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Neurobehavioral consequences of cortical adaptation disruption during ontogeny

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ABSTRACT

Filtering of redundant or stable inputs is a critical function of all sensory pathways. Normal sensory gating can allow processing resources to be differentially devoted to changing or otherwise biologically significant stimuli. In olfaction, short-term odor habituation is mediated by a metabotropic glutamate receptor (mGluR)-mediated depression of afferent synapses in the piriform cortex. Given the role of early experience in shaping cortical function and anatomy, the present experiments examined the effects of chronic habituation disruption during development on behavior and local circuit anatomy. Rats were chronically intra-cerebrally infused with the mGluR group III antagonist (*RS*)-a-cyclopropyl-4-phosphonophenylglycine (CPPG) during early development. The results demonstrated that early onset mGluRIII blockade resulted in a long-lasting decrement in odor habituation compared to controls, evident for at least 2 weeks post-infusion offset. Odor investigation time in the youngest animals was correlated with cortical laminar thickness, though the long-lasting behavioral effect showed no such correlation. No changes in apical dendritic spine density in the piriform cortex were detected. Combined with previous work, these results suggest that sensory gating disruption during development can have both immediate and long-lasting effects on sensory-guided behavior.

Filtering of redundant or stable inputs is a critical function of all sensory pathways. Normal sensory gating can allow processing resources to be differentially devoted to changing or otherwise biologically significant stimuli. Thus, sensory gating impairment may acutely disrupt ongoing information processing, leading to abnormal behavioral or perceptual responses. Disruptions of sensory gating are associated with a number of disorders including autism spectrum disorder [10,21] and schizophrenia [18]. However, in addition to the acute effects of sensory gating disorders, prolonged, abnormal responses to stimuli normally filtered out could leave lasting traces in behavioral or neural responses due to experience-dependent plasticity of local circuits. These lasting effects may be expected to be most pronounced following sensory gating disruption during early development, when effective connections become stabilized, while inactive or ineffective connections are pruned [14,16,19,26].

In the olfactory system, short-term habituation to stable, background odors is mediated by depression of afferent input to the piriform cortex [3,5,28]. Prolonged (10's of sec) exposure to odors induces depression of cortical afferent synapses from olfactory bulb mitral cells to piriform cortical pyramidal cells. This is a homosynaptic depression mediated by pre-synaptic group III metabotropic glutamate receptors (mGluRIII [5]). Blockade of these receptors with the antagonist (*RS*)-a-cyclopropyl-4-phosphonophenylglycine (CPPG) [5] or (*RS*)-a-methylserine-*O*-phosphate (MSOP; Kahohisa and Wilson, unpublished) prevents synaptic depression *in vitro*, and acute infusion of CPPG into the *in vivo* anterior piriform cortex prevents cortical adaptation to odors [5], habituation of odor-evoked autonomic reflexes [3], and reduces habituation of odor investigation in adult rats [30]. Furthermore, the mGluRIII-mediated synaptic depression can be expressed by at least the first postnatal week in rats [25], suggesting this mechanism is functional very early in development, as is habituation of some odor-evoked autonomic reflexes [9].

The present experiments examined the neurobehavioral consequences of prolonged sensory gating disruption during development. Animals were continuously infused intra-cranially with CPPG or artificial cerebrospinal fluid (aCSF) for 2 weeks beginning at postnatal day 14 (PN14). After the infusion, behavioral odor habituation, piriform cortex lamination and dendritic spine density were quantified. Prior work has demonstrated that reduced sensory input caused by naris occlusion during early development induces changes in piriform cortical lamination and dendritic complexity [29], along with changes in piriform cortical physiology [4,11]. It was hypothesized here that disruption of normal cortical

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adaptation should induce the opposite effects on neuroanatomy, and as well as a prolonged impairment in normal odor habituation.

Male Long-Evans hooded rats were used in all experiments in accordance with the Institutional Animal Care and Use Committee of the University of Oklahoma. Food and water were given *ad libitum* and a 12-h light cycle was used. Litters were culled to 12 on postnatal day 1 (PN1; PN0 is date of birth).

