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Research report

Adolescent and adult rats differ in the amnesic effects of acute ethanol in two hippocampus-dependent tasks: Trace and contextual fear conditioning

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HIGHLIGHTS

- Acute ethanol interferes with hippocampal function.
- Adolescents and adults differ in sensitivity to ethanol.
- Adolescents show ethanol disruption of trace conditioning.
- Adults show ethanol disruption of context conditioning.
- Age differences in cognitive impairments by acute ethanol.

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ABSTRACT

Experience-produced deficits in trace conditioning and context conditioning have been useful tools for examining the role of the hippocampus in learning. It has also been suggested that learning in these tasks is especially vulnerable to neurotoxic effects of alcohol during key developmental periods such as adolescence. In five experiments we systematically examined the presence and source of age-dependent vulnerability to the memory-disrupting effects of acute ethanol in trace conditioning and contextual fear conditioning. In Experiment 1a pre-training ethanol disrupted trace conditioning more strongly in adolescent (postnatal day, PD30-35) than adult rats (PD65-75). In Experiment 1b when pre-training ethanol was accompanied by pre-test ethanol no deficit in trace conditioning was observed in adolescents, suggesting that state-dependent retrieval failure mediated ethanol's disruption of trace conditioning at this age. Experiment 2a and b examined the effect of ethanol pretreatment on context conditioning. Here, adult but not adolescent rats were impaired in conditioned freezing to context cues. Experiment 2c explored state-dependency of this effect. Pre-training ethanol continued to disrupt context conditioning in adults even when ethanol was also administered prior to test. Collectively these findings reveal clear age-dependent and task-dependent vulnerabilities in ethanol's disruptive effects on hippocampus-dependent memory. Adolescents were more disrupted by ethanol in trace conditioning than adults, and adults were more disrupted by ethanol in context conditioning than adolescents. We suggest that adolescents may be more susceptible to changes in internal state (state-dependent retrieval failure) than adults and that ethanol disrupted performance in trace and context conditioning through different mechanisms. Relevance of these findings to theories of hippocampus function is discussed.

1. Introduction

Ethanol, depending upon dose, can have disruptive effects on learning and memory [1]. Interestingly, ethanol's effects depend on the type of memory assessed. In humans, implicit memory may be impervious to acute ethanol and is generally immune to ethanol-induced amnesia [2]. In contrast, acute ethanol impairs the acquisition of explicit, declarative memory and ethanol-induced deficits in declarative recall are often reported [2,3]. In non-human subjects, acute ethanol can also interfere with learning and memory in a task-dependent manner. Available reviews of this extensive literature suggest that ethanol has markedly detrimental effects on hippocampus-dependent forms of learning and memory [4,5].

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For example, in adult rats ethanol dose-dependently compromises performance on spatial memory tasks, such as the Morris water maze [6,7]. Weitemier and Ryabinin [8] showed that ethanol disrupted both trace and contextual fear conditioning in adult mice, while having no effect on delay conditioning (see also [9]). Similar effects of ethanol on contextual fear learning in rats have also been reported [10,11]. Importantly, these tasks that are affected by acute ethanol (spatial memory, trace conditioning, context conditioning) are known to involve the hippocampus. Performance on non-hippocampus variations of these tasks (delay conditioning, nonspatial/cue learning) is generally not affected by low to moderate doses of ethanol, although high doses can produce more general disruptions to learning [8,12,13].

While the literature presented above indicates that acute ethanol can produce substantial deficits in some types of memory in adults, less is known about age-related differences in sensitivity to ethanol-induced learning impairments [14,15]. Available evidence is mixed. Some research suggests that adolescents are more sensitive than adults to the amnesic effects of ethanol, while others report that adolescents are lesssensitive. For example, Markwiese et al. [16] found that adolescent rats were more impaired in acquisition of the Morris water maze spatial task by a moderate (1 or 2 g/kg) dose of ethanol than were adults. Chin et al. [17] showed that adolescents and adults were equally impaired in the water maze task when ethanol was acutely administered prior to a test for spatial memory. Land and Spear [18] reported a greater disruptive effect of ethanol in adolescents, compared to adults, on an appetitive odor discrimination task. These particular age-dependent differences in ethanol effects on memory may relate to developmental changes in ethanol's disruption of hippocampal activity. Ethanol is known to suppress the firing rate of pyramidal neurons, disrupt hippocampal theta rhythm, antagonize NMDA receptor sub-types and decrease glutamate release (see [15]). Moreover, Swartzwelder and colleagues [19,20,21] reported that hippocampal slices from juvenile and adolescent rats showed greater sensitivity to ethanol inhibition of both NMDA-mediated synaptic plasticity and induction of long-term potentiation than slices obtained from adults.

