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Unilateral whisker clipping exacerbates ethanol-induced social and somatosensory behavioral deficits in a sex- and age-dependent manner

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HIGHLIGHTS

- Prenatal ethanol exposure impairs social interaction and somatosensory performance.
- Neonatal sensory impoverishment potentiates prenatal ethanol-induced behavior deficits.
- Interactions of ethanol- and impoverishment-induced deficits are age and sex-dependent.
- Somatosensory function plays an important role in normal social development.
- Enhancement of somatosensory development may improve fetal alcohol outcomes.

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ABSTRACT

Prenatal exposure to ethanol results in sensory deficits and altered social interactions in animal and clinical populations. Sensory stimuli serve as important cues and shape sensory development; developmental exposure to ethanol or sensory impoverishment can impair somatosensory development, but their combined effects on behavioral outcomes are unknown. We hypothesized 1) that chronic prenatal ethanol exposure would disrupt social interaction and somatosensory performance during adolescence, 2) that a mild sensory impoverishment (neonatal unilateral whisker clipping; WC) would have a mildly impairing to sub-threshold effect on these behavioral outcomes, and 3) that the effect of ethanol would be exacerbated by WC. Long–Evans dams were fed a liquid diet containing ethanol or pair-fed with a non-ethanol diet on gestational days (G) 6–G21. Chow-fed control animals were also included. One male and female pup per litter underwent WC on postnatal day (P)1, P3, and P5. Controls were unclipped. Offspring underwent social interaction on P28 or P42, and gap-crossing (GC) on P31 or P42. Ethanol-exposed pups played less and crossed shorter gaps than control pups regardless of age or sex. WC further exacerbated ethanol-induced play fighting and GC deficits in all males but only in 28-day-old females. WC alone reduced sniffing in all males and in younger females. Thus, prenatal ethanol exposure induced deficits in social interaction and somatosensory performance during adolescence. Sensory impoverishment exacerbates ethanol's effect in 28-day-old male and female animals and in 42-day-old males, suggesting sex- and age-dependent changes in outcomes in ethanol-exposed offspring.

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1. Introduction

Developmental exposure to ethanol results in sensory deficits and altered social interaction in humans and in animal models [1–13]. The range and severity of these outcomes are sensitive to several factors including timing, dose, and duration of ethanol exposure, as well as maternal genetics, nutritional status, and age [14–19]. In humans, social deficits can range from minimal to severe depending on such factors, but can manifest as poor social skills, difficulties understanding social cues, and inappropriate social behavior that causes problems within the home, at school, or with the law [7,13,20,21]. Also apparent in this population are sensory deficits including sensory processing deficits and problems transferring somatosensory information between hemispheres [1,11,13,21].

Ethanol-induced alterations in social behavior have been described in rodent models; for example, switched sexual dimorphic social play patterns in adolescents [4,22], delayed maternal responses in dams that were prenatally exposed, increased aggression in prenatally exposed adult males [10,23], and altered sexual interactions in both sexes [24,25]. In addition to altered social behavior, sensory detection and processing of somatosensory stimuli are also impaired following prenatal ethanol exposure [2,6]. This may be due, in part, to the ethanol-induced alteration in the structure of somatosensory cortex [5,26–30].

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Sensory stimuli play an important role in both cueing and shaping social interaction in rodents [31–35]. Damage to or removal of the somatosensory cortex alters play behavior [31]. Similarly, numbing of the animals nape thereby decreasing sensation and inhibiting activity in the somatosensory system reduces play interaction [2,33].

Disrupting input into the somatosensory system during development also alters its structure and somatosensory-dependent behaviors. This can be modeled by damaging whisker follicles or clipping whiskers during the first postnatal week when thalamocortical afferents develop the typical barrel pattern [36,37]. These manipulations cause a sensory impoverishment that has long-term effects on cortical morphology and function of the somatosensory system, including increased neuronal activity and increased size of the excitatory receptive field of the rodent barrel cortex [38–41]. Impoverishment can also have a long-term effect on behavior; bilateral neonatal whisker clipping the first three days of life leads to decreased performance on a somatosensory-dependent task (gap crossing) and increased social interaction during play with no effect on anxiety as measured by elevated plus maze performance [38].

Chronic prenatal exposure to ethanol alters the structure of the somatosensory system; reducing neuronal numbers in trigeminal nuclei [28] and the somatosensory cortex [5], and stunting thalamocortical afferents to cortex [42]. There is also a delay in the emergence of barrels in the somatosensory cortex and lower neuronal density within barrels [26,27,29,30]. Depressed neuronal activity is seen in the adult somatosensory cortex of ethanol-exposed animals [43–45] and delays in cellular maturation, such as expression of N-methyl-D-aspartate receptor isoforms, have also been reported following prenatal ethanol exposure [6,46]. Taken together this shows that prenatal ethanol exposure alters the structure and function of this system.