Naïve PN14 ($n = 10$), PN21 ($n = 10$), PN28 ($n = 10$) and adult (>200 g, $n = 6$) animals were placed in a 50 cm × 27 cm × 30 cm glass aquarium with fresh shavings. After 2 min to allow acclimation to the chamber, an 80-mL glass jar containing a 3 cm × 3 cm paper towel square soaked with 100 μL of peppermint odor was added for a 10-min behavioral trial. All behaviors were videotaped with a camcorder and analyzed using JWatcher 0.9. Behaviors scored were rearing, walking, grooming self, scratching, digging, smelling the odor jar (nose actively sniffing within 1 cm of jar) and quiet time (no overt behavior observed). After testing, all animals were returned to their home cages.

PN14 ($n = 32$) animals were anesthetized with isoflurane and placed in a stereotaxic apparatus. A cannula attached to a micro-osmotic pump (Alzet) was unilaterally implanted into the forebrain, near the anterior piriform cortex (aPCX), while under isoflurane anesthesia. Cannulas were implanted at +1.0 mm anterior to Bregma, −4.0 mm lateral and −6.5 mm ventral. The pumps were placed subcutaneously on the back and filled with either aCSF or 2.5 mM CPPG [3,30]. The pumps supplied 0.25 μL ± 10% of fluid per hour for 14 days, and allowed for whole brain infusion. After surgery, animals were returned to their home cages until testing. There was no significant weight difference between CPPG- and aCSF-infused animals at any testing age. On PN21, animals were weaned.

Animals were tested 2 weeks (PN28) or 4 (PN42) weeks after implantation. Animals were placed in a glass aquarium and presented with peppermint odor as described above for the naïve animals. All behaviors were videotaped with a camcorder and analyzed blind with respect to drug condition following the same procedure as described above for the developmental test.

After all behavioral tests, cannula implanted animals were anesthetized with isoflurane and placed in a stereotaxic apparatus. Holes were drilled bilaterally over the olfactory bulbs. A total of 3 μL of 30% Neurobiotin–dextran (10,000 M.W.) was injected into each olfactory bulb distributed at −3 mm, −2 mm and −1.5 mm ventral to the bulb surface. Animals were returned to their home cages.

Five days later, animals were overdosed with an i.p. injection of urethane and perfused transcardially with 0.1 M PBS followed by 4% paraformaldehyde–0.1 M PB. The brains were removed and immersed in a 30% sucrose–4% paraformaldehyde solution for 2 days. Brains were sectioned coronally at 40 μm, treated with Avidin–SG to visualize the labeled axons in the aPCX and counterstained with nuclear red. Cortical laminar area was measured from photomicrographs taken of neurobiotin-labeled sections through the aPCX. Photomicrographs were coded and all measurements were done blind to drug condition. Measurements of the aPCX and aPCX layers Ia and Ib were taken from four aPCX sections (every third slice) for each brain. Cortical laminar area (mm^2) was measured by tracing the outline of each layer by hand from the photomicrographs and calculated by ImageJ. Total aPCX laminar area included all of layer I and the LOT, extending from the superficial edge of layer II to the brain surface. For measurements of individual sub-layers, layer Ia extended from the deep edge of the LOT to the superficial edge of layer Ib. Layer Ib extended from the deep edge of layer Ia to the superficial edge of layer II. As shown in Fig. 4, these boundaries were clearly visible in the stained tissue. While we have previously used laminar thickness as a measure of the effects of experience on cortical anatomy [29], laminar area measurements were chosen here to avoid possible artifacts based on where the thickness measurements were made. The area of each layer was determined, between the boundary between the piriform cortex and olfactory tubercle on the ventrolateral side to the apex of the piriform cortex at the rhinal fissure on the dorsolateral side. In a subset of the data, both laminar thickness and laminar were measured and were shown to be highly positively correlated ($r^2 = 0.82$).

Data were analyzed with ANOVA and post hoc tests, and cross-correlation determined between behavior and anatomical data with animals. Correlation significance determined from tables of critical values for Pearson correlation coefficients.