Not all of the data however, support the idea that adolescents are more sensitive to the amnesic effects of acute ethanol. Land and Spear [13] reported that adult rats exhibited greater disruption in fear conditioning than adolescents. This was evident in reduced conditioned freezing to both a tone conditioned stimulus (CS) and contextual cues. The finding that cue (CS) conditioned responding was impaired by a moderate dose of ethanol (1 g/kg) is perplexing, given that several other studies find no effect of ethanol on this type of fear conditioning with comparable doses [8,11]. In addition, Broadwater and Spear [22] recently reported a greater disruptive ethanol effect in adult rats, compared with adolescents, in contextual fear conditioning. Unlike the Land and Spear [13] results, no effect of ethanol was observed on CS conditioning at either age, a finding consistent with the reports cited above.

The primary question addressed in the present experiments was whether adolescents and adults are differentially sensitive to the memory-impairing effects of acute ethanol using two tasks known to require hippocampal function (trace and contextual fear conditioning). The literature concerning the effects of acute administration of alcohol on trace conditioning, one widely recognized form of hippocampus-dependent memory, is surprisingly limited. Only two studies have, to our knowledge, addressed this question. McKinzie et al. [10] used preweanling (17-day-old) rats and a study by Weitemier and Ryabinin [8] employed adult mice. Both reported detrimental effects of acute ethanol on trace, but not delay, fear conditioning. Another study by Melia et al. [11] examined the effects of acute alcohol on contextual fear conditioning, and alcohol was found to dose-dependently impair contextual fear conditioning in adult rats. The present experiments specifically compared the sensitivity of adolescent and adult rats to the effects of acute pre-training ethanol on delay, trace, and contextual fear conditioning in the same series of studies. Given that adolescent rats are more impaired by alcohol on hippocampus-dependent spatial learning tasks than are adults [16] and that adults may be more sensitive to ethanol in contextual fear conditioning [22], we expected that age-related differences in sensitivity to ethanol amnesia would be obtained in both trace and contextual fear conditioning but given existing discrepancies in the literature the exact direction of age-related vulnerability was not initially hypothesized.

Pre-training drug administration can result in state-dependent performance deficits that do not reflect deficits in learning or memory acquisition per se [23]. Therefore, a second goal of the present research was to systematically explore the contribution of state-dependent retrieval failure to any ethanol-induced deficits in trace and context conditioning, when observed (see [11]). Finally, none of the research previously exploring age differences in the effects of acute ethanol has permitted evaluation of sex differences. Most prior studies have employed only male subjects and the two that included both sexes [13,18] did not analyze the data for possible sex differences. In the present work, we extend the available literature further by including both males and females in order to assess whether age-dependent vulnerabilities in ethanol's memory impairing effects also depend on sex.

2. General method

2.1. Subjects

A total of 409 Sprague–Dawley-derived rats served as subjects in these experiments. Two hundred and fifteen animals were trained and tested as adolescents (range 30–35 days, derived from 29 litters) and 194 were trained and tested as adults (range 65–75 days, derived from 38 litters). Approximately equal numbers of male and female subjects were included in each treatment group whenever possible (all ns = 8 – 10). In each experiment, no more than one male and one female from a litter were assigned to each treatment group.

Subjects were born and raised at the College of William and Mary (Williamsburg, VA) in the Psychology Department's vivarium. Breeder animals (Charles River Laboratories, Wilmington, MA) were housed in 50.8 × 40.6 × 21.6 cm clear polycarbonate cages with pine chip bedding and wire tops. All animals had free access to water and high-protein rodent pellets (LabDiet Formula 5008). Cages were checked at 1000 h daily for pups, and the day of birth was designated Postnatal Day (PD) 0. On PD 2, litters were culled to 8–10 pups that remained with the dam until PD 21. At weaning, animals were housed with same-sex siblings in identical cages. On PD 40 animals were pair housed. The vivarium light:dark schedule was maintained at 14:10 h with light onset at 0600 h. All experimental procedures were carried out during the light portion of the cycle and were approved by the College of William and Mary's Institutional Animal Care and Use Committee that follows guidelines established by the NIH.

2.2. Apparatus

All delay and trace conditioning (Experiment 1a and b), and context conditioning (Experiment 2a, b, and c), occurred in two identical 38.0 × 26.0 × 22.0 cm modified Skinner boxes. Two of the four walls were made of clear Plexiglas and the other two were made of aluminum. The floor was constructed of 5 mm stainless steel rods spaced 1.5 cm apart (center to center). In all experiments