While both prenatal ethanol exposure and sensory impoverishment have distinct effects on the developing brain and consequent behavior, only one study has investigated the effect of disruption of somatosensory function and developmental ethanol exposure in concert on social behavioral outcomes [2]. In this study, rats were exposed to ethanol from gestational days (G)1 to G22 and postnatal days (P)2 to P10 and underwent a social interaction test during adolescence. Ethanol-exposed rats showed increased pinning during social play. Acute inhibition of tactile (somatosensory) input by numbing the nape depressed pinning in control animals at the highest dose of xylocaine tested. Ethanol-exposed animals that were numbed demonstrated increased pinning and were more sensitive to degrading touch cues, showing reductions in pinning at lower xylocaine doses during social interaction in comparison to controls. This suggests ethanol-induced difficulties in processing somatosensory cues alter social behaviors and that acute disruptions to sensory stimuli can directly exacerbate the ethanol effect.

The current study tested the hypotheses (1) that prenatal ethanol exposure disrupts social interaction, elevated plus maze, and whisker-related somatosensory performance (gap crossing) during adolescence, (2) that a modest sensory impoverishment during early development (neonatal unilateral whisker clipping; WC) would have mild but long-term effects on social interaction and gap crossing, and (3) that the double-hit of prenatal ethanol exposure and WC would have the greatest effect on the behaviors tested.

2. Methods

2.1. Subjects

Timed pregnant Long–Evans dams (Harlan, Frederick, MD, USA) were brought in on G3 (G1 was designated as the first day a sperm-plug was identified). Animals were housed in an AAALAC – approved facility at the University of Maryland, Baltimore that is humidity – (40–45%) and temperature-controlled (22 °C) and maintained on a 12/12-h light/dark cycle (lights on at 0700). All procedures were performed with approval of the Institutional Animal Care and Use Committee (IACUC) at the University of Maryland, Baltimore and were in accordance with the guidelines for animal care established by the National Institutes of Health.

2.2. Prenatal exposure

Starting on G6, dams were randomly assigned to one of three prenatal exposure conditions. Two groups received a liquid diet (L10251 and L10252, Bio-serve, Frenchtown, NJ). One group (ET) received diet containing 11.5% ethanol-derived calories (EDC) on G6 and G7, 22% EDC on G8–G10, and 35% EDC between G11 and G20. Blood ethanol concentrations typically reach 100–150 mg/dl [47,48]. A second group (PF) was pair fed an isonutritive, isocaloric liquid diet containing maltose in place of the ethanol. The third group (CH) received ad libitum access to laboratory chow. All animals had ad libitum access to water. On G21, liquid diet-fed dams were returned to regular chow. Birth typically occurred on G22 (also designated as P0).

2.3. Postnatal manipulation

Within 24 h of birth, all litters were surrogate fostered to a CH dam. Litter information was recorded (litter size, sex ratio, average pup weights) on P1, then litters were culled to 10 keeping the ratio of males to females at 6:4 as best as possible. One male and one female pup from each litter were randomly assigned to a postnatal unilateral whisker clip (WC) group; on P1, P3, and P5, the right whiskers were clipped 1 mm or less from the skin using a sharp surgical scissors. One male and one female pup from each litter was left unclipped and assigned to the non-whisker clipped (NWC) group. Pups were weaned on P21 and housed in same sex littermate pairs.

A total of 54 litters were used to generate 225 male and female offspring to serve as experimental subjects. An additional 32 untreated litters provided the 225 social interaction partners. To avoid potential litter bias no more than one male and one female from a litter was allotted to each treatment condition per testing age [49]. Animals were divided into two distinct cohorts. One cohort underwent social interaction (SI) testing at P28, followed by gap crossing at P31 and elevated plus maze testing at P35; a second cohort of animals underwent SI testing and gap crossing at P42.

2.4. Measurement of whisker length

On P42, a sub-set of 70 rats were anesthetized with 3% isoflurane (Vet One, Boise, ID) until unconscious, and C-row whiskers (C1 to C5) were plucked from the base of the muscle on both the clipped and non-clipped sides. The length (mm) for each whisker from the base to the tip of the whisker shaft was measured and recorded.

2.5. Social interaction test

On P28 or P42 rats were transported to a dimly lit testing room where they habituated to the room for 2 h before undergoing testing in a modified social interaction (SI) paradigm [9,50,51]. The SI apparatus was a perspex box (30 cm × 20 cm × 20 cm; Binghamton Plate Glass, Binghamton, NY). This box included a clear partition that divided it into two equal halves with a semicircular hole (7 cm × 5 cm) in the middle, which allowed the animals to temporarily avoid contact by moving between compartments [9,50]. Each test comprised a 10 min interaction between an experimental animal and an untreated play partner. Animals were matched for weight (weight difference no greater than ± 10 g), age, and sex.

All animals underwent a 30 min isolation; play partners spent the entire 30 min isolation in a holding cage. Experimental subjects had their sides marked with a non-toxic red Sharpie™ marker and then spent 20 min in a holding cage and 10 min in the SI box. During this habituation to the SI box, locomotor activity was tracked and recorded

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