For analysis of dendritic spine density, fifteen additional animals were implanted with cannulas and osmotic mini-pumps at PN14 ($n = 8$ aCSF; $n = 7$ CPPG) as described above. At PN28 animals were behaviorally tested in the odor investigation task, then had their brains removed and prepared for Golgi–Cox staining. Animals were sacrificed and brains removed and placed in 50 mL Golgi stain solution for 14 days in the dark [31]. Brains were then removed and sectioned in 6% sucrose at 200 μL on a vibratome [13], placed on microscope slides and staining completed. Apical dendrites within superficial regions of layer I in the aPCX were visualized, with a total of 10 dendrites from 5 different section sampled within each animal. Dendrites were photographed with a 40× objective (Olympus DP70 camera), enlarged images were displayed on computer monitor and dendritic spines quantified per unit distance of dendrite in dendritic sections of at least 50 μL. Behavior and dendritic spine density were compared between infusion groups with *t*-tests.

As shown in Fig. 1, naïve, non-manipulated pups at all ages tested investigated the scented object, and the duration of time spent directed toward the object decreased over the course of the session. Given the large difference in initial investigation time between ages, data were normalized to the investigation duration during the first minute (Fig. 1B). Animals at all ages, PN14 to adult, displayed similar odor habituation over the session (age by time repeated measures ANOVA, main effect of time, $F(9, 243) = 4.65$, $p < 0.01$), with no significant difference between ages (age × time interaction, $F(18, 243) = 1.01$, N.S.).

Chronic intra-cerebral infusions of the mGluRIII antagonist CPPG had a significant and long-lasting effect on odor investigation. Animals infused with CPPG for 2 weeks starting at PN14 showed a significant enhancement in cumulative odor investigation time over the 10 min exposure compared to littermate, aCSF-infused controls (Fig. 2). This enhancement was present not only at the end of the 2 week infusion (infused PN14–PN28, tested at PN28), but also in pups tested 2 weeks after the infusion was terminated (infused PN14–PN28, tested PN42). A two-way ANOVA showed a main effect of infusate on cumulative odor investigation (age × infusate ANOVA, main effect of infusate $F(1, 22) = 7.06$, $p < 0.02$), and post hoc Fisher tests revealed a significant difference between CPPG infusion and aCSF infusion at PN28 and PN42. Importantly, there was no effect of CPPG infusion on general activity levels at either age as assessed by time spent in non-odor directed behaviors (non-odor investigation time, age × infusate ANOVA, Main effect of infusate $F(1, 22) = 1.33$, N.S.). Thus, the increase in odor investigation did not reflect a CPPG induced general hyperactivity.

Given the effect of experience and synaptic activity on neural circuitry and anatomy, and the role of mGluRIII receptors in cortical adaptation described above, it was hypothesized that enhancing afferent activity to the piriform cortex by chronic blockade of

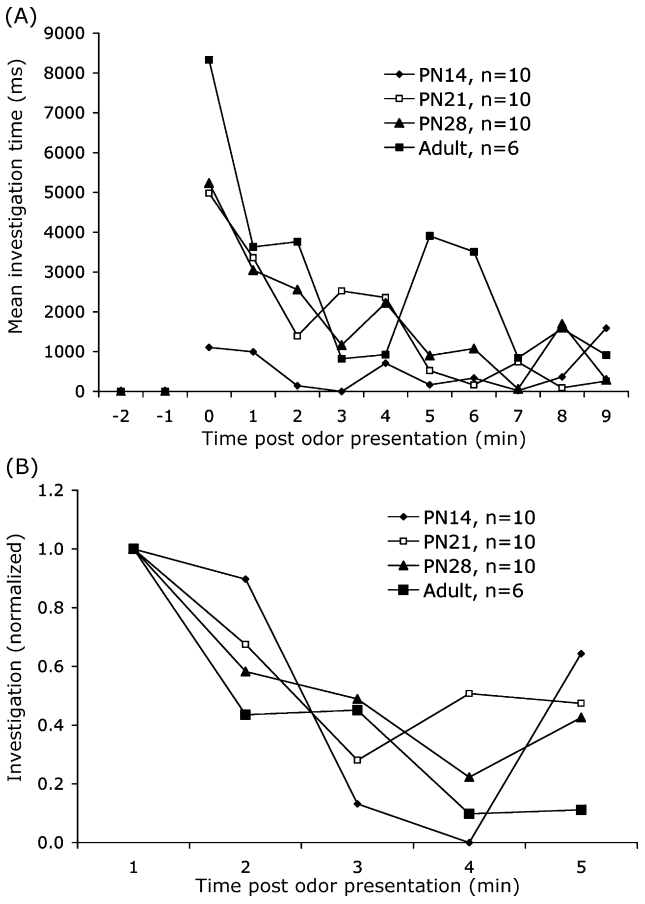


Fig. 1. Investigation of a scented object showed habituation at all developmental ages tested. There was no significant effect of age on habituation rate.

