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DEVELOPMENTAL ETHANOL EXPOSURE-INDUCED SLEEP FRAGMENTATION PREDICTS ADULT COGNITIVE IMPAIRMENT

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Abstract—Developmental ethanol (EtOH) exposure can lead to long-lasting cognitive impairment, hyperactivity, and emotional dysregulation among other problems. In healthy adults, sleep plays an important role in each of these behavioral manifestations. Here we explored circadian rhythms (activity, temperature) and slow-wave sleep (SWS) in adult mice that had received a single day of EtOH exposure on postnatal day 7 and saline littermate controls. We tested for correlations between slow-wave activity and both contextual fear conditioning and hyperactivity. Developmental EtOH resulted in adult hyperactivity within the home cage compared to controls but did not significantly modify circadian cycles in activity or temperature. It also resulted in reduced and fragmented SWS, including reduced slow-wave bout duration and increased slow-wave/fast-wave transitions over 24-h periods. In the same animals, developmental EtOH exposure also resulted in impaired contextual fear conditioning memory. The impairment in memory was significantly correlated with SWS fragmentation. Furthermore, EtOH-treated animals did not display a post-training modification in SWS which occurred in controls. In contrast to the memory impairment, sleep fragmentation was not correlated with the developmental EtOH-induced hyperactivity. Together these results suggest that disruption of SWS and its plasticity are a secondary contributor to a subset of developmental EtOH exposure's long-lasting consequences. **© 2016 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: fetal alcohol disorder, sleep fragmentation, slow-wave sleep, insomnia, circadian rhythm.

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Abbreviations: BAL, blood alcohol level; EtOH, ethanol; FASD, fetal alcohol spectrum disorder; FFT, Fast-Fourier Transform; LFP's, local field potentials; r.m.s., root mean square; SWS, slow-wave sleep.

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INTRODUCTION

Fetal alcohol spectrum disorder (FASD) is a primary cause of intellectual disability (Abel and Sokol, 1986; May and Gossage, 2001; Fox and Druschel, 2003), with neurobehavioral hallmarks such as deficits in learning, memory and mood. Developmental ethanol (EtOH) exposure disrupts proliferation, differentiation, migration, and survival of neurons (Bonthius and West, 1990; West et al., 1990; Ikonomidou et al., 2000; Klintsova et al., 2007; Gil-Mohapel et al., 2010), and FASD is associated with cognitive, behavioral, memory and sensory impairments, as well as heightened susceptibility to seizures (West et al., 1990; Berman and Hannigan, 2000; Riley and McGee, 2005; Morasch and Hunt, 2009; Bell et al., 2010; Carr et al., 2010; Mattson et al., 2010). The specific set of symptoms are dependent on the age, duration and intensity of the EtOH exposure (Riley and McGee, 2005; Sadrian et al., 2014). Beyond the initial wave of EtOH-induced damage such as cell death, there is a cascade of cellular, synaptic and network consequences induced by early EtOH exposure – some as a direct result of the EtOH insult, and some as a secondary response to cellular changes induced by that initial insult. One of the many functions that are disrupted by early EtOH exposure is sleep–wake structure (Criado et al., 2008; Pesonen et al., 2009; Jan et al., 2010; Wengel et al., 2011; Volgin and Kubin, 2012).

Slow-wave sleep (SWS) is characterized by up- and down-states in cell excitability in thalamocortical regions (Buzsaki, 2006), and by sharp-wave/ripple activity in both the hippocampal formation (Buzsaki, 1986) and olfactory (piriform) cortex (Murakami et al., 2005; Wilson, 2010; Manabe et al., 2011). These coordinated, brief (100's ms) periods of high-excitability appear to provide windows of opportunity for replay of recent experiences, and binding and/or transfer of learned information across distributed brain regions (Stickgold et al., 2001; Buzsaki, 2006; Stickgold and Walker, 2007; Barnes and Wilson, 2014). This activity may also be important for homeostatic regulation of synaptic strength (Liu et al., 2010; Bushey et al., 2011).

In individuals with FASD (Troese et al., 2008; Pesonen et al., 2009; Wengel et al., 2011; Chen et al., 2012) and in animal models of early EtOH exposure (Criado et al., 2008; Volgin and Kubin, 2012) sleep becomes more fragmented. Sleep fragmentation refers to shortened sleep bouts and frequent transitions between sleep and wake states. In both healthy and pathological populations, sleep deprivation and fragmentation are associated with

impaired cognitive function, attention and emotional regulation (Durmer and Dinges, 2005; Abel et al., 2013; Basner et al., 2013). Sleep onset and transitions between sleep states are controlled by a variety of sub-cortical nuclei, including regions of thalamus, hypothalamus and brainstem (Jones, 2005; Abel et al., 2013), and GABAergic neurons in these regions play a crucial role in sleep regulation (Brown and McKenna, 2015). Commonly used hypnotics target GABAergic receptors (Manfridi et al., 2001; Walsh et al., 2007; Brickley and Mody, 2012), and insomnia and sleep fragmentation have been associated with impaired GABAergic neuron function in these regions (Lundahl et al., 2007; Kalume et al., 2015). Developmental EtOH exposure results in dysregulation of GABAergic neurons, including the parvalbumin expressing subset, throughout many brain regions (Coleman et al., 2012; Sadrian et al., 2014; Skorput et al., 2015; Smiley et al., 2015), potentially further raising the possibility of sleep dysfunction.

