in context B and immediately shocked. Twenty-four hours later freezing was assessed in contexts A and B. **b**. During the test, VEH-treated and TMZ-treated mice exhibited equivalently low levels of freezing in contexts (*Treatment main* effect and *Treatment* × *Context* interaction, $p$s > .05), indicating that context discrimination depends upon prior experience in the to-be-discriminated contexts.




**Supplementary Figure S9. Genetic suppression of adult neurogenesis impairs behavioral discrimination of similar contexts. a**. Experimental design. Mice were pre-exposed to contexts A (triangle) and B (square). The following day they received an immediate shock in context B, and then 24 hours later freezing was assessed in contexts A and B. **b**. During the test, both GAN-treated WT ($n$ = 11) and GAN-treated TK$^+$ ($n$ = 8) mice froze more in context B vs. A (*Context* main effect, $F_{1,34}$ = 22.85, $p$ < .001) and freezing was reduced overall in TK$^+$ mice (*Genotype* main effect, $F_{1,34}$ = 7.68, $p$ < .01). **c**. However, discrimination (freezing$_A$ – freezing$_B$) was reduced in TMZ-treated mice (unpaired t-test, $t_{16}$ = 3.09, $p$ < .01). (**d**) Ki67$^+$ and (**e**) NeuroD$^+$ staining was reduced in GAN-treated TK$^+$ compared to WT mice ([Ki67: $t_4$ = 3.51, $p$ < .05; WT, $n$ = 3, TK$^+$, $n$ = 3]; [NeuroD: $t_5$ = 2.62, $p$ < .05; WT, $n$ = 4, TK$^+$, $n$ = 3]), confirming that GAN treatment (delivered via chow) reduced neurogenesis. Scale = 200 µm. Mo = molecular layer, GCL = granule cell layer.

**Supplementary Table S1. *arc* induction following context exposures**

| | | 1st exposure (%) | 2nd exposure (%) |
|---|---|---|---|
| Re-exposure to same context (AA) | VEH | 50.5 ± 2.0 | 55.5 ± 3.3 |
| | TMZ | 51.0 ± 2.2 | 54.1 ± 3.3 |
| Exposure to similar context (AB) | VEH | 43.2 ± 1.5 | 44.8 ± 3.0 |
| | TMZ | 48.6 ± 2.3 | 58.0 ± 3.7 * |
| Exposure to similar context (BA) | VEH | 43.2 ± 1.5 | 44.8 ± 3.0 |
| | TMZ | 48.6 ± 2.3 | 58.0 ± 3.7 * |
| Exposure to dissimilar context (AC) | VEH | 40.4 ± 1.9 | 42.1 ± 2.9 |
| | TMZ | 38.1 ± 3.0 | 39.8 ± 4.8 |
| Homecage (H) | VEH | 19.7 ± 3.1 | 24.0 ± 8.1 |
| | TMZ | 22.0 ± 6.5 | 18.9 ± 5.1 |

| | | 1st exposure (%) | 2nd exposure (%) |
|---|---|---|---|
| Re-exposure to same context (AA) | WT | 48.4 ± 3.0 | 56.1 ± 6.6 |
| | $TK^+$ | 46.8 ± 3.5 | 47.8 ± 2.2 |
| Exposure to similar context (AB) | WT | 40.0 ± 1.8 | 44.3 ± 3.9 |
| | $TK^+$ | 43.1 ± 3.6 | 54.7 ± 1.7 * |

Percent cells (of total $DAPI^+$ cells) expressing cytoplasmic vs. nuclear *arc* (indicated for different test conditions and treatments. Neither chemical (effects involving *Treatment*, *p*s > .05) or genetic (effects involving *Genotype*, *p*s > .05) suppression of adult neurogenesis altered likelihood of *arc* induction. However, in the similar context conditions (AB, BA), *arc* induction was elevated on the second exposure (i.e., nuclear *arc*) following chemical and genetic reduction of neurogenesis (Newman-Keuls test; *$p < .05$).

## Supplementary Methods

***Evaluation of general health***

To evaluate the impact of chemical and genetic suppression of adult neurogenesis on general health we examined weight gain during treatment, and exploratory behavior and immune function following the completion of treatment. For chemical suppression of adult neurogenesis, these tests were conducted in a separate cohort of TMZ- and VEH-treated mice. For genetic suppression of adult neurogenesis, exploratory behavior (open field) was examined in a separate cohort of mice, whereas weight and immune function were evaluated in mice in *arc* in situ gluorescent hybridization experiment.

***Body weight***

In the chemical suppression of neurogenesis experiments, mice were weighed prior to TMZ or VEH injections and testing. In the genetic suppression of neurogenesis experiments, mice were weighed before each surgery and testing (i.e., days 0, 14 28).

***Open field test***

Mice were placed in the center of a square-shaped open field (45 cm × 45 cm × 20 cm height) and allowed to explore for 5 min. The open field apparatus was constructed of Plexiglas, and was dimly-lit from above. Mouse location was tracked by a camera located above. Total distance travelled and time spent in 3 different zones (outer, middle, inner) were measured (Limelight2, Actimetrics, Wilmette, IL). Distribution of activity in different regions of the arena was used as a measure of anxiety-related behavior.

***Hematology***

Following decapitation, blood samples were collected from the heart. Samples were diluted in Tulk solution (0.01% glacial acetic acid, 0.01% Crystal violet) to make a 10% solution. Stained leukocytes were counted using a hemacytometer glass slide using stereomicroscopy.