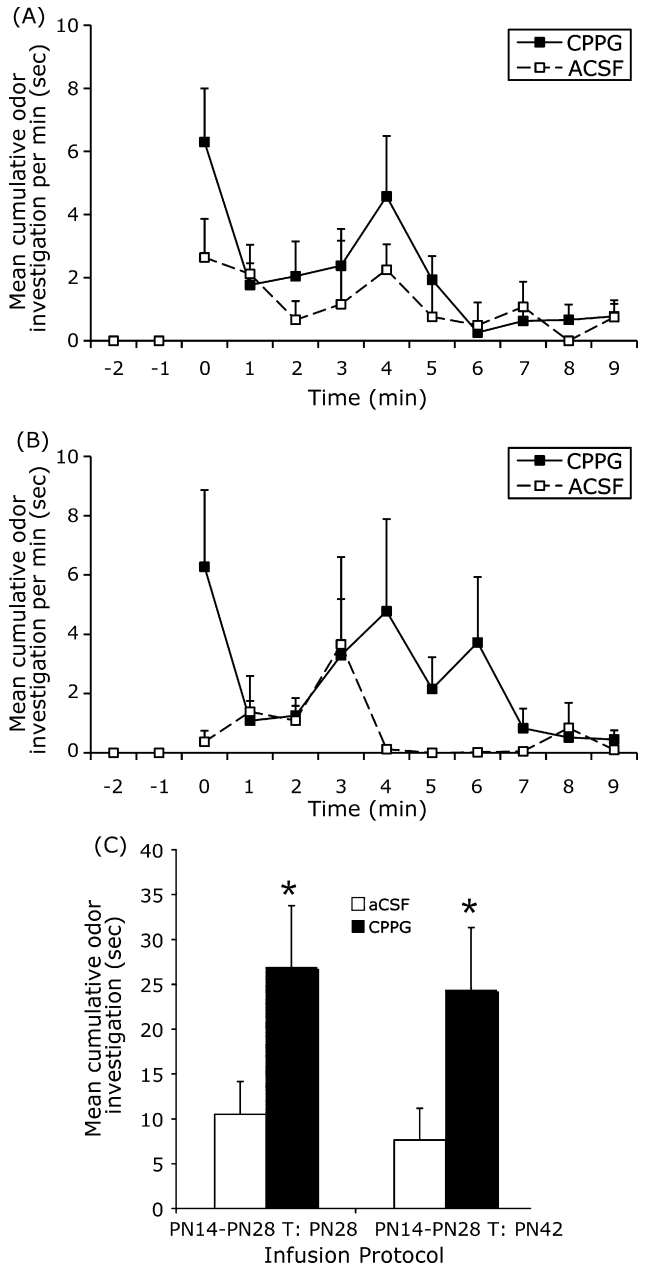


Fig. 2. Chronic CCPG infusion produced a long-lasting increase in odor investigation in young rats. Odor investigation time per minute for animals infused with aCSF or CPPG for 2 weeks and tested immediately after (PN28: A) or 2 weeks after (PN42: B) infusion offset. (C): Animals with CPPG infusion starting at PN14 and lasting for 2 weeks showed enhanced cumulative odor investigation (over 10 min) both at the end of infusion (tested at PN28) and 2 weeks after infusion termination (tested at PN42). Asterisks represent significant difference between CPPG- and aCSF-infused rats.

mGluRIII-mediated cortical adaptation would result in changes in cortical architecture. Furthermore, it was hypothesized that anatomical changes may underlie the observed behavioral changes. Based on past work examining experience-dependent piriform cortical anatomical plasticity [12,17,29], two measures were chosen for this assessment—cortical laminar thickness and cortical dendritic spine density.