Here, in an extension of previous work that focused on analysis of developmental EtOH effects on relatively brief periods of sleep/waking (Stone et al., 1996; Criado et al., 2008; Volgin and Kubin, 2012), we explored SWS over a multi-day period in adult mice exposed to a single exposure of EtOH on postnatal day 7 (P7). In the same mice, we examined developmental ethanol-induced behavioral hyperactivity in the home cage and hippocampal-dependent contextual fear memory impairment, to assess whether these behavioral outcomes correlated with sleep disruption. The results demonstrate both reduced time in SWS, and severe sleep fragmentation following developmental EtOH, as well as a significant correlation between sleep disruption and memory impairment. In contrast, developmental EtOH-induced hyperactivity was not correlated with sleep structure. The results suggest that SWS disruption may be an important secondary contributor to the long-lasting neurobehavioral consequences of developmental EtOH exposure.

EXPERIMENTAL PROCEDURES

Subjects

C57BL/6By mice, bred at the Nathan Kline Institute animal facility, were maintained on *ad lib* food and water at all times. Lights were on from 9 am to 9 pm for most animals, though for a subset lights were on from 8 am to 8 pm. Circadian measurements (see below) are expressed relative to the light cycle. All procedures were approved by the Nathan Kline Institute IACUC and were in accordance with NIH guidelines for the proper treatment of animals. On P7 pups were injected subcutaneously with saline or EtOH as described (Olney et al., 2002b; Saito et al., 2007). Each mouse in a litter was assigned to the saline or EtOH group at an equivalent proportion of the total number of mice with a distributed gender ratio. EtOH treatment (2.5 g/kg) was delivered twice in the same day at a 2-h interval as originally described for C57BL/6 mice (Olney et al., 2002b). Pups were returned to their home cage immediately following injections. Our previous studies showed that this P7 EtOH treatment induced a peak blood alcohol level (BAL) of 0.5 g/dL when truncal blood was collected at 0.5, 1, 3, and 6 h following the second EtOH injection and analyzed with an Alcohol Reagent Set (Pointe Scientific, Canton, MI, USA) (Saito et al., 2007). Under the same P7 EtOH treatment conditions, it has been reported that initial BAL peaks are attained approximately 1 h after each injection, with BAL falling below half of this level 8 h after first EtOH exposure (Wozniak et al., 2004; Young and Olney, 2006). Pups were weaned at P28 into group cages of littermates. Same-sex mice were housed together in cages in numbers between two and four per cage. Body weights measured using a set of C57BL/6By mice before (at P7) and after (at P14 and at 3-month old) saline/EtOH injections were as follows: P7 mice, 3.5 ± 0.12 g/3.44 ± 0.17 g (mean ± SEM of males/mean ± SEM of females) for saline-assigned groups and 3.64 ± 0.12 g/3.5 ± 0.13 g for EtOH-assigned groups; P14 mice, 6.73 ± 0.14 g/6.21 ± 0.29 g for saline-treated groups and 6.07 ± 0.14 g/5.47 ± 0.17 g for EtOH-treated groups; 3-month-old mice, 26.3 ± 1.0 g/20.2 ± 0.4 g for saline-treated groups and 25.5 ± 0.6 g/20.0 ± 0.3 g for EtOH-treated groups. An ANOVA indicated no significant main effects for gender or assigned groups and no significant interaction between these variables at P7. At P14, there were significant main effects for genders [$F(1,40) = 6.3$ ($p = 0.016$)] and for treatment groups [$F(1,40) = 10.0$ ($p = 0.003$)] without significant interaction between gender and treatment. Three-month-old mice only showed a significant main effect of gender [$F(1,42) = 78.5$ ($p = 0.001$)] without a significant main effect of treatment or a significant interaction between the variables. Thus, the differences in body weights observed in P14 mice between saline and EtOH groups seem to be diminished by 3 months of age when behavioral and electrophysiological studies were undertaken in the present study. Gender differences in the effects of P7 EtOH were not observed when studied previously (Wilson et al., 2011; Sadrian et al., 2012, 2014), nor were any significant differences observed between genders here, thus for most analyses both genders were combined.

Telemetry recordings and slow-wave analyses

Animals (postnatal age 85–100) were anesthetized with isoflurane and surgically implanted with a single stainless steel (125μ diameter) electrode in the frontal cortex. The electrode and reference were connected to a single-channel telemetry device implanted under the skin of the back. This telemetry transmitter (DSI, model ETA-F10) also transmitted body temperature and movement, which were extracted separately for analysis in a subset of animals. These transmitters did not allow EMG measures, and thus REM sleep was not monitored. Following surgery, animals were allowed to recover alone in their home cage for 4–7 days before 24-h recordings were begun. Basal sleep/wake and circadian activity were recorded continuously for 2–3 days in the home cage. All recordings were made from animals housed individually in a pairwise design, with a developmentally EtOH-exposed mouse and their littermate control recorded simultaneously. Data from no more than one pair/litter are included here.

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