CPPG infusion had no significant effect on cortical laminar area at any age (Fig. 3), though there was a slight increase in mean cortical area in the youngest age group (age × infusate ANOVA, age × infusate interaction $F(1, 20) = 2.83$, $p = 0.10$). When the afferent (layer Ia) and intrinsic (layer Ib) fiber layers were analyzed individually, there was similarly no significant effect on mean laminar area of drug infusion (data not shown).

Although mean cortical area did not reach significance across age and infusion, the trend for enhanced area in the youngest animals was more closely examined by correlating behavioral odor investigation time with layers Ia and Ib laminar area, within animals. Due to histological difficulties, only animals that had both behavioral measures and good laminar labeling were included, leading to reduced *n*s for this analysis. As shown in Fig. 4, animals infused with CPPG starting at PN14 and tested immediately after infusion termination (PN28), showed a significant positive correlation between odor investigation duration and layer Ia area ($r = 0.65$, $p < 0.05$, $n = 9$). Pups infused with aCSF showed no significant correlation between behavior and layer Ia ($r = 0.22$, N.S., $n = 7$). The increase in layer Ia in the CPPG infused pups was associated with a decrease in layer Ib area, with a strong negative correlation between odor investigation time and layer Ib area in the CPPG-infused pups ($r = -0.76$, $p < 0.05$). Combining the infusion groups ($n = 16$), revealed a significant positive correlation between odor investigation time and layer Ia ($r = 0.51$, $p < 0.05$), and a significant negative correlation with layer Ib ($r = -0.66$, $p < 0.05$). No consistent correlations between behavior and piriform laminar area were observed in the PN42 animals, and no significant correlations were observed between odor investigation and total cortical laminar area at any age.

In order to examine the effect of chronic CPPG infusion on dendritic spine density within piriform cortex, 15 additional ani-

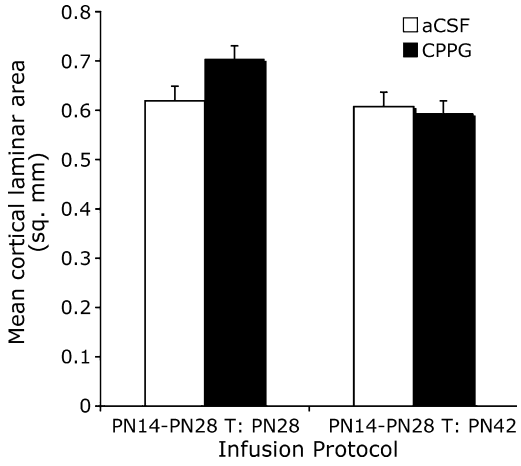
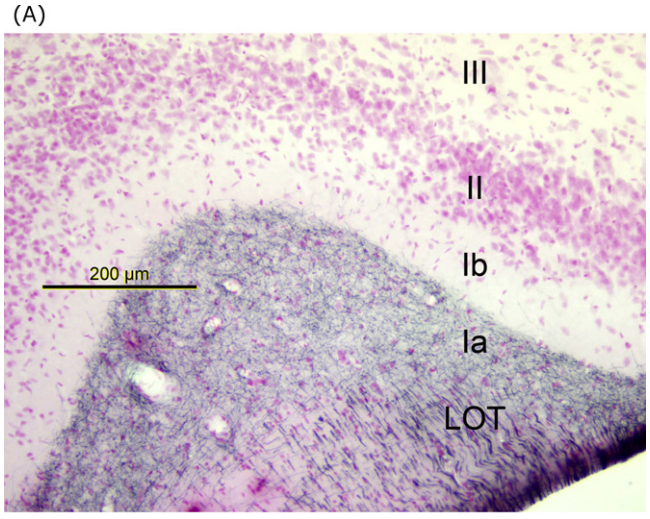


Fig. 3. CPPG infusion had no significant effect on mean piriform cortical laminar area (layer II to surface) at any age. Mean cortical laminar area included layers II, Ib, Ia and the lateral olfactory tract as described in the text.



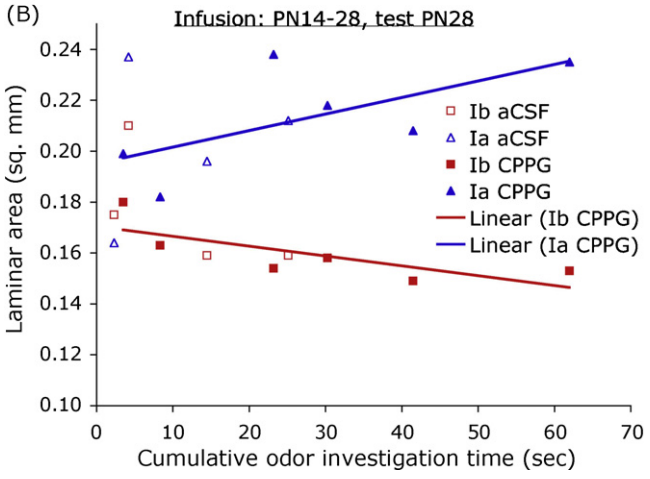


Fig. 4. Increases in odor investigation time were correlated with enlarged layer Ia (afferent fiber) laminar area and decreased layer Ib (intrinsic fiber) laminar area in PN28 rats. As described in the text, this effect was most pronounced in CPPG chronically infused pups compared to controls.

mals were implanted with cannulas and osmotic pumps at PN14 ($n = 8$ aCSF; $n = 7$ CPPG), and at PN28 tested in the odor investigation task, then had their brains removed and prepared for Golgi staining. Given that only this age group showed any trend for anatomical change in the laminar analysis, only this age was tested here. As shown in Fig. 5A, chronic CPPG infusion during early development significantly enhanced odor investigation compared to aCSF-infused pups ($t(13) = 2.30$, $p < 0.05$), replicating the findings above. No significant difference was detected between groups however, in apical dendritic spine density (Fig. 5C, $t(13) = 0.41$, N.S.).

Chronic intra-cerebral infusion of the mGluRIII antagonist CPPG for 2 weeks during early development produced a long-lasting increase in odor investigation behavior that was apparent at the end of the 2-week infusion period and 2 weeks after infusion termination. The increased odor investigation was not associated with general hyperactivity, as behaviors not directed at the scented object were unaffected. In young animals immediately post-infusion, the enhanced odor investigation was positively correlated with an increase in the laminar area corresponding to piriform cortical afferent termination (Ia), and negatively correlated with the laminar area corresponding to intrinsic cortical fiber termination (Ib). However, by 2 weeks post-infusion when odor investigation is still enhanced in CPPG treated rats, this anatomical correlation was not apparent. Finally, no significant effect on chronic CPPG infusion was detected on piriform cortex apical dendritic spine density. Given that acute infusion of CPPG is known to disrupt piriform cortical adaptation [5] and behavioral odor habituation [3,30], these results suggest that chronic disruption of cortical adaptation and sensory gating during early development leads to long-lasting changes in behavioral response to sensory inputs, consistent with behavioral perseveration.

Unilateral olfactory deprivation, which reduces piriform cortical afferent activity [15,22], reduces layer Ia thickness, expands layer Ib thickness and reduces dendritic complexity of semilunar pyramidal cells [29]. It was hypothesized here that chronic blockade of cortical adaptation may have the opposite effects of deprivation, and induce enlarged layer Ia, reduced layer Ib and decreased apical dendritic spine density. This hypothesis was not supported. Immediately after early onset chronic infusion, there was a significant positive correlation between odor investigation time and layer Ia area, however, this correlation is not required for the enhanced behavioral investigation as it was not apparent 2 weeks later when odor investigation was still enhanced but no anatomical were changes detected. The mechanism of the long-lasting, enhanced odor investigation following early onset blockade of cortical adaptation is thus still unclear.

Combined with previous work, these results suggest that disruptions of sensory gating can have both immediate and long-lasting effects on sensory-guided behavior, especially if the disruption begins early in development. Abnormally maintained or persistent response to sensory inputs that are normally filtered can modify central circuit function resulting in behavioral consequences outlasting the initial disruption. A variety of developmental disorders are associated with sensory gating disruption or perseverative behaviors, including schizophrenia [18] and autism spectrum disorder [21]. Importantly, metabotropic glutamate receptors have been shown to play a role in sensory gating or habituation not only in olfaction [3,20,30], but in several sensory systems [2,6,27] and have been linked to those same developmental disorders, including Fragile X [1,8], autism spectrum disorder [7,23,24] and schizophrenia [2,6]. The present results suggest a further potential link between this very basic sensory system function (habituation) and emergence of disrupted behavior.

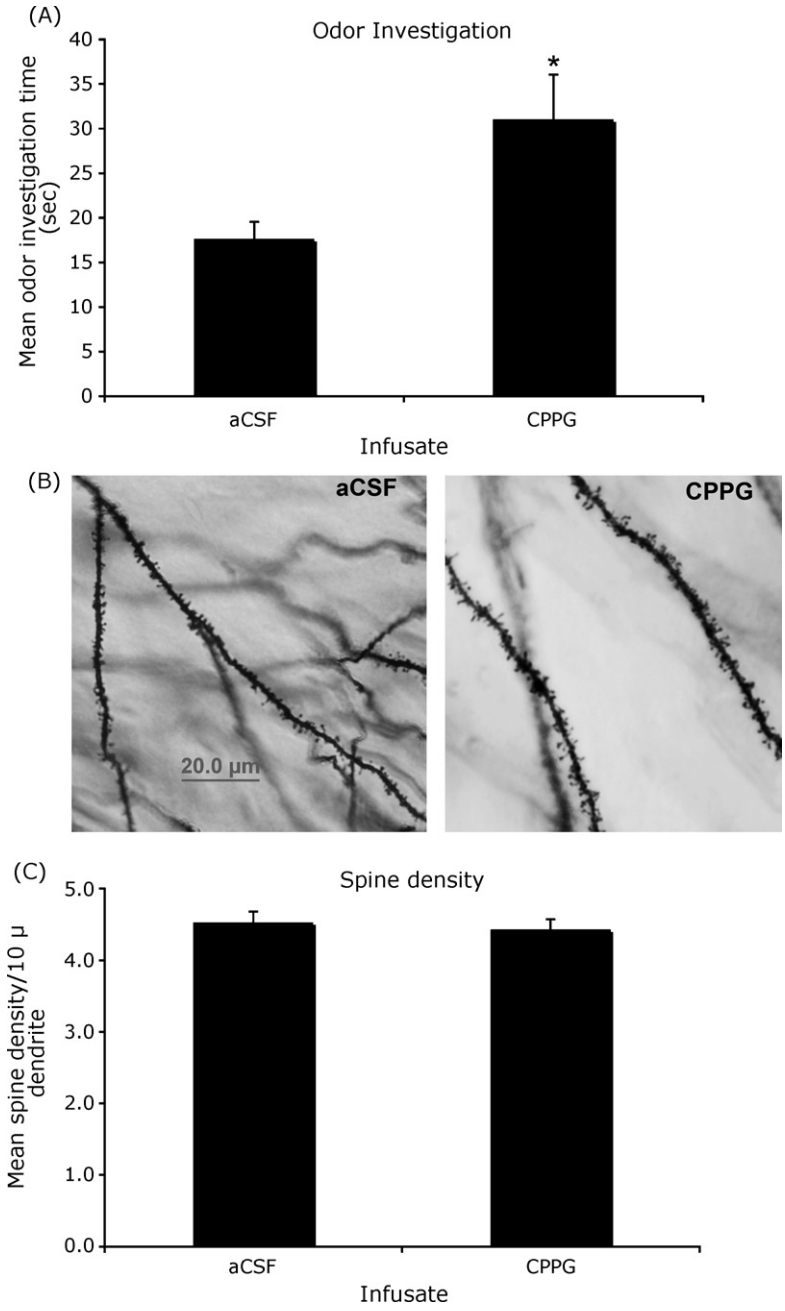


Fig. 5. (A) Chronic CPPG infusion enhanced cumulative odor investigation time in PN28 rats. (B) Representative examples of Golgi stained apical dendritic spines in piriform cortex in aCSF and CPPG-infused rats. (C) Chronic CPPG infusion had no significant effect on apical dendritic spine density in piriform cortex in the animals showing the behavioral change.

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